SØ- OG HANDELSRETTEN
KENDELSE

afsagt den 20. juni 2019

Sag BS-39398/2018-SHR

Fresenius Kabi Deutschland GmbH
(advokat Jakob Krag Nielsen og advokat Rasmus Vang)

mod

Biogen (Denmark) Manufacturing ApS
og
Biogen (Denmark) A/S
(advokat Nicolai Lindgreen og advokat Nicolaj Bording for begge)

Indtrædende part efter retsplejelovens § 420, stk. 1
Samsung Bioepis UK Limited
(advokat Klaus Ewald Madsen og advokat Søren Christian Søborg Andersen)

Denne afgørelse er truffet af vicepræsident Mads Bundgaard Larsen, dommer Claus Forum Petersen og sekretariatschef Mette Skov Larsen sammen med de sagkyndige medlemmer Ulla Klinge og Karin Verland.

Sagens baggrund og parternes påstande
Under denne sag, hvor sagsøgeren Fresenius Kabi Deutschland GmbH den 16. oktober 2018 med henvisning til to udstedte brugsmodeller BR 2018 00070 Y4 og BR 2018 00071 Y4 indgav begæring om midlertidigt forbud og påbud, der angår de to sagsøgte Biogen-selskabers fremstilling og udbud af lægemiddelproduktet Imraldi, er der – udover spørgsmålet om krænkelse af brugsmodellerne – spørgsmål om brugsmodellernes gyldighed og om, hvorvidt der tilkommer de sagsøgte selskaber en forbenyttelsesret, der i sig selv gør, at sagsøgers

påstande ikke kan fremmes. Brugsmodellerne er udstedt den 13. december 2018 med prioritet den 23. maj 2014.

Fresenius Kabi Deutschland GmbH har endeligt nedlagt følgende påstande:

1. Det forbydes Biogen (Denmark) Manufacturing ApS og Biogen (Denmark) A/S i Danmark at fremstille, udbyde, bringe i omsætning eller anvende Imraldi®, jf. markedsføringstilladelse EU/1/17/1216 (bilag 1), eller at importere eller besidde Imraldi® med sådant formål, så længe et enkelt og/eller en kombination af krav 1, 2, 5, 6, 7, 11 og/eller 12 i dansk brugsmodel nr. BR 2018 00070 Y4 (bilag 16) og/eller et enkelt og/eller en kombination af krav 1, 2, 3, 5, 7, 8, 12 og/eller 13 i dansk brugsmodel nr. BR 2018 00071 Y4 (bilag 17), er i kraft.

2. Det påbydes Biogen (Denmark) Manufacturing ApS og Biogen (Denmark) A/S at tilbagekalde allerede skete leverancer af Imraldi®, jf. markedsføringstilladelse EU/1/17/1216 (bilag 1), fra alle erhvervsmæssige kunder, herunder koncernforbundne selskaber, apoteker og hospitalsapoteker, hvortil levering er foretaget af Biogen (Denmark) Manufacturing ApS eller Biogen (Denmark) A/S.

3. Det påbydes Biogen (Denmark) Manufacturing ApS og Biogen (Denmark) A/S straks at afregistrere dets pris for Imraldi® i det danske prisregister (www.medicinpriser.dk)

Biogen (Denmark) Manufacturing ApS og Biogen (Denmark) A/S samt Samsung Bioepis UK Limited har heroverfor nedlagt påstand om, at anmodningen om midlertidigt forbud og midlertidige påbud nægtes fremme, subsidiært at det begærede midlertidige forbud og/eller de begærede midlertidige påbud fremmes alene på betingelse af etablering af sikkerhedsstillelse.

Oplysningerne i sagen

Sagens parter og de omhandlede lægemidler

Fresenius Kabi Deutschland GmbH (herefter Fresenius)
Fresenius, der er et selskab i Fresenius-koncernen, er en virksomhed inden for health care-sektoren, som primært er hjemmehørende i Tyskland. I september 2017 trådte Fresenius ind på markedet for biosimilære lægemidler, da selskabet erhvervede samtlige produkter under udvikling fra det tyske selskab Merck KGaA for ca. 656 millioner EUR.

I december 2017 indgav Fresenius en ansøgning til EMA (Det Europæiske Lægemiddelagentur) om godkendelse af et biosimilært lægemiddel indeholdende adalimumab med serienummeret MSB 11022. MSB 11022 var oprindeligt blevet udviklet af Ares Trading, som siden 2006 har været en del af den tyske Merck-koncern.

Der blev den 3. april 2019 udstedt markedsføringstilladelse til Fresenius' adalimumab-produkt under navnet Idacio.

I forbindelse med erhvervelsen af Ares Trading blev Fresenius også indehaver af en ansøgning om udstedelse af et europæisk patent, der førte til udstedelsen af DK/EP 3148510 T3 ("EP '510"). Fresenius er også registreret som ejer af brugsmodellerne BR 2018 00070 ("BR '070") og BR 2018 00071 ("BR '071"), der tilhører samme patentfamilie som EP '510.

Biogen (Denmark) Manufacturing ApS og Biogen (Denmark) A/S (herefter Biogen) samt Samsung Bioepis UK Limited (herefter SB)
De to nævnte danske Biogen-selskaber er datterselskaber af Biogen Inc. (tidligere Biogen Idec Inc.), et biotekselskab etableret i 1978 med hovedsæde i Cambridge, Massachusetts, USA, der udvikler og leverer behandlingsformer til behandling af alvorlige neurologiske, autoimmune og sjældne sygdomme. Blandt øvrige datterselskaber kan nævnes Biogen MA Inc. (USA), Biogen International Holding Limited (Bermuda) og Biogen Therapeutics Inc. (USA).

I december 2011 indgik Biogen Idec Therapeutics Inc i et joint venturesamarbejde med Samsung Biologics Co. Ltd., som er et selskab med base i lncheon, Sydkorea, om etablering af selskabet Samsung Bioepis Co. Ltd. (herefter Samsung Bioepis).

Samsung Bioepis forestår udvikling og fremstilling af en række biosimilære produkter, hvoraf fire, herunder Imraldi, på nuværende tidspunkt bliver markedsført i Europa. Imraldi er af Biogen oplyst at svare til SB5 som den tidligere anvendte produktbetegnelse.

SB er et datterselskab af Samsung Bioepis og var den oprindelige ejer af den europæiske markedsføringstilladelse til Imraldi, men markedsføringstilladelsen er blevet overført til et af SB's søsterselskaber, Samsung Bioepis NL B.V.

Biogen (Denmark) A/S (sagsøgte 2) er ansvarlig for markedsføring og salg af Imraldi i Danmark. Biogen (Denmark) Manufacturing ApS (sagsøgte 1) fremstiller Imraldi på sin fabrik i Hillerød.

<u>Biologiske og biosimilære lægemidler</u>

Humira, Imraldi og Idacio er såkaldte biologiske lægemidler.

Biologiske lægemidler fremstilles generelt af aktivt biologisk materiale, og de fremstilles af eller separeres fra levende celler eller væv. Dette står i kontrast til den kemiske syntese, som bruges i fremstillingen af "*small molecule*"-lægemidler.

En vigtig gruppe af aktivstoffer i biologiske lægemidler er monoklonale antistoffer. Antistoffer spiller en vigtig rolle i kroppens immunsystem. Monoklonale antistoffer binder sig til specifikke mål, som kaldes "antigener". Et antigen kan være en receptor bundet til overfladen af en celle, et frit protein eller polysakkarid i kropsvæske (f.eks. blod, synovialvæske) osv. Ved at binde sig til disse strukturer, kan det monoklonale antistof gribe ind i signalvejene – dvs. monoklonale antistoffer forhindrer visse processer i kroppens immunsystem i at blive gennemført. Forskellige monoklonale antistoffer kan derfor udgøre grundlaget for terapeutisk behandling af et antal forskellige indikationer, herunder autoimmune sygdomme (sygdomme, der er forårsaget af eller påvirket af patientens eget immunsystem).

Biosimilære lægemidler er lægemidler, der er udviklet til at udvise en (i) terapeutisk effekt, (ii) sikkerhedsprofil og (iii) stabilitetsprofil, der er "similær" i forhold til det originale biologiske lægemiddel. I Europa bliver biosimilære lægemidler godkendt af EMA.

Biosimilære lægemidler må ikke forveksles med generiske lægemidler. Sidstnævnte er baseret på aktivstoffer med små molekyler fremstillet ved kemisk syntese. Det gør det forholdsvist enkelt at fremstille alternative lægemidler med fuldstændigt identiske molekyler som aktivstoffer.

Biosimilære lægemidler er karakteriseret ved, at aktivstoffet består af store molekyler fremstillet ved hjælp af levende celler, hvilket gør dem sværere at udvikle og fremstille. Eftersom det ikke er muligt at fremstille et identisk lægemiddel, er biosimilære lægemidler underlagt langt mere restriktive regulatoriske krav, herunder krav om kliniske studier, end generiske lægemidler.

<u>Markedet for salg af lægemidler indeholdende adalimumab</u>

Af Medicinrådets vurderingsrapport af 16. august 2018 vedrørende ibrugtagning af biosimilært adalimumab fremgår det bl.a.:

Medicinrådets konklusion

Medicinrådet vurderer, at biosimilært adalimumab i dermatologien, gastroenterologien og reumatologien kan tages i brug til alle referencelægemidlets indikationer, til følgende patientgrupper:

a) Nye patienter, som ikke før har modtaget behandling med adalimumab.
b) Patienter, der tidligere har været i behandling med adalimumab, som får tilbagefald af sygdom og skal genoptage adalimumab behandling.
c) Patienter, som er i igangværende behandling med adalimumab.

Desuden vurderer Medicinrådet, at der ikke er faglige grunde til at begrænse antallet af efterfølgende skift mellem biosimilære adalimumabpræparater, men at antallet af skift bør minimeres af ressourcemæssige hensyn og patienthensyn. Endelig er det Medicinrådets vurdering, at god patientinformation er vigtig for implementeringen.

Af rapporten fremgår endvidere bl.a.:

> "…
> Biosimilært adalimumab med handelsnavn Amgevita fik EMA-godkendelse i marts 2017. Amgevita er godkendt i formuleringerne forfyldt pen og forfyldt sprøjte til de samme indikationer som Humira.
>
> Biosimilært adalimumab med handelsnavn Imraldi fik EMA-godkendelse i august 2017. Imraldi er godkendt i formuleringerne forfyldt pen og forfyldt sprøjte til de samme indikationer som Humira.
> …
> Fagudvalget vurderer, at der vil være omkostninger forbundet med at skifte patienter fra Humira til biosimilært adalimumab, da skiftet indebærer, at patienterne undervises i brug af nye forfyldte sprøjter og penne samt modtager information om biosimilære lægemidler generelt. Det forventes, at information og undervisning gives af sygeplejesker. …"

Medicinrådet udsendte den 14. november 2018 en pressemeddelelse, hvoraf fremgår bl.a.:

> Regningen for Humira alene har været på omtrent 387 millioner kroner de seneste 12 måneder. Men i august 2018 – nogle måneder inden at patentet på Humira udløb - anbefalede Medicinrådet, at nye og billigere præparater med adalimumab – såkaldt biosimilær medicin – kunne tages i brug på landets sygehuse, når Humiras patent udløb.
> …
>
> De nye præparater, som kan erstatte Humira, kommer ifølge Amgros til at koste regionerne omtrent 52 millioner kroner årligt - en årlig besparelse på 335 millioner kroner.

<u>Fresenius' rettigheder</u>

Prioritetsdagen for de udstedte brugsmodeller er angivet til at være den 23. maj 2014, hvor Ares Trading S.A. indgav patentansøgning EP 14169754 ("EP '754").

Den 15. maj 2015 blev EP '510-ansøgningen indgivet, og der blev den 16. juli 2018 udstedt patent på baggrund heraf (EP 3148510 T3).

Det fremgår af patentet bl.a.:

> "PATENTKRAV
> 1. Vandig farmaceutisk sammensætning, der omfatter:
> (a) adalimumab;
> (b) histidinbuffermiddel (eller histidinbuffersystem);
> (c) sukkerstabilisator valgt fra gruppen, der indbefatter trehalose, saccharose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol; og
> (d) 0,05 mg/ml til 2 mg/ml overfladeaktivt stof valgt blandt polysorbat 20 og polysorbat 80;
> hvor sammensætningen:
> • har et pH på mellem 5,0 og 6,7;
> • enten er fri for andre aminosyrer end histidin eller omfatter en eller flere andre aminosyrer end histidin ved en (samlet) koncentration på højst 0,1 mM; og
> • enten er fri for phosphatbuffermidler eller omfatter et phosphatbuffersystem ved en koncentration på højst 0,1 mM.
> …
> 4. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen omfatter sukkerstabilisatoren ved en koncentration på 50 til 400 mM.
> …
> 7. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sukkerstabilisatoren er sorbitol.
> 8. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor det overfladeaktive stof er polysorbat 20.
> 9. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen yderligere omfatter en citratbuffer."

Den 7. september 2018 indgav Fresenius de to ansøgninger, der førte til, at Patent- og Varemærkestyrelsen den 13. december 2019 udstedte de danske brugsmodeller nr. BR 2018 00070 Y4 og BR 2018 00071 Y4.

Det fremgår af brugsmodel BR 2018 00070 Y4 bl.a.:

> "Indledning
> Frembringelsen angår en hidtil ukendt proteinformulering. I særdeleshed angår frembringelsen en væskeformig farmaceutisk sammensætning af adalimumab, et sæt indeholdende sammensætningen og en pakning indeholdende sammensætningen.
>
> Baggrund
> Behandling af tumornekrosefaktor-alfa(TNF-α)-forbundne autoimmunsygdom, såsom arthritis rheumatoides, psoriasis og andre autoimmunsygdomme er opnået ved anvendelse af FDA-godkendte lægemidler såsom Adalimumab (HUMIRA®, Abbott Corporation). Adalimumab er et humant monoklonalt antistof, som hæmmer human TNF-α -aktivitet …

Adalimumab indgives i almindelighed til en patient via subkutan injektion, og det gives således på flydende form, typisk i pakninger såsom hætteflasker, forfyldte sprøjter eller forfyldte "penneanordninger". … Handelsformuleringer (HUMIRA®) af Adalimumab indeholder følgende bestanddele:

Bestanddel	**Mængde per beholder (mg); (fyldvolumen=0,8 ml)**	**Mængde (mg/ml)**
Adalimumab	40	50
Citronsyre-monohydrat	1,04	1,3
Dibasisk natrium-phosphat-dihydrat	1,22	1,53
Mannitol	9,6	12
Monobasisk Natri-umphosphat-dihydrat	0,69	0,86
Polysorbat 80	0,8	1
Natrium-chlorid	4,93	6,16
Natriumcit-rat	0,24	0,3
WFI og natri-umhydroxid	q.b. til at indstille pH-vær-dien til 5,2	q.b til at indstille pH-vær-dien til 5,2

…

Selv om den førnævnte handelsformulering af Adalimumab er stabil (i det mindste i nogen grad), kan det relevante antistof være ustabilt over længere tidsrum eller under belastede forhold, hvilket udelukker længere tids lagring af formuleringerne. En sådan nedbrydning af formuleringen kan skyldes flere faktorer, herunder:

Fysiske virkninger, såsom:

- Utilstrækkelig aggregeringshæmning af de relevante proteinmolekyler (en funktion, der skulle varetages af Tween-80);
- Utilstrækkelig udfældningshæmning;
- Utilstrækkelig adsorptionshæmning af de relevante proteinmolekyler i grænsefladen mellem vand og luft eller ved kontaktoverfladen af et hvilket som helst emballagemateriale (en funktion, der skulle varetages af Tween-80);
- Utilstrækkelig regulering af osmotisk tryk (en funktion, der skulle varetages af mannitol);

Kemiske virkninger, såsom:

- Utilstrækkelig oxidationsregulering (en funktion, der skulle varetages af mannitol, og som potentielt undermineres af Tween-80, som kan fremme oxidering af dobbeltbindinger);

- Utilstrækkelig fotooxidationshæmning;
- Utilstrækkelig hæmning af hydrolyse af esterbindinger, der leder til dannelse af syre-, aldehyd- og peroxidprodukter og derved påvirker antistoffets stabilitet;
- Utilstrækkelig stabilisering og opretholdelse af pH-værdien;
- Utilstrækkelig hæmning af proteinfragmentering;
- Utilstrækkelig hæmning af proteinudfoldning.

En hvilken som helst, nogle eller alle ovennævnte faktorer kan lede til enten et uholdbart lægemiddelprodukt (som kan være usikkert til anvendelse i medicinske behandlinger) eller et lægemiddelprodukt, hvis levedygtighed er variabel og uforudsigelig, navnlig i lyset af forskellige belastninger (bevægelse, varme, lys), som forskellige partier af lægemiddelproduktet kan være udsat for under fremstilling, transport og oplagring.

Med hensyn til den fysiske og kemiske stabilisering af Adalimumab, ser den komplekse række bestanddele i de førnævnte handelsformuleringer ud til at klare sig dårligere end forventet, navnlig i lyset af det store antal bestanddele. Selv om denne særlige kombination af excipienser utvivlsomt repræsenterer en "delikat balance" (i betragtning af samspillet mellem forskellige tekniske faktorer) og var resultatet af omfattende forskning og udviklingsarbejde, er det i lyset af den tilsyneladende risiko for dårligere ydelse tvivlsomt, hvorvidt et sådant højt antal af forskellige excipienser er berettiget, specielt i betragtning af at dette uundgåeligt forøger fremstilling- og omkostningsbyrderne, toxicitetsrisici og risikoen for skadelige samvirkninger mellem bestanddele, som kan kompromittere formuleringen. Selv hvis den overordnede funktion af handelsformuleringerne ikke skulle kunne overgås, ville en alternativ formulering med sammenlignelig funktion men indeholdende færre bestanddele repræsentere en højst ønskelig erstatning for formuleringerne i handlen af i hvert fald de førnævnte grunde.

For at garantere reproducerbar klinisk funktion af et proteinbaseret farmaceutisk produkt må det forblive i en stabil og konsistent form over tid. Det er velkendt, at molekylære forandringer kan indtræde under alle stadier af fremstillingsprocessen, herunder under produktionen af den endelige formulering og under lagring. Molekylære forandringer kan ændre en kvalitetsegenskab ved et biofarmaceutisk produkt, hvilket resulterer i en uønsket ændring af produktets identitet, styrke eller renhed. Nogle sådanne problemer er skitseret ovenfor.

Det primære mål med formuleringsudviklingen er at tilvejebringe en farmaceutisk sammensætning, som vil understøtte stabiliteten af et biofarmaceutisk protein under alle stadier af des produktion, oplagring, transport og anvendelse. Formuleringsudvikling af et innovativt biofarmaceutisk protein eller et biosimilært monklonalt antistof (mAb) er afgørende for dets sikkerhed, kliniske effektivitet og kommercielle succes.

Der er derfor et behov for at tilvejebringe alternative eller forbedrede flydende formuleringer af adalimumab. Fortrinsvist skal nye formuleringer løse mindst et af de førnævnte problemer og/eller mindst et problem, der er iboende i den kendte teknik, og kunne passende løse to eller flere af disse problemer. Det var ønskeligt, om problemet eller problemerne i den kendte teknik kunne løses, mens formuleringens kompleksitet mindskes.

<u>Sammendrag af frembringelsen</u>

Ifølge et første aspekt af frembringelsen tilvejebringes en væskeformig farmaceutisk sammensætning ifølge kravene. Sammensætningen omfatter eventuelt (eller udelukker) en eller flere yderligere bestanddele defineret heri i forbindelse med en væskeformig farmaceutisk sammensætning (f.eks. indbefattende toniseringsmiddel, uden arginin, osv.), eventuelt i en hvilken som helst mængde, koncentration

eller form fastsat heri; og hvor sammensætningen eventuelt udviser en eller flere parametre eller egenskaber, der nævnes heri i forbindelse med en væskeformig farmaceutisk sammensætning (f.eks. pH-værdi, osmolalitet, ophobning/aggregering, fragmentering, proteinudfoldning, turbiditet osv.).

…

Detaljeret beskrivelse af frembringelsen

Definitioner

…

Henvisninger heri til "adalimumab" indbefatter den oprindelige lægemiddelsubstans (som tilgængeligt i handelen) adalimumab som defineret i WO97/29131 (BASF) (navnlig D2E7 deri) og andetsteds inden for det tekniske område, og også biosimilære midler deraf. …

…

Betegnelsen "buffer" eller "bufferopløsning" henviser til en i almindelighed vandig opløsning omfattende en blanding af en syre (almindeligvis en svag syre, f.eks. eddikesyre, citronsyre, imidazoliumform af histidin) og dens korresponderende base (f.eks. et acetat- eller citratsalt, for eksempel natriumacetat, natrium-citrat eller histidin) eller alternativt en blanding af en base (normalt en svag base, f.eks. histidin) og dens korresponderende syre (f.eks. protoneret histidinsalt). pH-værdien af en bufferopløsning vil kun ændre sig ganske lidt ved tilsætning af en lille mængde stærk syre eller base på grund af pufringsvirkningen, der bibringes af buffermidlet.

Et "buffersystem" omfatter heri et eller flere buffermidler og/eller en korresponderende syre/base dertil, og omfatter passende kun ét buffermiddel og en korresponderende syre/base dertil. Med mindre andet fremgår, henviser koncentrationer, der heri fastsættes i forbindelse med et buffersystem (altså en buffer-koncentration) til den samlede koncentration af alle de relevante bufferelementer (dvs. elementerne i forbindelse med hinanden, f.eks. citrat/citronsyre). Som sådan angå en given koncentration af et histidinbuffersystem i almindelighed den samlede koncentration af histidin og imidazoliumformen af histidin. Med hensyn til histidin kan sådanne koncentrationer dog sædvanligvis beregnes uden videre med udgangspunkt i den tilførte mængde histidin eller et salt deraf. Den samlede pH-værdi for sammensætningen omfattende det relevante buffersystem er i almindelighed en afspejling af ligevægtskoncentrationen for hver af den relevante buffer-elementer (dvs. balancen mellem buffermidler og korresponderende syrer og baser dertil).

…

En "stabilisator" refererer til en bestanddel, som letter opretholdelse af den strukturelle integritet af det biofarmaceutiske lægemiddel, særligt under frysning og/eller frysetørring og/eller lagring (navnlig under udsættelse for belastninger). Denne stabiliserende virkning kan opstå af allehånde grunde, dog kan sådanne stabilisatorer typisk optræde som osmolytter, som beskytter mod proteindenaturering. Typisk indbefatter stabilisatorer aminosyrer (dvs. frie aminosyrer, der ikke indgår i et peptid eller protein – f.eks. glycin, arginin, histidin, asparaginsyre, lysin) og sukkerstabilisatorer såsom en sukkerpolyalkohol (f.eks. mannitol, sorbitol) og/eller et disaccharid (f.eks. trehalose, sukrose, maltose, laktose), selv om de væskeformige farmaceutiske sammensætninger ifølge frembringelsen indbefatter en stabilisator, hvoraf mindst én er en sukkerstabilisator (dvs. enten en sukkeralkohol eller et disaccharid). Fortrinsvis er den mindst ene sukker stabilisator et ikke-reducerende sukkerstof (de være sig en sukkeralkohol eller et disaccharid).

…

En "tonicitetsmodifikator" eller et "toniseringsmiddel" refererer til et middel, hvis medtagelse i en sammensætning på passende vis bidrager til (eller forøger)

sammensætningens overordnede osmolalitet og osmolaritet. Fortrinsvis indbefatter et toniseringsmiddel som anvendt heri et middel, som gør en opløsning lig fysiologiske væsker med hensyn til osmotiske karakteristika.

…

Betegnelsen "stabil" refererer heri generelt til den fysiske stabilitet og/eller kemiske stabilitet og/eller biologiske stabilitet af en bestanddel, typisk et aktivstof eller en sammensætning deraf under konservering/lagring.

…

Væskeformig farmaceutisk sammensætning

Den væskeformige farmaceutiske sammensætning omfatter fortrinsvis et humant monoklonalt antistof, fortrinsvis et, der hæmmer human TNF-α-aktivitet, fortrinsvis så aktivering af TNF-receptorer hindres. Mest foretrukket omfatter de væskeformige farmaceutiske sammensætninger adalumimab, som selv fortrinsvis indbefatter eventuelle biosimilære midler dertil. Sammensætninger omfatter fortrinsvis et histidinbuffermiddel (eller histidinbuffersystem). Sammensætningen omfatter fortrinsvis en sukkerstabilisator. Sammensætningen har fortrinsvis en pH-værdi over eller lig med 6,30. Sammensætningen er fortrinsvis (i det væsentlige eller fuldstændigt) fri for arginin eller omfatter arginin enten i en koncentration på højst 0,1 mM, i et molforhold mellem arginin og histidinbuffermiddel (eller histidinbuffersystem) på højst 1:150, eller i et vægtforhold mellem arginin og adalimumab på højst 1:3000 (dvs. mindre end eller svarende til en del histidin efter vægt for hver 3000 dele histidinbuffermiddel efter vægt.). Alternativt eller derudover kan sammensætningen passende indbefatte en hvilken som helst eller flere yderligere bestanddele defineret heri i forbindelse med en væskeformig farmaceutisk sammensætning (dvs. inklusiv toniseringsmiddel, eksklusiv arginin, osv.), eventuelt i en hvilken som helst mængde, koncentration eller form fastsat heri; og hvor sammensætningen eventuelt udviser en hvilken som helst eller flere parametre eller egenskaber givet heri i forbindelse med en væskeformig farmaceutisk sammensætning (f.eks. pH-værdi, osmolalitet).

Frembringelsen tilvejebringer med fordel alternative og forbedrede væskeformige farmaceutiske sammensætninger, som i almindelighed udviser bedre stabilitet og levedygtighed end den kendte tekniks. Som vist heri (se Eksempler) har de væskeformige farmaceutiske formuleringer ifølge frembringelsen sammenlignelige eller forbedrede egenskaber i sammenligning med konventionelle formuleringer af adalimumab, for eksempel den i handlen tilgængelige formulering Humira®, når de underkastes diverse belastende betingelser (termiske, mekaniske og lys). Deres ydelse er også generelt sammenlignelig med eller bedre end mange andre sammenligningsformuleringer, som underkastedes samme stresstest. Da disse belastende betingelser er særdeles repræsentative for den type belastninger, som sådanne formuleringer udsættes for under fremstilling, transport og lagring, giver de en glimrende indikation af frembringelsens fordele. At en sådan god stabilitet kan opnås med mindre komplekse formuleringer med færre excipienser, betragtedes som overraskende i betragtning af den almene lære i den kendte teknik.

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Buffer, buffermiddel og pH-værdi

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Mest foretrukket er buffersystemet et histidinbuffersystem, fortrinsvis omfattende histidin i ligevægt med dets imidazoliumform.

Den væskeformige farmaceutiske sammensætning omfatter fortrinsvis højst ét buffermiddel. Fortrinsvis omfatter den væskeformige farmaceutiske sammensætning højst ét buffersystem.

Den væskeformige farmaceutiske sammensætning har en pH-værdi større end eller lig med 5,0. Fortrinsvis har den væskeformige farmaceutiske sammensætning

en pH-værdi større end eller lig med 6,3. Fortrinsvis har den væskeformige farmaceutiske sammensætning en pH-værdi mindre end eller lig med 6,7.
I en særlig udførelsesform, specielt hvor buffermidlet er et histidinbuffermiddel, har den væskeformige farmaceutisk sammensætning en pH-værdi mellem 6,0 og 6,6. I en særlig udførelsesform har den væskeformige farmaceutisk sammensætning en pH-værdi mellem 6,3 og 6,5. I en særlig udførelsesform har den væskeformige farmaceutiske sammensætning en pH-værdi omkring 6,4.
…
Som illustreret i eksempelafsnittet, klarer væskeformige farmaceutiske sammensætninger ifølge frembringelsen indbefattende et histidin-buffermiddel/buffersystem sig særligt godt i belastningsprøver, navnlig med hensyn til fragmentering og proteinudfoldning, som kan være vigtige indikatorer på stabilitet og lægemiddelprodukthold barhed. Desuden klarer væskeformige farmaceutiske sammensætninger, hvis histidinbuffersystem opretholder en stabil pH-værdi på 6,4, sig særligt godt.

Sukkerstabilisator
Den væskeformige farmaceutiske sammensætning omfatter fortrinsvis en stabilisator, mest foretrukket en sukkerstabilisator. En sådan bestanddel letter fortrinsvis opretholdelse af den strukturelle integritet af det biofarmaceutiske lægemiddel, navnlig under frysning og/eller frysetørring og/eller lagring (i særdeles under stresseksponering).
Den væskeformige farmaceutiske sammensætning kan omfatte en eller flere sukkerstabilisatorer, endskønt kun en enkelt sukkerstabilisator er til stede i foretrukne udførelsesformer.
Fortrinsvis er sukkerstabilisatoren en sukkerpolyalkohol (herunder sukkeralkoholer) og/eller et disaccharid.
Sukkerstabilisatoren er fortrinsvis udvalgt fra gruppen indbefattende trehalose, mannitol, sukrose, sorbitol, maltose, laktose, xylitol, arabitol, erythritol, laktitol, maltitol, inositol.
I en særlig udførelsesform er sukkerstabilisatoren udvalgt fra gruppen indbefattende trehalose, mannitol, sukrose, maltose, laktose, xylitol, arabitol, erythritol, laktitol, maltitol, inositol.
I en særlig udførelsesform er sukkerstabilisatoren et ikke-reducerende sukkerstof, eventuelt et ikke-reducerende sukkerstof anført hvor som helst heri.
I en særlig udførelsesform er sukkerstabilisatoren trehalose. …
Den væskeformige farmaceutiske formulering omfatter fortrinsvist højst én sukkerstabilisator, fortrinsvist højst én sukkerpolyol og/eller disaccharid. Fortrinsvis omfatter den væskeformige farmaceutiske sammensætning trehalose som eneste sukkerstabilisator.
…
Dette princip kan benyttes for enhver sukkerstabilisatorbestanddel. Koncentrationer, når de gives som en molær koncentration, vil selvfølgelig være de samme uafhængig af sukkerstabilisatorens hydratiseringstilstand.
Den væskeformige farmaceutiske sammensætning omfatter fortrinsvis sukkerstabilisatoren (mest foretrukket trehalose) i en koncentration på fra 50 til cirka 400 mM, mere foretrukket fra cirka 100 til cirka 300 mM, mere foretrukket fra cirka 150 til cirka 250 mM. I en udførelsesform er sukkerstabilisatoren til stede i en koncentration på mellem 190 og 210 mM, mest foretrukket cirka 200 mM. I en udførelsesform er trehalose til stede i en koncentration på 200 mM.
Den væskeformige farmaceutiske sammensætning omfatter fortrinsvis sukkerstabilisatoren (mest foretrukket trehalose) i en koncentration på fra cirka 15 mg/ml til cirka 140 mg/ml ……

Som vist i eksempelafsnittet klarer væskeformige farmaceutiske sammensætninger ifølge frembringelsen indbefattende en sukkerstabilisator som defineret heri sig særligt godt i belastningsprøvninger, navnlig med hensyn til ophobning, fragmentering og proteinudfoldning, som kan være vigtige indikationer på stabilitet og lægemiddelproduktholdbarhed. Desuden klarer væskeformige farmaceutiske sammensætninger omfattende trehalose som sukkerstabilisator sig særligt godt.
…
Fraværende eller sparsomt tilstedeværende bestanddele
…
Sparsomme/ingen overfladeaktive stoffer.
Den væskeformige farmaceutiske sammensætning er enten (i det væsentlige eller fuldstændigt) fri for overfladeaktive stoffer (det være sig kationiske, anioniske, amfotere eller non-ioniske) med den mulige undtagelse af polysorbat 80 (polyoxyethylen(20)sorbitanmonoeleat) eller omfatter en eller flere af nævnte overfladeaktive stoffer (eventuelt uden polysorbat 80) i en (samlet) koncentration på højst 1 mM, mere foretrukket højst 0,1 mM, mere foretrukket højst 0,01 mM, mere foretrukket højst 0,001 mM, mest foretrukket højst 0,00001 mM. …
…
Den væskeformige farmaceutiske sammensætning er enten (i det væsentlige eller fuldstændigt) fri for overflade aktive stoffer i form af polysorbat 20 (også kendt som Tween 20 -polyoxyethylen(20)sorbitanmonolaurat) eller omfatter et eller flere af nævnte overfladeaktive stoffer i en mængde, koncentration, molforhold, eller vægtforhold på højst det, der er fastsat i et hvilken som helst af de foregående afsnit i dette underkapitel med hensyn til overfladeaktive stoffer mere generelt.
…
Eventuelle yderligere bestanddele
Toniseringsmiddel.
Den væskeformige farmaceutiske sammensætning omfatter fortrinsvis en "tonicitetsmodifikator" (eller "toniseringsmiddel") eller et eller flere toniseringsmidler, fortrinsvis som defineret heri.
Et hvilket som helst egnet toniseringsmiddel kan anvendes. …
…
I en særlig udførelsesform er eller omfatter toniseringsmidlet natriumchlorid. I en særlig udførelsesform er toniseringsmidlet natriumchlorid. Natriumchlorid er en særlig fordelagtig stabilisator til brug sammen med et histidinbuffermiddel/buffersystem i væskeformige adalimumabformuleringer.
Fortrinsvis omfatter den væskeformige farmaceutiske sammensætning toniseringsmidlerne (mest foretrukket natriumchlorid) i en koncentration på …
…
Overfladeaktivt middel.
Den væskeformige farmaceutiske sammensætning kan omfatte et overfladeaktivt middel eller en eller flere overfladeaktive midler, fortrinsvis som defineret heri.
Ethvert egnet overfladeaktivt middel kan anvendes. Det overfladeaktive middel er imidlertid fortrinsvis et non-ionisk overfladeaktivt middel, mest foretrukket et overfladeaktivt middel i form af polysorbat (polyoxyethylenglykolsorbitanalkylestre) eller span (sorbitanalkylestre).
…
De overfladeaktive stoffer er fortrinsvis udvalgt blandt Polysorbat 20 (polyoxyethylen(20)sorbitanmonolaurat), Polysorbat 40 (polyoxyethylen(20)sorbitanmonopalmitat), Polysorbat 60 (polyoxyethylen(20)sorbitanmonostearat), Polysorbat 80 (polyoxyethylen(20)sorbitanmonooleat) ….
I en særlig udførelsesform er de overfladeaktive stoffer udvalgt blandt Polysorbat 20, Polysorbat 40, Polysorbat 60 og/eller Polysorbat 80. …

I en særlig udførelsesform er det overfladeaktive middel polysorbat 80 eller polysorbat 20. I en særlig udførelsesform er det overfladeaktive middel polysorbat 80.
…
Den væskeformige farmaceutiske sammensætning omfatter fortrinsvis de overfladeaktive midler (mest foretrukket polysorbat 80) i et molforhold mellem overfladeaktive stoffer og adalimumab …
I foretrukne udførelsesformer er den væskeformige farmaceutiske sammensætning imidlertid (i det væsentlige eller fuldstændigt) fri for polysorbat 80 og fortrinsvis (i det væsentlig eller fuldstændigt) fri for nogle overfladeaktive stoffer overhovedet.

Andre parametre vedrørende frembringelsen
Osmolalitet.
…
Proteinudfoldningstemperatur.
…
Parametre under udsættelse for varmestress.
Mængden (eller koncentrationen) af aggregater (fortrinsvis afledt fra adalimumab og fortrinsvis som bestemt ved SE-HPLC-protokollerne defineret heri) til stede i den væskeformige farmaceutiske sammensætning stiger fortrinsvis med højst en faktor 4 (dvs. 4 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen varmebelastes til 40 °C (dvs. sammensætningen holdes ved en temperatur på 40 °C) over en periode på 28 dage, fortrinsvis med en faktor på højst 3, fortrinsvis højst 2,5, fortrinsvis højst 2,2.
Mængden (eller koncentrationen) af fragmenter (fortrinsvis afledt fra adalimumab og fortrinsvis målt ved bioanalysatorprotokollerne defineret heri) til stede i den væskeformige farmaceutiske sammensætning stiger fortrinsvis med højst en faktor 4 (dvs. 4 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen varmebelastes til 40 °C (dvs. sammensætningen holdes ved en temperatur på 40 °C) over en periode på 28 dage, fortrinsvis med en faktor på højst 3, fortrinsvis højst 2,5, fortrinsvis højst 2,2.
Turbiditeten (fortrinsvis målt ved nefelometri i overensstemmelse med protokollerne gengivet heri) af den væskeformige farmaceutiske sammensætning stiger fortrinsvis med højst en faktor 2 (dvs. 2 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen varmebelastes ved 40 ° (dvs. sammensætningen holdes ved en temperatur på 40 °C) over en periode på 28 dage, fortrinsvis med en faktor på højst 1,5, fortrinsvis med en faktor på højst 1,3, og fortrinsvis stiger turbiditeten slet ikke.
pH-værdien for den væskeformige farmaceutiske sammensætning ændrer sig (enten ved stigning eller fald, dog normalt ved et fald i pH-værdien) fortrinsvis med højst 0,5 pH-enheder, når sammensætningen varmebelastes ved 40 °C (dvs. sammensætningen holdes ved en temperatur på 40 °C) over en periode på 28 dage, fortrinsvis med højst 0,2 pH-enheder, fortrinsvis med højst 0,1 pH-enheder, mest foretrukket ændrer pH-værdien sig slet ikke (med en decimals nøjagtighed).

Parametre under udsættelse for mekanisk belastning.
Mængden (eller koncentrationen) af aggregater (fortrinsvis afledt fra adalimumab og fortrinsvis som bestemt ved SE-HPLC-protokollerne defineret heri) til stede i den væskeformige farmaceutiske sammensætning stiger fortrinsvis med højst en faktor 2 (dvs. 2 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen belastes mekanisk (dvs. rystes ifølge protokollerne givet heri) over en periode på 48 time, fortrinsvis med højst en faktor 1,5, fortrinsvis højst en faktor 1,2, fortrinsvis højst en faktor 1,1.

Mængden (eller koncentrationen) af fragmenter (fortrinsvis afledt fra adalimumab og fortrinsvis målt ved bioanalysatorprotokollerne defineret heri) til stede i den væskeformige farmaceutiske sammensætning stiger fortrinsvis med højst en faktor 2 (dvs. 2 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen belastes mekanisk (dvs. rystes ifølge protokollerne givet heri) over en periode på 48 time, fortrinsvis med højst en faktor 1,5, fortrinsvis højst en faktor 1,2, fortrinsvis højst en faktor 1,1.
Turbiditeten (fortrinsvis målt ved nefelometri i overensstemmelse med protokollerne gengivet heri) af den væskeformige farmaceutiske sammensætning stiger fortrinsvis med højst en faktor 2 (dvs. 2 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen belastes mekanisk (dvs. rystes ifølge protokollerne givet heri) over en periode på 48 timer, fortrinsvis med højst en faktor 1,5, fortrinsvis højst en faktor 1,2, fortrinsvis højst en faktor 1,1, og fortrinsvis stiger turbiditeten slet ikke.
pH-værdien for den væskeformige farmaceutiske sammensætning ændrer sig (enten ved stigning eller fald, dog normalt ved et fald i pH-værdien) fortrinsvis med højst 0,5 pH-enheder, når sammensætningen belastes mekanisk (dvs. rystes ifølge protokollerne givet heri) over en periode på 48 timer, fortrinsvis med højst 0,2 pH-enheder, fortrinsvis med højst 0,1 pH-enheder, mest foretrukket ændrer pH-værdien sig slet ikke (med en decimals nøjagtighed).
Parametre under udsættelse for lysbelastning.
Mængden (eller koncentrationen) af aggregater (fortrinsvis afledt fra adalimumab og fortrinsvis som bestemt ved SE-HPLC-protokollerne defineret heri) til stede i den væskeformige farmaceutiske sammensætning stiger fortrinsvis med højst en faktor 50 (dvs. 50 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen lysbelastes (dvs. sammensætningen udsættes for lys i overensstemmelse med protokollerne beskrevet heri, dvs. 7 timer ved 765 W/m^2), fortrinsvis med højst en faktor 45, fortrinsvis med højst en faktor 35, fortrinsvis med højst en faktor 30.
Mængden (eller koncentrationen) af fragmenter (fortrinsvis afledt fra adalimumab og fortrinsvis målt ved bioanalysatorprotokollerne defineret heri) til stede i den væskeformige farmaceutiske sammensætning stiger fortrinsvis med højst en faktor 4 (dvs. 4 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen lysbelastes (dvs. sammensætningen udsættes for lys i overensstemmelse med protokollerne beskrevet heri, dvs. 7 timer ved 765 W/m^2), fortrinsvis med højst en faktor 3, fortrinsvist med højst en faktor 2,5, fortrinsvist med højst en faktor 2.
Turbiditeten (fortrinsvis målt ved nefelometri i overensstemmelse med protokollerne gengivet heri) af den væskeformige farmaceutiske sammensætning stiger fortrinsvis med højst en faktor 2 (dvs. 2 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen lysbelastes (dvs. sammensætningen udsættes for lys i overensstemmelse med protokollerne beskrevet heri, dvs. 7 timer ved 765 W/m^2), fortrinsvis med højst en faktor 1,5, fortrinsvis med højst en faktor 1,2 og fortrinsvis stiger turbiditeten slet ikke.
pH-værdien for den væskeformige farmaceutiske sammensætning ændrer sig (enten ved stigning eller fald, dog normalt ved et fald i pH-værdien) fortrinsvis med højst 0,5 pH-enheder, når sammensætningen lysbelastes (dvs. sammensætningen udsættes for lys i overensstemmelse med protokollerne beskrevet heri, dvs. 7 timer ved 765 W/m^2), fortrinsvis med højst 0,2 pH-enheder, fortrinsvis med højst 0,1 pH-enheder, mest foretrukket ændrer pH-værdien sig slet ikke (med en decimals nøjagtighed).

Parametre under udsættelse for fryse/tø-cykler.

Mængden (eller koncentrationen) af aggregater (fortrinsvis afledt fra adalimumab og fortrinsvis som bestemt ved SE-HPLC-protokollerne defineret heri) til stede i den væskeformige farmaceutiske sammensætning stiger fortrinsvis med højst en faktor 1,5 (dvs. 1,5 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen udsættes for fem fryse/tø-cykler (dvs. sammensætningen fryses og tøs fem gange i overensstemmelse med protokoller fremlagt heri, dvs. -80 °C til 20 °C fem gange), fortrinsvis med højst en faktor 1,2, fortrinsvis med højst en faktor 1,1, fortrinsvis er der (i det væsentlige) ingen stigning overhovedet i mængden (eller koncentrationen) af aggregater.
Mængden (eller koncentrationen) af ikke-synlige partikler eller udfældninger med en partikelstørrelse under eller lig med 25 mikrometer til stede i den væskeformige sammensætning stiger fortrinsvis med højst en faktor 4 (dvs. 4 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen underkastes fem fryse/tø-cykler (dvs. sammensætningen fryses og tøs fem gange i overensstemmelse med protokoller beskrevet heri, dvs. -80 °C til 20 °C fem gange), fortrinsvis med højst en faktor 3, fortrinsvist med højst en faktor 2,5, fortrinsvist med højst en faktor 2,2.
Mængden (eller koncentrationen) af ikke-synlige partikler eller udfældninger med en partikelstørrelse under eller lig med 10 mikrometer til stede i den væskeformige sammensætning stiger fortrinsvis med højst en faktor 4 (dvs. 4 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen underkastes fem fryse/tø-cykler (dvs. sammensætningen fryses og tøs fem gange i overensstemmelse med protokoller beskrevet heri, dvs. -80 °C til 20 °C fem gange), fortrinsvis med højst en faktor 3, fortrinsvist med højst en faktor 2,5, fortrinsvist med højst en faktor 2,2.
Mængden (eller koncentrationen) af ikke-synlige partikler eller udfældninger med en partikelstørrelse under eller lig med 25 mikrometer til stede i den væskeformige sammensætning stiger fortrinsvis med højst en faktor 4 (dvs. 4 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen underkastes 5 fryse/tø-cykler, fortrinsvis med højst en faktor 3, fortrinsvist med højst en faktor 2,5, fortrinsvist med højst en faktor 2,2.
Mængden (eller koncentrationen) af ikke-synlige partikler eller udfældninger med en partikelstørrelse under eller lig med 10 mikrometer til stede i den væskeformige sammensætning stiger fortrinsvis med højst en faktor 4 (dvs. 4 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen underkastes 5 fryse/tø-cykler, fortrinsvis med højst en faktor 3, fortrinsvist med højst en faktor 2,5, fortrinsvist med højst en faktor 2,2.

Fremgangsmåder til stabilisering af antistof.
I lyset af de førnævnte punkter i dette underafsnit og data gengivet i eksemplerne tilvejebringes også en fremgangsmåde til stabilisering af væskeformige adalimumabsammensætninger (kemisk og/eller fysisk, eventuelt med hensyn til en eller flere af førnævnte parametre/egenskaber), omfattende at blande adalumimab med en hvilket som helst relevant bestanddel, der er fornøden til dannelse af en væskeformig sammensætning som defineret heri. Forskellige udførelsesformer vil fortrinsvis kræve blanding af forskellige kombinationer af bestanddele, potentielt i forskellige mængder, og fagmanden kan uden videre udlede sådanne kombinationer og mængder ved at henholde sig til den foregående beskrivelse vedrørende den væskeformige farmaceutiske sammensætning. Sådanne forskellige kombinationer af bestanddele kan stabilisere væskeformige adalimumabsammensætninger i forskellige henseender. For eksempel kan blanding af adalimumab med de førnævnte bestanddele til dannelse af en væskeformig farmaceutisk sammensætning som defineret heri stabilisere adalimumab ved:

i) at øge adalimumabs proteinudfoldningstemperatur;
ii) at hæmme dannelsen af aggregater;
iii) at hæmme dannelsen af fragmenter
iv) at hæmme dannelsen af ikke-synlige partikler (enten ≤25 mikrometer eller ≤10 mikrometer);
v) at hæmme turbidificering;
vi) at hæmme pH-ændringer;
vii) at hæmme fotooxidation, og/eller
at mindske ustabilitet efter fryse/tø-cykler.
…
De væskeformige farmaceutiske sammensætninger ifølge frembringelsen har fortrinsvis en lagerholdbarhed på mindst 6 måneder, fortrinsvis mindst 12 måneder, fortrinsvis mindst 18 måneder, mere foretrukket mindst 24 måneder. De væskeformige farmaceutiske sammensætninger ifølge frembringelsen har fortrinsvis en lagerholdbarhed på mindst 6 måneder, fortrinsvis mindst 12 måneder, fortrinsvis mindst 18 måneder, mere foretrukket mindst 24 måneder, ved en temperatur på 2-8 °C.

At sætte fagmanden i stand til at optimere væsentlige stabilitetsegenskaber.
Den nye kombination af bestanddele, der fremlægges til anvendelse i væskeformige farmaceutiske sammensætninger af frembringelsen sætter fagmanden i stand til at danne (og efter skønsom vurdering finjustere) sammensætninger, som udviser sammenlignelige eller forbedrede egenskaber i forhold til den kendte tekniks sammensætninger. I særdeleshed, stiller nærværende beskrivelse nu alle nødvendige værktøjer til optimering af formuleringsstabiliteten til rådighed vor fagmanden, navnlig med henblik på optimering af en eller flere blandt: aggregationshæmning, fragmentering, proteinudfoldning, udfældning, pH-glidning og oxidation (navnlig fotooxidation). Desforuden vejledes fagmanden til opnåelse af sådanne optimeringer (gennem ved skønsom vurdering at variere sammensætningerne) og til minimering af skadelige bivirkninger undervejs. Nærværende beskrivelse sætter fagmanden i stand til at udøve frembringelsen over hele dens beskyttelsesomfang til dannelse af allehånde specifikke sammensætninger, som udviser sammenlignelige eller forbedrede egenskaber i forhold til den kendte tekniks sammensætninger, og dette kan opnås under anvendelse af færre bestanddele.

Særlige udførelsesformer
I en udførelsesform omfatter den væskeformige farmaceutiske sammensætning:
- adalimumab;
- et histidinbuffermiddel (f.eks. histidin) (eller histidinbuffersystem);
- en sukkerstabilisator (f.eks. trehalose); og
- et overfladeaktivt stof (f.eks. polysorbat 80).

I en udførelsesform omfatter den væskeformige farmaceutiske sammensætning:
- adalimumab;
- et histidinbuffermiddel (f.eks. histidin) (eller histidinbuffersystem);
- en sukkerstabilisator (f.eks. trehalose);
- et toniseringsmiddel (f.eks. natriumchlorid); og

eventuelt et overfladeaktivt stof (f.eks. polysorbat 80).
…
Lægemiddeldispenseringsanordning
…
Sæt af dele
…
Analytiske teknikker og protokoller

…

9. Partikeltælling – Ikke-synlige partikler

…

Eksempel 1 – Formuleringer til første formuleringsscreening

…

Tabel 1: Liste af DoE1 formuleringer til senere screeningsforsøg 1

Form #	Salt (NaCl) konc (mM)	Buffertype (10 mM)	pH	Stabilisator
18	25	Histidin	6,0	Trehalose dihydrat (200 mM)
19	50	Histidin	6,0	Lysin Hydrochlorid (100 mM)
20	100	Histidin	6,0	Mannitol (200 mM)
21	50	Histidin	6,2	Lysin hydrochlorid (100 mM)
22	50	Histidin	6,2	Arginin monohydroclorid + asparaginsyre (80 mM + 20 mM)
23	75	Histidin	6,2	Trehalose dihydrat (200 mM)
24	25	Histidin	6,4	Mannitol (200 mM)
25	100	Histidin	6,4	Trehalose dihydrat (200 mM)

…

Eksempel 2 – Formuleringer til anden formuleringsscreening

…

Tabel 3: Liste af DoE2-formuleringer til næste Screeningsforsøg 2 (formuleringer stammende fra de, der er vist i tabel 4, med det ekstra overfladeaktive stof som angivet)

Formuleringer	Polysorbat 80 koncentration (mg/mL)		
	0	**0,5**	**1**
Form 7 (stammende fra Form C, **Tabel 4**)	X	-	-
Form 8 (stammende fra Form C, **Tabel 4**)	-	X	-
Form 9 (stammende fra Form C, **Tabel 4**)	-	-	x

…

SCREENING

…

Screeningseksperiment 1 – analyse og screening af formuleringer fra Eksempel 1 i forhold til sammenligningsformuleringerne i Eksempel 3

…

Tabel 7: Liste over DoE1-formuleringer (Trin 1), der er screenet under varmestress-betingelser (stabilitet ved 40 °C) og højhastighedsbestemmelse af proteinudfoldningstemperatur (DSF).

Form #	Salt (NaCl) konc (mM)	Buffertype (10 mM)	pH	Stabilisator
18	25	Histidin	6,0	Trehalose dihydrat (200 mM)
19	50	Histidin	6,0	Lysin hydrochlorid (100 mM)
20	100	Histidin	6,0	Mannitol (200 mM)
21	50	Histidin	6,2	Lysin hydrochlorid (100 mM)
22	50	Histidin	6,2	Arginin monohydrocloride + asparaginsyre (80 mM + 20 mM)
23	75	Histidin	6,2	Trehalose dihydrat (200 mM)
24	25	Histidin	6,4	Mannitol (200 mM)
25	100	Histidin	6,4	Trehalose dihydrat (200 mM)
Ref-1 (MS)	Humira-sammensætning (formulering fremstillet med MS-lægemiddelsubstans) – Eksempel 3			
Ref-2 (RMP US)	Kommerciel Humira-DP (USA) - Eksempel 3			

Ref-3 (RMP EU)	Kommerciel Humira-DP (EU) - Eksempel 3

...

1.4 Fragmentering (Bioanalyzer)

…

Ved pH > 6,0 og i nærvær af sukker/polyalkoholer er alle formuleringerne, herunder referencerne, sammenlignelige (fragmentering under 1 % efter 1 måned ved 40 °C.

…

1.6 Udfoldningstemperatur (DSF)

…

Derfor bekræftede denne test de tidligere opnåede resultater for fragmentering med Bioanalyzer: polyalkoholer/sukkerstoffer kan positivt påvirke proteinets varmestabilitet, navnlig ved pH ≥ 6,2, medens natriumchlorid ikke ser ud til signifikant at påvirke dets optræden.

…

2.16 pH-screening med lysbelastning

…

Tabel 18: DoE2-screening: pH-værdi (lyseksponering)

Form #	Salt (NaCl) koncentration (mM)	Buffer-type (10 mM)	pH	Stabilisator	Overfladeaktivt stof (Polysorbat 80) koncentration (mg/ml)	Tid 0	Efter eksponering
DoE2-7	50	Histidin	6,4	Trehalose dihydrat (200 mM)	0	**6,4**	**6,5**
DoE2-8	50	Histidin	6,4	Trehalose dihydrat (200 mM)	0,5	**6,4**	**6,5**
DoE2-9	50	Histidin	6,4	Trehalose dihydrat (200 mM)	1	**6,4**	**6,5**

…

2.17 Virkning af overfladeaktivt stof på fryse-tø-cykler

…

Konklusion på screeningseksperiment 2

…

… Formuleringen uden Polysorbat 80 i denne gruppe (DoE2 – 7) er stadig lidt ringere end RMP, men langt bedre end de andre histidin + Polysorbat 80 (0,5 eller 1,0 mg/ml).

Tilstedeværelsen af Polysorbat 80 er blevet opgjort for at vurdere dets effektivitet og funktion som proteinbeskytter (beskyttelse mod fryse-tø-cykler). Efter 5 fryse-tø-cykler (-80 °C -> stuetemperatur) sås det, at det overfladeaktive stof ikke giver nogen ekstra virkning, og anbefalingen er at gå videre med DoE2 – 7, som er fri for overfladeaktivt stof (50 mg/ml adalimumab, 200 mM trehalosedihydrat, 50 mM natriumchlorid i 10 mM histidin, pH 6,4).

…

… er den bedste sammensætning, som viser sammenlignelige eller endog forbedrede egenskaber i forhold til Humira efter forskellige belastende betingelser (varmebelastning, mekansik belastning, lys) blevet identificeret som:

Ingrediens	Mængde (mg/ml)
Adalimumab	50
Histidin (vandfri)	1,55 *

Trehalosedihydrat	75,67 **
Natriumchlorid	2,92 ***
WFI og natriumhydroxid	q.b. til indstilling af pH til 6,4

* svarende til 10 mM histidin; **svarende til 200 mM; *** svarende til 50 mM

…

Yderligere udførelsesformer:

Yderligere aspekter og udførelsesformer af frembringelsen gengives i de nummererede afsnit nedenfor:

1. Væskeformig farmaceutisk sammensætning omfattende:
   (a) adalimumab;
   (b) et histidinbuffermiddel (eller histidinbuffersystem); og
   (c) en sukkerstabilisator;

hvor sammensætningen har en pH-værdi større end eller lig med 6,30.

2. Væskeformig farmaceutisk sammensætning som beskrevet i afsnit 1, hvor sammensætningen har en pH-værdi mellem 6,3 og 6,5.

Væskeformig farmaceutisk sammensætning som beskrevet i et hvilket som helst foregående afsnit, hvor sukkerstabilisatoren er trehalose.

…

6. Væskeformig farmaceutisk sammensætning som beskrevet i et hvilket som helst foregående afsnit, hvor sammensætningen enten er (i det væsentlige eller fuldstændigt) fri for overfladeaktive stoffer eller omfatter et eller flere overfladeaktive stoffer i en (samlet) koncentration på højst 0,001 M.

…

14. Væskeformig farmaceutisk sammensætning som beskrevet i et hvilket som helst foregående afsnit, hvor sammensætningen omfatter:
    - 45 til cirka 55 mg/ml adalimumab;
    - 5 til 14 mM histidin (eller histidinbuffersystem);
    - 190 til 210 mM trehalose;
    - 40 til 60 mM natriumchlorid;
    - vand (af injektionsrenhed);

    hvor sammensætningen:
    - har en pH-værdi mellem 6,3 og 6,5;
    - er fri for arginin eller omfatter arginin i en koncentration på højst 0,001 mM;
    - er fri for andre aminosyrer end histidin eller omfatter en eller flere andre aminosyrer end histidin i en (samlet) koncentration på højst 0,001 mM;
    - er fri for overfladeaktive stoffer eller omfatter et eller flere overfladeaktive stoffer i en (samlet) koncentration på højst 0,0001 mM; og/eller
    - er fri for phosphatbuffermidler (f.eks. natriumdihydrogenphosphat, dinatriumhydrogenphosphat) eller omfatter et phosphatbuffersystem i en koncentration på højst 0,001 mM.

…

BRUGSMODELKRAV

1. Vandig farmaceutisk sammensætning, der omfatter:
   (a) adalimumab;
   (b) histidinbuffermiddel eller histidinbuffersystem;
   (c) sukkerstabilisator valgt fra gruppen, der indbefatter trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol; og

(d) 0,05 mg/ml til 2 mg/ml overfladeaktivt stof valgt blandt polysorbat 20 og polysorbat 80;

hvor sammensætningen:

- har et pH på mellem 5,0 og 6,7;
- enten er fri for andre aminosyrer end histidin eller omfatter en eller flere andre aminosyrer end histidin ved en samlet koncentration på højst 0,1 mM; og
- enten er fri for phosphatbuffermidler eller omfatter et phosphatbuffersystem ved en koncentration på højst 0,1 mM;

hvor sammensætningen yderligere omfatter en citratbuffer og
hvor sammensætningen omfatter sukkerstabilisatoren ved en koncentration på 50 til 400 mM.

2. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen omfatter adalimumab ved en koncentration på 25 mg/ml til 75 mg/ml.

3. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen omfatter histidinbuffermidlet eller histidinbuffersystemet ved en koncentration på 2 til 50 mM.

4. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen omfatter det overfladeaktive stof ved en koncentration på 0,9 til 1,5 mg/ml.

5. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sukkerstabilisatoren er en sukkeralkohol valgt fra gruppen, der består af sorbitol, xylitol, arabitol, erythritol, lactitol, maltitol og inositol.

6. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sukkerstabilisatoren er sorbitol.

7. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor det overfladeaktive stof er polysorbat 20.

8. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor natriumchlorid er til stede ved en koncentration på mellem 25 og 100 mM, hvis sammensætningen omfatter natriumchlorid som et eventuelt tonicitetsmiddel.

9. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen omfatter:

(a) 45 til 55 mg/ml adalimumab;
(b) 2 til 50 mM histidinbuffermiddel eller histidinbuffersystem;
(c) 50 til 300 mM sorbitol; og
(d) 0,05 til 2 mg/ml polysorbat 20;

hvor sammensætningen:

- enten er fri for andre aminosyrer end histidin eller omfatter en eller flere andre aminosyrer end histidin ved en samlet koncentration på højst 0,1 mM; og
- enten er fri for phosphatbuffermidler eller omfatter et phosphatbuffersystem ved en koncentration på højst 0,1 mM.

10. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen omfatter:

(a) 45 til 55 mg/ml adalimumab;
(b) 2 til 50 mM histidinbuffermiddel eller histidinbuffersystem;
(c) 50 til 300 mM sorbitol; og
(d) 0,9 til 1,5 mg/ml polysorbat 20;

hvor sammensætningen:

- har et pH på mellem 5,0 og 6,7;
- er fri for andre aminosyrer end histidin; og
- er fri for phosphatbuffermidler.

11. Lægemiddeldispenseringsanordning, der omfatter en vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav.
12. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1 til 11 til anvendelse til behandling af rheumatoid arthritis, psoriatisk arthritis, ankyloserende spondylitis, Crohns sygdom, ulcerativ colitis, moderat til svær kronisk psoriasis og/eller juvenil idiopatisk arthritis."

Det fremgår af brugsmodel BR 2018 00071 Y4 bl.a.:

"…
BRUGSMODELKRAV

1. Vandig farmaceutisk sammensætning, der omfatter:
(e) adalimumab;
(f) histidinbuffermiddel eller histidinbuffersystem;
(g) sukkerstabilisator valgt fra gruppen, der indbefatter trehalose, sucrose, mannitol, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol; og
(h) polysorbat 20;
hvor sammensætningen:
- enten er fri for andre aminosyrer end histidin eller omfatter en eller flere andre aminosyrer end histidin ved en samlet koncentration på højst 0,1 mM; og
- enten er fri for phosphatbuffermidler eller omfatter et phosphatbuffersystem ved en koncentration på højst 0,1 mM;

hvor sammensætningen yderligere omfatter en citratbuffer og
hvor sammensætningen omfatter sukkerstabilisatoren ved en koncentration på 50 til 400 mM.
2. Vandig farmaceutisk sammensætning ifølge krav 1, hvor sammensætningen har en pH-værdi på mellem 5,0 og 6,7.
3. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen omfatter adalimumab ved en koncentration på 25 mg/ml til 75 mg/ml.
4. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen omfatter histidinbuffermidlet eller histidinbuffersystemetved en koncentration på 2 til 50 mM.
5. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen omfatter polysorbat 20 ved en koncentration på 0,05 til 2 mg/ml.
6. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen omfatter polysorbat 20 ved en koncentration på 0,9 til 1,5 mg/ml.
7. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sukkerstabilisatoren er en sukkeralkohol valgt fra gruppen, der består af sorbitol, xylitol, arabitol, erythritol, lactitol, maltitol og inositol.
8. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sukkerstabilisatoren er sorbitol.
9. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor natriumchlorid er til stede ved en koncentration på mellem 25 og 100 mM, hvis sammensætningen omfatter natriumchlorid som et eventuelt tonicitetsmiddel.

10. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen omfatter:
(e) 45 til 55 mg/ml adalimumab;
(f) 2 til 50 mM histidinbuffermiddel eller histidinbuffersystem;
(g) 50 til 300 mM sorbitol; og
(h) 0,05 til 2 mg/ml polysorbat 20;
hvor sammensætningen:
- enten er fri for andre aminosyrer end histidin eller omfatter en eller flere andre aminosyrer end histidin ved en samlet koncentration på højst 0,1 mM; og
- enten er fri for phosphatbuffermidler eller omfatter et phosphatbuffersystem ved en koncentration på højst 0,1 mM.

11. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav, hvor sammensætningen omfatter:
(e) 45 til 55 mg/ml adalimumab;
(f) 2 til 50 mM histidinbuffermiddel eller histidinbuffersystem;
(g) 50 til 300 mM sorbitol; og
(h) 0,9 til 1,5 mg/ml polysorbat 20;
hvor sammensætningen:
- har et pH på mellem 5,0 og 6,7;
- er fri for andre aminosyrer end histidin; og
- er fri for phosphatbuffermidler.

12. Lægemiddeldispenseringsanordning, der omfatter en vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav.
13. Vandig farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1 til 11 til anvendelse til behandling af rheumatoid arthritis, psoriatisk arthritis, ankyloserende spondylitis, Crohns sygdom, ulcerativ colitis, moderat til svær kronisk psoriasis og/eller juvenil idiopatisk arthritis."

Der er efterfølgende rejst indsigelser mod EP '510, og Patent- og Varemærkestyrelsens beslutning om at registrere de danske brugsmodeller er anket til Ankenævnet for Patenter og Varemærker.

Patent- og Varemærkestyrelsen har den 29. marts 2019 afgivet en udtalelse til brug for ankenævnets behandling af anken vedr. BR 2018 00070 Y4, hvoraf fremgår bl.a.:

"…
Nyhed
Manning beskriver vandige farmaceutiske formuleringer omfattende adalimumab, en polyol, en overfladeaktiv forbindelse og en buffer. Formuleringen har en pH på 5-6. Manning beskriver mange forskellige formuleringer og formulering 11 i Block H (side 88, tabel H) er tættest pa formuleringen ifølge BR 2018 00070:

Adalimumab	50 mg/ml
Histidin	10 mM
Mannitol	65 mM
Polysorbat 80 (PS 80)	1 mg/ml (0.1 wt%)
NaCl	100 mM
Citrat	10 mM
pH	5.2

Ifølge Krav 1 i BR 2018 00070 som registreret vælges sukkerstabilisatoren 'fra gruppen, der indbefatter trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol'. Klager argumenterer at termen 'indbefatter' betyder, at der kan være flere end de nævnte sukkerstabilisatorer i gruppen nævnt i krav 1.

Det er ikke klart om mannitol er en del af den gruppe af sukkerstabilisatorer, der er eksemplificeret i krav 1 i BR 2018 00070. Vi har imidlertid læst krav 1, således at sukkerstabilisatoren skal vælges fra gruppen, der består aftrehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol. Mannitol er således ikke en del af gruppen af sukkerstabilisatorer nævnt i krav l.

Indholdet af krav 1 som registreret afviger derfor fra formulering 11, tabel H i Manning ved at sukkerstabilisatoren er valgt fra trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol.

Indholdet af krav 1 og afhængige krav 2-12 er derfor nyt i forhold til Manning.

Tydelig adskillelse

Indholdet af krav 1-6, 8 og 1 1-12 ifølge BR 2018 00070 som registreret afviger fra formulering 11, tabel H i Manning ved at sukkerstabilisatoren er valgt fra trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol.

Det objektive tekniske problem, som bliver løst ved indholdet af krav 1-6, 8 og 11-12, er anvisning af en alternativ sukkerstabilisator til brug i formuleringer af adalimumab.

Det er dog kendt inden for vandige formuleringer af adalimumab, at mannitol kan byttes ud med andre sukkerstabilisatorer f.eks. sorbitol og trehalose, som foreslået i Manning (se side 7, linie 22-29) og f.eks. sucrose som foreslået i WO 2011104381 A2 (NOVO NORDISK A/S) 01 September 201 1 (herefter Parshad) (se side 9, linie 10-25).

Fagmanden, der arbejder med vandige formuleringer af adalimumab, og som ønsker at løse ovennævnte problem, vil efter vores vurdering være inspireret af sin fagmandsviden til at anvise indholdet af krav 1-6, 8 og 11-12, som løsning på dette problem.

Indholdet af krav 1-6, 8 og 11-12 adskiller sig dermed ikke tydeligt fra kendt teknik.

Indehaver af BR 2018 00070 argumenterer, at det objektive tekniske problem, som bliver løst ved indholdet i krav 1 i forhold til formulering 11, tabel H i Manning er anvisning af en brugbar vandig adalimumab formulering, der tillader færre excipienser, idet NaCl ikke er en nødvendig excipiens i krav 1 ifølge BR 2018 00070. Manning skriver dog, at resultater fra deres studier indikerer, at fjernelse af NaCl eller reduktion i koncentration af NaCl har en gavnlig effekt på stabiliteten af adalimumab formuleringen (se Manning, side 57, linie 17-24). Derudover er indholdet af krav I ifølge BR 2018 00070

ikke begrænset til, at formuleringen ikke må indeholde andre end de nævnte komponenter.

Indholdet af krav 7 og 9-10 ifølge BR 2018 00070 som registreret afviger yderligere fra formulering 11, tabel H i Manning ved den specifikke overfladeaktive forbindelse polysorbat 20 (PS 20).

Det objektive tekniske problem, som bliver løst ved indholdet af krav 7 og 9-10, er anvisning af en alternativ overfladeaktiv forbindelse i stabile vandige formuleringer af adalimumab.

Det er kendt inden for vandige formuleringer af adalimumab, at anvende forskellige overfladeaktive forbindelser f.eks. PS 20, men ifølge Manning har PS 80 en overraskende fordel i forhold til termisk stabilitet af adalimumab formuleringen sammenlignet med PS 20 (se side 7, linie 30-33).

Fagmanden, der arbejder med vandige formuleringer af adalimumab og som ønsker at løse ovennævnte problem, vil efter vores vurdering derfor ikke være inspireret af sin fagmandsviden til at anvise indholdet af krav 7 og 9-10 det vil sige brugen af PS 20 som overfladeaktiv forbindelse.

Indholdet af krav 7 og 9-10 adskiller sig dermed tydeligt fra kendt teknik.

Utilladelig udvidelse
Med henvisning til vores redegørelse ovenfor i forhold til opfattelsen af termen 'indbefatter' og nyhed, er det vores opfattelse, at der ikke er tale om en utilladelig udvidelse."

Patent- og Varemærkestyrelsen har den 29. marts 2019 afgivet en udtalelse til brug for ankenævnets behandling af anken vedr. BR 2018 00071 Y4, hvoraf fremgår bl.a.:

"…
Nyhed
Manning beskriver vandige farmaceutiske formuleringer omfattende adalimumab, en polyol, en overfladeaktiv forbindelse og en buffer. Formuleringen har en pH på 5-6. Manning beskriver mange forskellige formuleringer og formulering 11 i Block H (side 88, tabel H) er tættest pa formuleringen ifølge BR 2018 00071:

Adalimumab	50 mg/ml
Histidin	10 mM
Mannitol	65 mM
Polysorbat 80 (PS 80)	1 mg/ml (0.1 wt%)
NaCl	100 mM
Citrat	10 mM
pH	5.2

Indholdet af krav 1 som registreret afviger fra formulering 11, tabel H i Manning ved den specifikke overfladeaktive forbindelse polysorbat 20 (PS 20).

Indholdet af krav 1 og afhængige krav 2-13 er derfor nyt i forhold til Manning.

Tydelig adskillelse
Indholdet af krav 1 ifølge BR 2018 00071 som registreret afviger fra formulering 11, tabel H i Manning ved den specifikke overfladeaktive forbindelse PS 20.

Det objektive tekniske problem, som bliver løst ved indholdet af krav 1, er anvisning af en alternativ overfladeaktiv forbindelse i stabile vandige formuleringer af adalimumab.

Det er kendt inden for vandige formuleringer af adalimumab at anvende forskellige overfladeaktive forbindelser f.eks. PS 20 (se WO 2011104381 A2 (NOVO NORDISK A/S) September 2011 (herefter Parshad), side 7, linie 23-35), men ifølge Manning har PS 80 en overraskende fordel i forhold til termisk stabilitet af adalimumab formuleringen sammenlignet med PS 20 (se side 7, linie 30-33).

Fagmanden, der arbejder med vandige formuleringer af adalimumab og som ønsker at løse ovennævnte problem, vil efter vores vurdering derfor ikke være inspireret af sin fagmandsviden til at anvise indholdet af krav 1, det vil sige brugen af PS 20 som overfladeaktiv forbindelse.

Indholdet af krav 1 og afhængige krav 2-13 adskiller sig dermed tydeligt fra kendt teknik.

Utilladelig udvidelse
Vi er af den opfattelse, at der ikke er forekommet utilladelig udvidelse."

Krænkelse, basis, nyhed og frembringelseshøjde

Lægemidlet Imraldi har følgende formulering:

Component[a]	Nominal Quantity/ 0.8 mL	Function
Adalimumab	40 mg	Active substance
Sodium citrate dihydrate	1.6 mg	Buffer
Citric acid monohydrate	0.544 mg	Buffer
L-Histidine	0.96 mg	Stabiliser
L-Histidine hydrochloride monohydrate	8.64 mg	Stabiliser
Sorbitol	20.0 mg	Tonicity agent
Polysorbate 20	0.64 mg	Surfactant
Water for injection	*q.s.*	Solvent

Der er under sagen til illustration af kendt teknik henvist til og dokumenteret fra bl.a. følgende videnskabelige litteratur o.lign.:

- W. Wang (1999), *"Instability, stabilization, and formulation of liquid protein pharmaceuticals*,
- Kieran F. Lim (2006), "Negative pH Does Exist"

- W. Wang et al. (2007), *"Antibody Structure, Instability, and Formulation"*,
- Wiley (2010), *"Formulation and Process Development Strategies for Manufacturing Biopharmaceuticals"*, bog, kapitel 6,
- Nicholas W. Warne (2011), *"Development of high concentration protein biopharmaceuticals: The use of platform approaches in formulation development"*, European Journal of Pharmaceuticals and Biopharmaceutics 78, side 208-212,
- David Sek (2012), *"Breaking old habits: Moving away from commonly used buffers in pharmaceuticals"*,
- Frøkjær m.fl. (2013), *Pharmaceutical Formulation Development of Peptides and Proteins*,
- A. Bender (2013), *"Alternative buffers for pharmaceutical anti-TNFalpha monoclonal antibody formulations"*, Prior Art Publishing, (herefter: "Bender") og
- David Erskine and John Minshull (2018), *"Update on development of biosimilar versions of adalimumab with particular focus on excipients and injection site reactions"*, NHS Specialist Pharmacy Service.

Sagsøgeren vil under denne sag ikke protestere mod de sagsøgtes angivelse af, at Bender er publiceret i patentretlig forstand.

Af patentansøgning WO 2014/039903 A2, indgivet den 6. september 2013 (herefter "Manning"), fremgår bl.a.:

"**Field of the Invention**
The present invention relates to aqueous Pharmaceutical compositions suitable for long-term storage of adalimumab (including antibody proteins considered or intended as "biosimilar" of "bio-better" variants of commercially available adalimumab), methods of manufacture of the compositions, methods of their administration, and kits containing the same.
…

TABLE H-1
Measured pH for Block H formulations at t0, t1 (one week, 40° C), and t2 (two weeks, 40° C)

Form No.	protein	Citrate	Phosphate	Succinate	Histidine	acetate	Gly	Arg	Mannitol	NaCl	PS80	t0	t1	t2
1	100	8	18	0	0	0	0	0	65	100	0.1	5.19	5.30	5.29
2	100	0	0	0	10	0	120	120	0	0	0.1	5.20	5.19	5.15
3	50	0	0	0	0	0	0	0	65	100	0.1	5.21	5.23	5.21
4	50	0	0	0	0	0	120	120	0	0	0.1	5.21	5.41	5.46
5	50	0	0	0	0	0	120	120	0	0	0	5.21	5.30	5.39
6	50	0	0	0	10	10	0	0	65	100	0.1	5.20	5.28	5.28
7	50	0	0	10	10	0	0	0	65	100	0.1	5.21	5.24	5.24
8	50	0	10	0	10	0	0	0	65	100	0.1	5.20	5.17	5.16
9	50	0	0	10	0	10	0	0	65	100	0.1	5.21	5.24	5.29
10	50	10	0	10	0	0	0	0	65	100	0.1	5.20	5.24	5.26
11	50	10	0	0	10	0	0	0	65	100	0.1	5.21	5.24	5.26
12	50	0	0	10	10	0	120	100	0	0	0.1	5.21	5.26	5.29

…

SUMMARY OF FINDINGS FOR BLOCKS A THROUGH H

The formulation studies in Blocks A through H evaluated adalimumab formulations stored at elevated temperature and held for either one week at 40° C or for two weeks at 25° C. The stability was monitored using SEC, RP HPLC, clEF and CE-SDS.

The optimal pH appears to be 5.2 ± 0.2. Of all of the buffer compositions tested, the citrate-phosphate combination is inferior to nearly any other buffer system evaluated, hence an important aspect of the present invention is the avoidance of this combined buffer system altogether. The best single buffer appears to be His, while a His-succinate buffer also offers very good stability. Even buffer-free systems, which rely on the ability of the protein to buffer the formulation, appear to have acceptable stability profiles under accelerated stress conditions.

Of all of the stabilizers/tonicity modifiers evaluated, both Arg and Gly elicit very good stabilization of adalimumab. They both work better than mannitol. Mannitol does appear to be a stabilizer, however we have discovered that if used it should be at the highest possible concentrations, but in any event exceeding about 150 mM, a[n]d most preferably at or exceeding about 200 mM. By comparison, NaCl is clearly a destabilizer, especially when the concentrations exceed 75-100 mM; hence, NaCl, if present should be controlled to levels below about 75 mM. Other polyols, such as sorbitol and trehalose, appear to work about as well as mannitol and therefore may be substituted for mannitol if desired.

Surprisingly, polysorbate 80 (PS 80) provides significant protection against thermal stress. While the mechanism of stabilization is not known, it appears that other surfactants tested (PS 20 and F-68), do not appear to be nearly as effective as PS 80. Hence the selection of PS80 versus PS 20 is a preferred feature of the present invention. Formulations according to the present invention preferably contain […] at least 0.04% (w/v) PS 80.

Based on the findings in the formulation studies of Blocks A through H, the following are particularly preferred adalimumab formulations according to the present invention.

TABLE M
SELECTED FORMULATIONS

Form No	pH	His (mM)	succinate (mM)	Gly (mM)	Arg (mM)	mannitol (mM)	NaCl (mM)	PS 80 (wt %)
A	5.2	30	0	240	0	0	0	0.1
B	5.2	30	0	240	0	0	0	0.02
C	5.2	30	0	0	0	240	0	0.1
D	5.2	30	15	0	0	220	0	0.1
E	5.2	30	0	90	0	150	0	0.1
F	5.2	30	0	240	0	0	0	0
G	5.2	20	0	0	0	240	0	0
H	5.4	30	0	240	0	0	0	0.02
I	5.2	30	0	120	80	0	0	0.1
J	5.2	30	15	90	80	0	0	0.1
K	5.2	30	0	0	0	240	0	0.1
L	5.2	30	0	0	50	160	0	0.1
M	5.2	30	0	90	100	0	0	0.1
N	5.2	20	0	120	90	0	0	0.1
O	5.4	30	0	120	80	0	0	0.1
P	5.2	30	0	120	0	0	50	0.01
Q	5.2	30	0	0	0	240	0	0.02

…"

Sagsøgte har under denne sag anført, at formulering 11 i tabel H-1 i Manning ("Manning H11") må anses for nærmest kendte teknik, hvilket sagsøgeren ikke har villet protestere mod under denne sag.

Bender og Manning er endvidere behandlet og omtalt i de sagkyndige erklæringer, hvortil henvises.

Sagkyndige erklæringer

Der er under sagen afgivet erklæringer af Anette Müllertz (14. marts 2019, 11. april 2019 og 6. maj 2019), Michael Bech Sommer (4. marts 2019, 11. april 2019 og 6. maj 2019), Sven Frøkjær (8. februar 2019, 3. april 2019 og 25. april 2019) og Daniel Erik Otzen (14. februar 2019 og 24. april 2019).

Sven Frøkjær har i erklæring af 8. februar 2019 bl.a. anført:

> "**Kvalifikationer og erfaring**
>
> 1. Jeg er professor i lægemiddelformulering ved Institut for Farmaci ved det Sundhedsvidenskabelige Fakultet på Københavns Universitet. Min forskning koncentrerer sig om peptid- og proteinformulering, med særlig vægt på drug delivery-systemer. Jeg har arbejdet med lægemiddelformulering siden 1973 og har haft en række ledende stillinger i industrien (Novo Nordisk) og i den akademiske verden. Jeg har publiceret mere end 130 forsknings- og reviewartikler på det farmaceutiske område, mange vedrørende formuleringen af proteiner. Jeg har også bidraget til en række lærebøger, herunder "Pharmaceutical Formulation Development of Peptides and Proteins", redigeret af Lars Hovgaard, Sven Frøkjær og Marco van de Weert (2. udgave 2013, 1. udgave 2000). Mit CV er vedlagt som underbilag 1.
>
> **Indledning**
>
> 2. Med henblik på at udfærdige denne erklæring har jeg modtaget og læst kopier af brugsmodellerne DK 2018 00070 Y4 ("BM '070") og DK 2018 00071 Y4 ("BM '071") (samlet "Brugsmodellerne"). Brugsmodellerne er registreret som tilhørende Fresenius Kabi Deutschland GmbH. Jeg forstår, at de vedrører alternative adalimumab-formuleringer til Humira® (det originale adalimumab-produkt).
>
> 3. Jeg har også modtaget og læst en kopi af patentansøgningen WO 2014/039903 A2 ("Manning").
>
> 4. De spørgsmål, jeg er blevet stillet i forbindelse med udfærdigelsen af denne erklæring, vedrører hvad en "fagmand" ville have gjort, eller hvilke overvejelser fagmanden ville have gjort sig, per 23. maj 2014. Jeg er blevet bedt om at antage, at fagmanden i denne sag er en formuleringskemiker eller en proteinkemiker

med en interesse for formulering af proteiner, herunder antistoffer til terapeutisk brug. Jeg har forstået, at fagmanden ville være i besiddelse af en generel almenviden ("fagmandsviden") for en, der arbejder indenfor dette område, og ville have adgang til al relevant litteratur. Jeg har desuden fået at vide, at fagmanden ville være fortrolig med almindeligt anvendte metoder på området og vil have mulighed for at udføre rutinearbejde og almindelige eksperimenter. Jeg har tillige fået at vide, at fagmanden i denne forbindelse ikke besidder opfinderiske færdigheder, men har en rutinepræget tilgang til sit arbejde.

5. Som jeg vil komme nærmere ind på nedenfor, er jeg blevet forelagt nogle udtalelser, som Patent- og Varemærkestyrelsen ("PVS") har afgivet i forbindelse med det tekniske eftersyn af ansøgningerne om registrering af Brugsmodellerne vedrørende fagmandens viden, og jeg er blevet spurgt, om jeg er enig i disse udtalelser.

6. Jeg har vurderet, om kravene i Brugsmodellerne bidrager med nogen teknisk lære, som jeg ikke finder i Manning, eller som kun adskiller sig fra Manning på en måde, der er oplagt for en fagmand på området.

Brugsmodellerne

7. Krav 1 i BM '070 og krav 1 i BM '071 er en anelse forskellige. Begge vedrører en vandig formulering af adalimumab, hvor visse hjælpestoffer enten er til stede eller ej, som følger:

- et histidinbuffermiddel eller histidinbuffersystem,
- en citratbuffer,
- en sukkerstabilisator, valgt fra en liste, ved en koncentration på 50 til 400 mM,
- fri for andre aminosyrer end histidin, eller at sådanne er omfattet ved en samlet koncentration på højst 0,1 mM, og
- fri for phosphatbuffer eller omfattende en phosphatbuffer ved en koncentration på højst 0,1 mM.

8. Forskellene på krav 1 i BM '070 og krav 1 i BM '071 er som følger:

- mannitol er udtrykkeligt nævnt på listen over sukkerstabilisatorer i BM '071, mens dette ikke gælder for BM '070,
- mens begge krav forudsætter tilstedeværelsen af et overfladeaktivt stof, så forudsætter BM '071, at dette er polysorbat 20 (uden angivet koncentration), hvor BM '070 forudsætter "*0,05 mg/ml til 2 mg/ml overfladeaktivt stof valgt blandt polysorbat 20 og polysorbat 80*", og

- BM '070 har i krav 1 en yderligere forudsætning om, at sammensætningen skal have en pH-værdi på mellem 5,0 og 6,7, og selvom dette ikke er en forudsætning i krav 1 i BM '071, så bemærker jeg, at det er en forudsætning ifølge krav 2 i BM '071.

9. Disse krav beskriver således en adalimumab-formulering indeholdende følgende hjælpestoffer: et "*histidinbuffermiddel eller histidinbuffersystem*", en "*citratbuffer*", en "*sukkerstabilisator*" og et "*overfladeaktivt stof*" og med en pH-værdi mellem 5,0 og 6,7 (jf. krav 1 i BM '070 og krav 2 i BM '071).

I 2014 var det, og er stadig, meget almindeligt at fremstille en vandig formulering af et antistof (eller af andre proteiner), som omfatter et buffersystem, en stabilisator og et overfladeaktivt stof. De hjælpestoffer, der er nævnt i kravene i Brugsmodellerne, er (og var i 2014) blandt de mest almindeligt anvendte hjælpestoffer til stabilisering af antistoffer i vandig opløsning. Med henvisning til udsagnet i Brugsmodellerne om det påståede store antal af hjælpestoffer i Humira® bemærker jeg, at antallet af hjælpestoffer i denne formulering er sammenligneligt med antallet i andre antistofprodukter (se vedlagte Tabel I, underbilag 2).

10. En række forskellige vandige adalimumab-formuleringer beskrevet i eksemplerne blev i Brugsmodellerne testet i to formuleringsscreeninger. Disse formuleringer blev udsat for forskellige fysiske belastninger, herunder varme, nedfrysning/optøning og mekanisk påvirkning. Formuleringernes fysiske stabilitet sammenlignet med stabiliteten af HUMIRA® referenceprøver blev undersøgt ved brug af en række sædvanlige metoder (proteinindhold, aggregering (bestemt ved SE-HPLC), fragmentering (bestemt ved hjælp af Bioanalyzer), pH-screening og isoformprofilændring).

11. Brugsmodellernes overordnede konklusion på side 82, linje 22-28 (BM '070) / linje 15-20 (BM '071), er, at

"*den bedste sammensætning, som viser sammenlignelige eller endog forbedrede egenskaber i forhold til Humira® efter forskellige belastende betingelser (varmebelastning, mekanisk belastning, lys) blev identificeret som* [50 mg/mL adalimumab, 10 mM histidin, 200 mM trehalosedihydrat, 50 mM natriumchlorid og WFI og natriumhydroxid, q.b. til indstilling af pH til 6,4]."

12. Efter min opfattelse er der ikke data, der indikerer, at nogen af de testede formuleringer har forbedrede egenskaber i forhold til Humira®. Faktisk indikerer Fig. 5, at DoE2-8 og -9 klarede sig dårligere end Humira® US (og også dårligere end Humira® EU efter 2 uger). DoE2-7 (uden overfladeaktivt stof) klarer sig en smule bedre end Humira®, men giver en højere fragmentering (Fig. 6), selv om dette (uden yderligere dokumentation) tilskrives et kontamineringsproblem.

13. Baseret på de udførte tests og de opnåede resultater er det efter min mening ikke muligt at fastlægge, hvilken effekt (om nogen) de enkelte hjælpestoffer, enten alene eller i kombination, kan have på de undersøgte formuleringers fysiske stabilitet. Brugsmodellerne berører ikke på tilstrækkelig vis de forskellige hjælpestoffers indflydelse på proteinstabilitet (fx ved at teste stabilitet ved tilstedeværelse og fravær (og ved forskellige koncentrationer) af et givent hjælpestof).

14. Konkluderende er det min opfattelse, at de forsøg, der fremlægges i Brugsmodellerne, tester formuleringer, som indeholder sædvanlige hjælpestoffer, som alle var velkendte indenfor proteinformulering længe inden 2014. Der er ikke noget usædvanligt eller overraskende ved nogen af de testede hjælpestoffer. De anvendte metoder til at screene og teste stabilitet var også alle sammen almindelige. Desuden blev der, selv for den formulering, der klarede sig bedst i Brugsmodellernes forsøg, ikke vist nogen forbedring i forhold til Humira®.

Manning

15. Jeg forstår, at Manning blev publiceret den 13. marts 2014. Titlen på Manning er "*Stable Aqueous Formulations of Adalimumab*", og som det forklares på side 1, angår dokumentet farmaceutiske sammensætninger, der er egnede til langtidsopbevaring af både adalimumab selv og af biosimilære produkter.

16. Den første del af Manning (fra side 1 til 26) beskriver baggrunden for opfindelsen, som der søges patent på, og præsenterer diverse "udførselsformer" deraf. I den anden del af Manning, fra side 26 til 109, beskrives de forskellige forsøg, der er blevet udført, og de opnåede data, og konklusionerne på forsøgene diskuteres.

<u>Beskrivelse (siderne 1-26)</u>

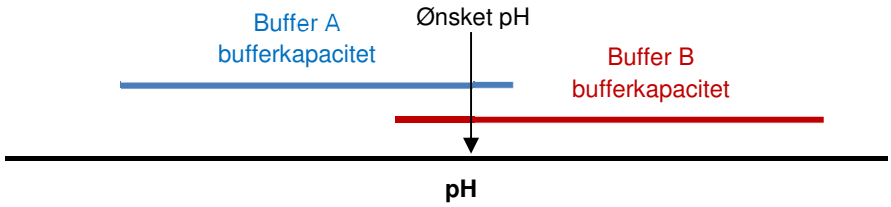
17. En række "Embodiments of the Invention", udførselsformer, beskrives. Eksempelvis beskriver Udførselsform I på side 17 en formulering, som fortrinsvis omfatter en polyol og et overfladeaktivt stof (polysorbater og poloxamerer gives som eksempler). Derudover kan formuleringen omfatte "one, or any combination of two or more buffers" af citrat, fosfat, succinat, histidin, tartrat og maleat (men ikke den specifikke kombination af fosfat og citrat [note: Humira®-formuleringen anvendte en kombination af fosfat og citrat]), og en pH-værdi fortrinsvis mellem cirka 5 til 6. Som fagmanden ville have vidst, var pH for Humira®-formuleringen 5,2, så dette pH-interval er fuldt ud forventeligt.

18. De vigtigste hjælpestoffer i en antistofformulering, som jeg mener, fagmanden ville forvente at se, er til stede i Udførselsform I på side 17 – buffer, stabilisator, overfladeaktivt stof, og formuleret til et sædvanligt pH-interval.

19. En mere specifik Udførselsform af denne type findes på siderne 5-6, hvor en adalimumab-formulering, som omfatter histidinbuffer, mannitol (eller sorbitol eller trehalose) og polysorbat 80, beskrives. Som sådan omfatter den alle kategorierne af bestanddele fra side 17, men med større bestemthed (fx polysorbat 80 specifikt, frem for "*a surfactant*").

20. Øverst side 6 fremgår det også, at denne udførselsform omfatter muligheden for at kombinere histidin med citrat-, acetat-, fosfat-, maleat- og/eller tartratbuffere. Generelt omfatter de fleste formuleringer en buffer, og bufferne der nævnes i listen over buffere på side 6 og i Udførselsform I på side 17 er meget almindelige, selv om fagmanden ville vide at tartrat og maleat er mindre almindelige.

Dog var og er det kendt, at der findes omstændigheder, hvor det kan være en fordel at anvende to buffere, og fagmanden ville være klar over, at der i Humira®-formuleringen indgik to buffere. En grund til at anvende to buffere kan være, hvis den ønskede pH er tæt på grænsen for en enkelt buffers effektive bufferkapacitet, i hvilket tilfælde yderligere en buffer kan tilføjes for at tilvejebringe overlappende bufferkapacitet ved den ønskede pH, og på den måde "forstærke" bufferkapaciteten for formuleringen på det kritiske punkt. Dette er vist nedenfor:



Som vist ovenfor øger brugen af to buffere også det samlede effektive interval for formuleringens bufferkapacitet.

21. Manning angiver også forskellige andre udførselsformer, som er beskrevet på de indledende sider. Eksempelvis er Udførselsform II på side 17 kendetegnet ved, at der kun anvendes én buffer per formulering, ikke kombinationer, Udførselsform III på side 19 indeholder ingen buffer, Udførselsform IV mangler det overfladeaktive stof, osv. Overordnet set virker disse andre udførselsformer alle til at være variationer over Udførselsform I, som omfatter alle de basale og kendte hjælpestoffer for en antistofformulering.

Forsøg (siderne 26-109)

22. Forsøgene i Manning er inddelt i "*Blocks*" benævnt A til H. I hovedtræk synes tanken med hver blok at være at foretage en undersøgelse af givne forskellige aspekter af formuleringen (eller flere forskellige aspekter på samme tid). Eksempelvis anføres det øverst på side 32 at Blok A-forsøgene testede forskellige buffersystemer ved anvendelse af Humira®, Blok B gentog Blok A-forsøgene under

anvendelse af produkter, som var biosimilære til Humira®, osv. Der er som sådan en logisk opbygning i måden, som forsøgene er gennemført på i Manning.

23. Jeg er blevet bedt om særligt at kommentere på Blokkene D og H.

Blok D

24. Blok D omfatter 16 formuleringer "*designed to evaluate other stabilizers as alternatives to mannitol, such as sorbitol and trehalose*".

Formuleringerne vises i Tabel D på side 47, og jeg bemærker, at formuleringerne D1, D7 og D8 er ens, bortset fra, at de indeholder henholdsvis mannitol, sorbitol og trehalose (ved 65 mM). På samme vis er formuleringerne D10, D11 og D12 ens, bortset fra, at de indeholder henholdsvis mannitol, sorbitol og trehalose (ved 240 mM). Det er min erfaring, og jeg mener, det også er fagmandens erfaring, at begge disse sukkerkoncentrationer ligger pænt inden for det interval, der normalt ville forventes.

25. Resultaterne af de forskellige forsøg i Blok D viser, at de formuleringer, der indeholder sorbitol, trehalose og mannitol alle klarer sig godt. På side 57 giver Manning udtryk for, at sorbitol og trehalose kan være bedre end mannitol under visse forhold, men overordnet mener jeg, at fagmanden i hvert fald ville konkludere, at sorbitol og trehalose er, hvis ikke bedre end mannitol, så i hvert fald mindst lige så gode som mannitol, og de tre sukkerstoffer har således en stabiliseringsevne, der er cirka lige god i de testede adalimumab-formuleringer og kan erstatte hinanden i en 1:1 koncentration (om end en udskiftning af trehalose med sorbitol eller mannitol ved samme koncentration ville have indflydelse på formuleringens tonicitet) [note: Mens sorbitol og mannitol begge er monosaccharider (de er isomerer af hinanden), så er trehalose et disaccharid (bestående af to glykoseenheder). Ved samme massekoncentration (g/L) ville sorbitol og mannitol således have den dobbelte molarkoncentration (mol/L) som trehalose og ville således udøve et dobbelt så stort osmotisk tryk som trehalose. Dette skyldes, at det osmotiske tryk for et stof i opløsning er proportionalt med dette stofs molarkon-centration.].

26. Dette er også i overensstemmelse med, hvad der anføres i "*Summary of Conclusions"* i Manning på side 108, om at "*other polyols, such as sorbitol and trehalose, appear to work about as well as mannitol and therefore may be substituted for mannitol if desired*", og med en udførselsform beskrevet på side 5, der behandler mannitol, sorbitol og trehalose som alternativer, idet det anføres, at formuleringen omfatter "*mannitol (or sorbitol or trehalose)*", samt adskillige andre indikationer i Manning (fx på side 3, linje 25-26; side 7, linje 6-9 og linje 22-29; side 18, linje 15-17; og side 22, linje 1-3), som peger på sukkersubstitution.

Blok H

27. Som det forklares på side 87, havde Blok H-forsøgene tre formål, hvoraf det ene var at teste forskellige kombinationer af buffere. Tabel H på side 88 viser, at følgende kombinationer blev testet:

Fosfat og citrat (som anvendt i Humira® - det originale adalimumab-produkt)
Histidin og acetat
Histidin og succinat
Histidin og fosfat
Histidin og citrat
Succinat og acetat
Succinat og citrat
Bufferfri
De følgende sider viser undersøgelserne af formuleringerne, og resultaterne er lovende. Resultaterne i Blok H diskuteres på side 94, hvor det fremføres, at pH-stabiliteten var acceptabel for alle de testede formuleringer, bortset fra de bufferfri formuleringer. Derudover konstateres det, at "*in general, the best buffer combination appears to be His*[tidine]-*succinate*", men ingen klar "bedste" eller "værste" identificeres. Jeg mener, at dette er i tråd med, hvad fagmanden ville konkludere, nemlig at alle de testede kombinationer udviser sammenlignelig stabilitet.

28. Jeg bemærker, at det under *"Summary of Conclusions"* på side 107 anføres, at hvis en enkelt buffer anvendes, så ser histidin ud til at være bedst, hvor histidin-acetatbufferkombinationen også viser "*very good stability*".

Sagsbehandlingen ved Patent- og Varemærkestyrelsen (PVS)

29. Jeg forstår, at sagsbehandleren ved PVS henviste til Manning og et andet modhold i forbindelse med behandlingen af, om ansøgningen om BM '070 og ansøgningen om BM '071 kunne registreres. Jeg er blevet oplyst om, at sagsbehandleren fremkom med udtalelser i relation til fagmandens viden under behandlingen af ansøgningen om registrering af BM '070 og BM '071.

<u>Sagsbehandlingen vedrørende BM '070</u>

30. Med hensyn til valget af buffer har jeg fået oplyst, at sagsbehandleren bemærkede, at:
"*The subject matter of claims 1, 3 and 9 differs from D1* [det andet modhold] *in that the composition comprises a citrate buffer"*

Det blev videre, under henvisning til Manning, fremført, at:
"However, in the field of antibody compositions it is common knowledge to use a buffer system comprising citrate in compositions comprising adalimumab (see e.g. D2 (WO2014039903) [dvs. Manning], *page 5, line 32 – page 6, line 2).*

We consider that the person skilled in the art of antibody compositions who would like to provide an alternative buffer system for an adalimumab composition would be inspired by this common knowledge to suggest the solution mentioned in claims 1, 3 and 9 of your application. We cannot see that the subject matter of claims 1, 3 and 9 presents a surprising effect."

31. Jeg er enig med sagsbehandleren i, at fagmanden ville have anset anvendelsen af en citratbuffer som et oplagt valg. Humira® havde været på markedet i mange år i 2014 og var derfor et velkendt produkt for fagmanden, og det omfattede en citratbuffer i formuleringen (sammen med fosfat). Desuden var citrat en af de mest almindelige buffere til brug i proteinformuleringer, med en typisk effektiv bufferkapacitet på cirka pH 2,5-6 (se tabel 8.2 i "Pharmaceutical Formulation Development of Peptides and Proteins" fra 2013 (underbilag 3), som jeg er medforfatter af).

32. Som bemærket af sagsbehandleren (og som jeg forklarede ovenfor), bekræfter Manning også den antagelse, at en kombination af buffere kan anvendes i en adalimumab-formulering, idet Manning på side 5, linjelinje 32 – side 6, linje 2, anfører:

"*The present invention also contemplates modification of this formulation to combine the histidine buffer with one or more of citrate, acetate, phosphate, maleate, tartrate buffers*".

33. Jeg har fået oplyst, at sagsbehandleren også kom med følgende udtalelse vedrørende valget af sukker og valget af overfladeaktivt stof til brug i en adalimumab-formulering:

"*The further features…, i.e. the sugar is chosen amongst other sugars than sucrose…and the surfactant is polysorbate 20 seem to be arbitrarily selected alternatives or additional features obvious for a person skilled in the art*."

34. Hvad angår valget af sukker, så anfører Brugsmodellerne på side 14, linje 21-23 (BM '070) / linje 19-21 (BM '071), at sukkerstofferne kunne være en sukkerpolyalkohol så som mannitol og sorbitol eller et disaccharid så som trehalose, sukrose, maltose og laktose – og dermed omfattes de sukkerstoffer, der er de mest anvendte i antistofformuleringer.

Jeg bemærker, at Tabel I i underbilag 2 viser en liste over antistofformuleringer, som alle var godkendt før 2014, og mange indeholder en af disse almindelige sukkerstoffer. Derfor er jeg enig i sagsbehandlerens bemærkning om, at valget af sukker i Brugsmodellerne forekommer vilkårligt og omfatter mange almindeligt anvendte sukkerstoffer og dermed oplagte valg.

35. Hvad angår valget af overfladeaktivt stof er jeg enig i, at fagmanden, som vil lave en antistofformulering, generelt kun ville overveje nogle få velkendte, hyppigt anvendte overfladeaktive stoffer. I særdeleshed var de to mest gængse overfladeaktive stoffer klart polysorbat 80 og polysorbat 20 (jf. underbilag 3, side 167, afsnit 8.4.4 og tabel 8.5).

Jeg mener, at fagmanden ville forvente, at enten polysorbat 80 eller 20 ville være oplagte og passende at vælge som overfladeaktivt stof, idet de er nært beslægtede kemiske forbindelser. Mens der kan være ganske små forskelle på, hvor godt de to klarer sig, hvilket ville kunne afklares ved simple, rutinemæssige tests, så ville fagmanden forvente, at de begge to vil have en tilfredsstillende overfladeaktiv effekt.

Sagsbehandlingen vedrørende BM '071

36. Jeg har fået oplyst, at sagsbehandleren under sagsbehandlingen af ansøgningen om BM '071 fremkom med yderligere udtalelser vedrørende fagmandens viden. Jeg har fået at vide, at sagsbehandleren bemærkede, at:

"The subject matter of claims 1-2, 4, 6 and 10 differs from D1 [det andet modhold] *in two ways:*

1. *The surfactant is polysorbate 20*
2. *The composition comprises a citrate buffer*

The subject matter of claims 1-2, 4, 6 and 10 addresses two independent problems:

1. *Alternative surfactant*
2. *Alternative buffer system."*

37. Sagsbehandleren henviste derefter til det andet modhold og til Manning og fremførte, at:

"However, in the field of antibody compositions it is common knowledge to use different surfactants; in fact D1 mentions polysorbate 20. Furthermore, it is also common knowledge in the field to use a buffer system comprising citrate in compositions comprising adalimumab (see e.g. D2 (WO2014039903) [dvs. Manning]*, page 5, line 32 – page 6, line 2).*

We consider that the person skilled in the art who would like to solve the above-mentioned problems would be inspired by this specialist knowledge to suggest the solution mentioned in claims 1-2, 4, 6 and 10 of your application. We cannot see that the subject matter of claims 1-2, 4, 6 and 10 presents a surprising effect."

Som anført ovenfor i relation til sagsbehandlingen af ansøgningen om registrering af BM ´070 er jeg helt enig i den forståelse, sagsbehandleren har givet udtryk for.

Sammenfatning

38. Sammenfattende er jeg således enig i udtalelserne fra sagsbehandleren om, at fagmanden, som vil udvikle en adalimumab-formulering som alternativ til Humira®, ville 1) finde det oplagt at vælge en hvilken som helst af de i denne sammenhæng mest gængse sukkerstoffer med en forventning om, at de ville fungere tilfredsstillende, og 2) finde det oplagt at vælge en hvilken som helst af polysorbat 80 og polysorbat 20 med en forventning om, at de ville fungere tilfredsstillende, og 3) finde det oplagt at vælge en citratbuffer og muligvis anvende en citratbuffer i kombination med en anden buffer, i begge tilfælde med en forventning om, at de ville fungere tilfredsstillende.

Jeg mener, at fagmanden ville være af den opfattelse, at hver eneste af de gængse sukkerstoffer og overfladeaktive stoffer ville kunne anvendes i en adalimumab-formulering med godt resultat, og i det omfang, der kunne være små forskelle i virkningen af de forskellige hjælpestoffer (fx sukrose vs. sorbitol, polysorbat 80 vs. 20 osv.), ville dette kunne vurderes ved simple, rutinemæssige tests.

Sammenligning af Manning og Brugsmodellerne

39. Jeg er blevet bedt om at vurdere, hvorvidt nogen af de to Brugsmodeller ville have bibragt fagmanden nogen yderligere viden i sammenligning med Manning.

40. Overordnet vedrører Brugsmodellerne vandige formuleringer omfattende følgende bestanddele: (a) **adalimumab** antistof, (b) en k**ombination af histidin- og citratbuffere**, (c) en **sukkerstabilisator** udvalgt fra en given liste ved en koncentration mellem 50 og 400 mM, (d) et specificeret **overfladeaktivt stof**, og (e) et **pH-interval på** 5,0 – 6,7 (jf. krav 1 i BM '070 og krav 2 i BM '071). Kravene forudsætter, at formuleringerne er fri for (eller kun indeholder lave niveauer af) fosfatbuffer og aminosyrer bortset fra histidin.

41. Nedenfor vil jeg først kort sammenfatte min opfattelse af, hvad Manning lærer fagmanden vedrørende disse aspekter, hvorefter jeg vil tage stilling til om nogen af de to Brugsmodeller bidrager med noget yderligere.

Manning

42. Manning bidrager efter min opfattelse med følgende for hvert af de centrale elementer:

Antistof: Fokus er alene på vandige adalimumab-formuleringer.
Buffer: Et antal buffere tages i betragtning, herunder histidin, citrat, fosfat, succinat og acetat, og en række kombinationer testes også. Som jeg bemærkede vedrørende resultaterne for Blok H, udviser de forskellige bufferkombinationer (herunder kombinationen af histidin og citrat) gode resultater.

Sukker: De fleste formuleringer indeholder en sukkerstabilisator, og den, der oftest anvendes, er mannitol. Jeg mener ikke, dette ville være nogen overraskelse for fagmanden, eftersom det var en sædvanlig og velkendt bestanddel af mange formuleringer på det tidspunkt. Men som jeg forklarede ovenfor, er der andre udsagn i Manning, der peger på, at sorbitol og trehalose er mindst lige så gode til at stabilisere disse adalimumab-formuleringer som mannitol, og at der oplagt kan substitueres med dem. I langt den største del af de testede formuleringer var sukkeret til stede i en koncentration på mellem 50 og 400 mM.
Overfladeaktivt stof: Det mest almindeligt anvendte overfladeaktive stof i Manning er polysorbat 80. Igen tror jeg ikke, dette ville komme som nogen overraskelse for fagmanden. Efter min opfattelse ville fagmanden forvente, at andre overfladeaktive stoffer også ville være egnede, herunder polysorbat 20. Jeg bemærkede ovenfor, at jeg mener, at fagmanden bestemt ville have været interesseret i at tage begge overfladeaktive stoffer i betragtning.
pH: Langt størstedelen af formuleringerne i Manning blev holdt på pH 5,2, og det er den klart foretrukne pH-værdi.

43. Hvis fagmanden tager den samlede lære fra Manning i betragtning, vil fagmanden efter min vurdering blive forvisset om, at mange formuleringer er blevet testet, og at langt størstedelen udviser lovende stabilitet.

Fagmanden ville efter min vurdering tage dette som et udtryk for, at adalimumab er et robust antistof, som er egnet til at kunne formuleres ved brug af de sædvanlige buffere, sukkerstabilisatorer og overfladeaktive stoffer med henblik på at opnå et alternativ til Humira®-formuleringen.

Analyse i forhold til BM '070

44. Som jeg har forklaret, viste langt størstedelen af de i Manning testede formuleringer gode resultater. Fagmanden ville efter min vurdering være af den opfattelse, at der er en lang række lovende formuleringer i Manning, som man kunne vælge med henblik på nærmere undersøgelse. En af disse er formulering H11 på side 88. Denne formulering indeholder hvert af de træk, der fremgår af krav 1, bortset fra, at den indeholder mannitol som sukkerstabilisator:

Form No.	API	protein	citrate	phosphate	succinate	HIS	ACETATE	Gly	Arg	mannitol	NaCl	PS80
11	***	50	10	0	0	10	0	0	0	65	100	0.1

45. Formuleringen indbefatter 50 mg/ml adalimumab, 10 mM citrat, 10 mM histidin, 65 mM mannitol, 100 mM natriumchlorid (ikke relevant for krav 1) og 0,1% (1 mg/ml) polysorbat 80. Tabel H-1 på side 89 bekræfter, at pH for formuleringen er 5,2. Det bekræftes også, at formuleringen ikke indeholder fosfat eller glycin eller arginin (to andre ofte anvendte aminosyrestabilisatorer).

17. Som jeg forklarede ovenfor, bidrager Manning med den lære, som er understøttet af data, at enten sorbitol eller trehalose (som begge er på listen i del (c) af krav 1) ville kunne substituere mannitol i en 1:1 koncentration.

Det at foretage sådan en substitution er mere end blot et hypotetisk forslag, idet Manning positivt anfører, at sorbitol og trehalose "*may be substituted*" med mannitol, om ønsket.

46. Under alle omstændigheder er det min opfattelse – på linje med den opfattelse, som PVS' sagsbehandler gav udtryk for i sine udtalelser under sagsbehandlingen af ansøgningen om registrering af BM '070 – at det baseret på fagmandens viden og erfaring med formulering ville være oplagt for fagmanden at foretage sådan en substitution.

Analyse i forhold til BM '071

48. Den ovenfor viste formulering H11 i Manning adskiller sig kun fra krav 1 i BM '071 ved at formulering H11 indeholder polysorbat 80 og ikke polysorbat 20 som det overfladeaktive stof.

49. Jeg har forklaret, at polysorbat 80 og 20 i 2014 begge var velkendte og i vid udstrækning brugt i antistofformuleringer, og at fagmanden ville være erfaren i brugen af dem begge.

50. Det er derfor min opfattelse, som også anført af sagsbehandleren under sagsbehandlingen af ansøgningerne om registrering af Brugsmodellerne, at eftersom både polysorbat 80 og 20 har samme funktion, er kemisk nært beslægtede forbindelser, og begge var meget velkendte inden for antistofformulering (og to ud af et meget lille antal hyppigt anvendte overfladeaktive stoffer), så ville fagmanden se det som oplagt og helt rutinemæssigt at skifte mellem de to.

Konklusion

51. Der er i Brugsmodellerne anvendt sædvanlige måder at teste formuleringer indeholdende hjælpestoffer, som var velkendte og sædvanlige i andre antistofformuleringer, der var på markedet i 2014. På grund af problemerne med den måde, hvorpå forsøgene i de beskrevne Eksempler blev udført på, kan der ikke lægges megen vægt på de konklusioner, der drages i Brugsmodellerne.

Selv hvis dataene tages efter pålydende, viser de ikke på nogen måde noget, der er ud over det sædvanlige eller noget uventet. Selv for den formulering, der klarede sig bedst af formuleringerne testet i Brugsmodellerne, kan der ikke registreres nogen forbedring i forhold til Humira®.

Formuleringer indeholdende polysorbat 20 eller kombinationen af citrat og histidin, som forudsættes i Brugsmodellernes krav, blev end ikke testet i Eksemplerne.

52. Overordnet set ligger Manning meget tæt op ad Brugsmodellerne. Som jeg har forklaret ovenfor, beskriver Manning en række lovende formuleringer, hvoraf nogle svarer til det, der fremgår af kravene ifølge Brugsmodellerne. I det omfang der er forskelle på de specifikke formuleringer fra Manning, som jeg har fremhævet ovenfor, og de formuleringer, Brugsmodellerne vedrører (vandige formuleringer af: (a) adalimumab, (b) en kombination af histidin- og citratbuffere, (c) en sukkerstabilisator valgt fra en given liste ved en koncentration mellem 50 og 400 mM, (d) et specificeret overfladeaktivt stof, og (e) et pH-interval på 5,0 – 6,7 (jf. krav 1 i BM '070 og krav 2 i BM '071)), så er forskellen banal. At skifte fra det ene hjælpestof til det andet ville givet være rutinemæssigt formuleringsarbejde, baseret på data og læren fra Manning, fagmandens viden og erfaring med proteinformulering."

Daniel Erik Otzen har i erklæring af 14. februar 2019 bl.a. anført:

"1. **Kvalifikationer og erfaring**

1. 1 Jeg er professor i nanobioteknologi ved Interdisciplinary Nanoscience Center, Aarhus Universitet. Jeg har arbejdet med protein-stabilitet og formuleringer siden 1993 og har haft en række stillinger i industrien og i den akademiske verden. For tiden vedrører min forskning protein stabilitet og formuleringer, med særlig vægt på fibrillering og aggregering af proteiner, protein interaktioner med overfladeaktive stoffer og protein vekselvirkninger med fedtstoffer samt membran-protein biofysik, herunder faktorer, som påvirker proteinernes stabilitet.

1.2 Jeg er forfatter eller medforfatter til mere end 300 forskningsartikler og oversigtsartikler om proteiner, heraf mange vedrørende protein stabilitet. Jeg har også bidraget til en række lærebøger, ligesom jeg er reviewer (bedømmer) for mere end 50 forskellige videnskabelige tidsskrifter, og jeg er redaktør på et videnskabeligt tidsskrift. […]

2. Indledning

2.1 Man har på vegne af Samsung Bioepis UK Limited ("SB") og Biogen (Denmark) Manufacturing ApS og Biogen (Denmark) A/S (samlet "Biogen") bedt mig udfærdige denne erklæring.

2.2 Med henblik på at udfærdige denne erklæring har jeg modtaget og læst en kopi af patentansøgningen WO 2014/039903 A2 ("Manning").

2.3 Jeg har også modtaget og læst kopier af brugsmodellerne DK 2018 00070 Y4 og DK 2018 00071 Y4 (samlet "Brugsmodellerne"). Brugsmodellerne er registreret som tilhørende Fresenius Kabi Deutschland GmbH.

2.4 Herudover har jeg modtaget og læst professor Sven Frøkjærs erklæring af 8. februar 2019, og jeg er blevet bedt om at overveje, hvorvidt og i hvilket omfang jeg er enig i professor Frøkjærs erklæring, både i forhold til professorens vurdering af, hvordan en fagmand den 23. maj 2014 ville have forstået læren ifølge Manning i lyset af vedkommendes almenviden, ekspertviden eller fagspecifikke viden ("fagmandsviden"), og i forhold til professorens vurdering af, hvorvidt kravene ifølge Brugsmodellerne bidrager med noget, som ikke findes i Manning, eller som kun adskiller sig fra Manning på en måde, der er oplagt for en fagmand på området.

2.5 Spørgsmålene, som professor Frøkjær blev stillet i forbindelse med forberedelsen af sin erklæring, angår, hvad "fagmanden" ville have gjort, eller hvilke overvejelser fagmanden ville have haft i 2014. Jeg er blevet bedt om at antage, at fagmanden er en formuleringskemiker eller en proteinkemiker med en interesse for formuleringen af proteiner, herunder antistoffer til terapeutisk brug. Jeg har forstået, at fagmanden vil have en fagmandsviden for en, der arbejder inden for dette område, og ville have adgang til al relevant litteratur og vil have mulighed for at udføre rutinearbejde og almindelige eksperimenter. Jeg har tillige fået at vide, at fagmanden ikke besidder opfinderiske færdigheder, men har en rutinepræget tilgang til sit arbejde.

3. Brugsmodellerne

3.1 Jeg har læst Brugsmodellerne og professor Frøkjærs gennemgang af kravene og deres indhold samt beskrivelsen af de to formuleringsscreeninger (punkt 7-11 i hans erklæring). Jeg er enig i professor Frøkjærs betragtninger og konklusioner, der er beskrevet i punkt 12-24 i hans erklæring. Dermed deler jeg hans opfattelse af, at der ikke er noget usædvanligt eller overraskende ved nogen af de testede hjælpestoffer, og at metoderne, som er beskrevet i Brugsmodellerne, er almindelige.

4. Manning

4.1 Jeg har læst Manning og professors Frøkjærs gennemgang af opfindelsen beskrevet i dette stykke kendte teknik (punkt 15-28 i hans erklæring), og jeg er enig i professor Frøkjærs opsummering af dets lære. Jeg er også enig i de konklusioner, professor Frøkjær fremdrager i sin erklæring vedrørende spørgsmålet om, hvad der er læren ifølge Manning, herunder at fagmanden ville konkludere, at adalimumab er et relativt robust antistof, som er egnet til at kunne formuleres ved brug af en række almindeligt brugte buffere, sukkerstabilisatorer og overfladeaktive stoffer med henblik på at opnå et alternativ til Humira®-formuleringen.

5. Sammenligning af Manning og Brugsmodellerne

5.1 Professor Frøkjær blev bedt om at vurdere, hvorvidt nogen af de to Brugsmodeller ville have bibragt fagmanden nogen yderligere viden i sammenligning med Manning. Professor Frøkjær har lavet en sammenligning mellem læren ifølge Manning og Brugsmodellerne i punkt 39-50.

5.2 Jeg er enig i hans betragtninger om, at Manning beskriver en række alternative formuleringer af adalimumab, hvoraf nogle svarer til det, der fremgår af kravene ifølge Brugsmodellerne. Det ville endvidere være rutinemæssigt formuleringsarbejde, baseret på data og læren fra Manning, at skifte fra det ene hjælpestof til det andet.

6. Konklusion

6.1 I punkt 51-52 konkluderer professor Frøkjær på sine observationer. På grundlag af min læsning af de dokumenter, jeg har fået stillet til rådighed i nærværende sammenhæng, herunder professor Frøkjærs erklæring, og på grundlag af min egen tekniske viden og baggrund, kan jeg efter en nøje gennemgang af Manning og Brugsmodellerne erklære mig fuldt ud enig i professor Frøkjærs udsagn."

Anette Müllerz har i erklæring af 4. marts 2019 bl.a. anført:

1. PREAMBLE

In the context of the Maritime and Commercial High Court case no. BS-39398/2018-SHR, Jakob Krag Nielsen and Rasmus Vang have as attorneys for Fresenius Kabi Deutschland GmbH asked me to answer the below questions.

I understand that I have been retained to answer the below questions with a view to assist the Maritime and Commercial High Court in considering whether the technology defined in claim 1 of UM '70 and claim 1 of UM '71, respectively, involves a so-called creative step when compared to formulation H11 in Manning, page 88. In my understanding the defendants have identified this formulation as the so-called "closest prior art". Please appreciate that my below observations are provided within this context and with a view to be used only in the context of the Maritime and Commercial High Court's decision in the above matter. I am not aware of Fresenius' position with respect to what is to be considered as the "closest prior art", or how the technology defined in claim 1 of UM '70 and claim 1 of UM '71, in Fresenius' view may differ from such.

I am professor at the Department of Pharmacy at the University of Copenhagen and Head of Center at Bioneer: FARMA. I attach a copy of my CV as exhibit AM 1.

I have been provided with copies of the below documents which I have reviewed before providing my answers to the below questions:

- DK 201800070 Y4 ("UM '70") (exhibit 16)
- DK 201800071 Y4 ("UM '71") (exhibit 17)
- WO 2017/039903 A2 ("Manning") (exhibit X)
- Product composition description, Imraldi® (exhibit AB)
- Assessment report, Imraldi® (exhibit AE)
- Declaration of professor Sven Frøkjær of 8 February 2019 (exhibit AO)

- Defence filed in BS-39398/2018-SHR

I have been advised that the pH of Imraldi® is around 5.2-5.3.

I have been asked to perform some of my assessments using a prism denoted as the 'person skilled in the art'. I have been told that a 'person skilled in the art' is presumed to be a skilled practitioner in the relevant field of technology, who is possessed of average knowledge and ability and is aware of what was common general knowledge in the art on 23 May 2014. He is also presumed to have had access to all relevant literature, and to have had at his disposal the means and capacity for routine work and experimentation which are normal for the field of technology in question. I have been told that the 'person skilled in the art' does not possess any inventive or creative capacity. With respect to the delimination of 'the relevant field of technology', I have been asked to base my assessment on the defendants' suggestion that the 'person skilled in the art' is a "formuleringskemiker" [formulation chemist] or "proteinkemiker" [protein chemist] "med interesse for formulering af proteiner, herunder antistoffer til terapeutisk brug" [with a interest in the formulation of proteins, including antibodies, for therapeutic use].

2. THE TECHNOLOGY DEFINED IN CLAIM 1 OF UM '70 AND UM '71

2.1 According to the product composition description of Imraldi® (exhibit AB), Imraldi® comprises i.a. histidine and sorbitol. According to same document, the "Function" of "L-Histidine" and "L-Histidine hydrochloride monohydrate" is denoted as "Stabiliser", while the "Function" of "Sorbitol" is denoted as "Tonicity agent". Besides having these functions, (i) do "L-Histidine" and/or "L-Histidine hydrochloride monohydrate" also function as a buffer in Imraldi®, and (ii) does sorbitol also function as a sugar stabiliser in Imraldi®?

I can answer both questions in the affirmative.

<u>Histidine is a buffer</u>

According to the assessment report pertaining to Imraldi® (exhibit AB), page 14, "Imraldi active substance is formulated with sodium citrate, citric acid monohydrate, <u>histidine buffer</u>, sorbitol, po-lysorbate 20 and water for injections." [emphasis added]

As set out in Hovgaard et al. (ed), 2013, page 155 et seq. (exhibit to Frøkjær's declaration, exhibit AO), histidine is a well known buffer with pKa at 1.8; 6.1 and 9.2. As explained in the written defence, page 14, last paragraph, a rule of thumb is that a buffer is most effective when used to maintain pH within about +/- 1 unit from its pKa. In Imraldi®, histidine is close to 1 unit from its pKa at 6.1. Use of histidine at this pH level is facilitated by doing two things. First, the alkaline form of histidine (L-Histidine) is added in a low amount of 0.96 mg while the acidic form of histidine (L-Histidine hydrochloride monohydrate) is added in an amount of 8.64 mg. Further, histidine is combined with citrate (pKa 3.1; 4.8 and 5.2), that is a good buffer at pH levels around its pKa at e.g. 5.2. By combining these two buffers, the pH 5.2-5.3 of Imraldi® is placed at a point where the buffers used have overlapping buffer capacity, see hereto Frøkjær's illustration at page 5.

Apart from having a buffer function capacity, the histidine used in Imraldi® will inherently contribute to the tonicity of the solution and therefore always work as a tonicity agent. Hovgaard et al. (ed), 2013, page 155, observes that "Buffers are used

to prevent small changes in solution pH that can affect protein solubility and stability". Moreover, histidine also has a protein stabilising effect – beyond the stabilising effect that is a result of its buffering property, see to this end Manning, page 96, line 18, where it is specifically observed that histidine is found to be a stabiliser in the tested adalimumab solutions. Also in the defence, it is observed that histidine and other amino acids are "known to be useful stabilisers", see page 16, paragraph 7.5.3.

Sorbitol is a sugar alcohol and has a stabilising effect

Sorbitol belongs to a general class of organic compounds called "polyols", subclass "sugar alcohols". I have observed that claims 1, sub-section (c) of UM '70 and UM '71 list a number of sugar alcohols, including sorbitol.

Sugar alcohols are well known for use as protein stabilisers in solutions.

Hovgaard et al. (ed), 2013, page 162 observes that sorbitol generally works as a stabilising agent:

> A variety of cosolvents can stabilize proteins in solutions because the cosolvent is preferentially excluded from surface interaction with the protein (Arakawa et al., 1991). Cosolvents behaving this way include glycerol and sorbitol. Bhat and

Frøkjær specifically observes that i.a. sorbitol works as a stabilising agent in the tested adalimumab solutions, see Frøkjær page 6, paragraph 25, where he with reference to Manning observes that "de tre sukkerstoffer [hvor sorbitol er et af disse] har således en stabiliseringsevne" [in English: the three sugar compounds [sorbitol being one of them] thus have a stabilising effect]. Also in the defence, it is observed that "sugars" such as sorbitol, "may assist in stabilising proteins", see page 16, paragraph 7.5.2.

For the sake of completeness, I note that in a formulation such as Imraldi®, sorbitol will – as histidine - inherently always work as a tonicity agent. The fact that sorbitol works as a tonicity agent is also observed in the defence, page 16, paragraph 7.5.2.

3. MANNING VS UM '70 OR UM '71, CLAIM 1

3.1 What would a 'person skilled in the art' consider if asked to formulate a protein based pharmaceutical product such as one comprising adalimumab?

A key task when formulating a protein based pharmaceutical product is to design a formulation that keeps the protein structure stable. This is usually not a problem when formulating a small molecule product.

Hovgaard et al. (ed), 2013, page 162, explains:

8.4 OPTIMIZING PHYSICAL STABILITY

Unlike small molecules where physical instability is rarely encountered except for poorly water-soluble compounds, proteins, because of their unique ability to adopt three-dimensional forms, tend to undergo a number of structural changes, independent of chemical modifications. Physical instability of proteins is sometimes a greater cause for concern and is more difficult to control than chemical instability. All protein structures are hydrophobic to some extent. Many proteins, particularly when exposed to stressful conditions, for example, extremes in temperature, will unfold such that the hydrophobic portions become exposed to the aqueous environment. Such exposure will promote aggregation or self-association, possibly leading to physical instability and loss of biological activity, since the interaction with the receptor site requires folded structures with correct conformation.

To elaborate further, please consider the below two figures.

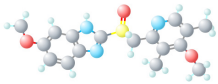


Figure 1 displays the molecular structure of omeprazole. (https://pubchem.ncbi.nlm.nih.gov/compound/omeprazole#section=3D-Conformer) Omeprazole is a very frequently used pharmaceutical compound in the treatment of gastric ulcer. Omeprazole comprises approximately 40 atoms – corresponding to 2 amino acids. The 3D-structure of omeprazole is relatively stable.

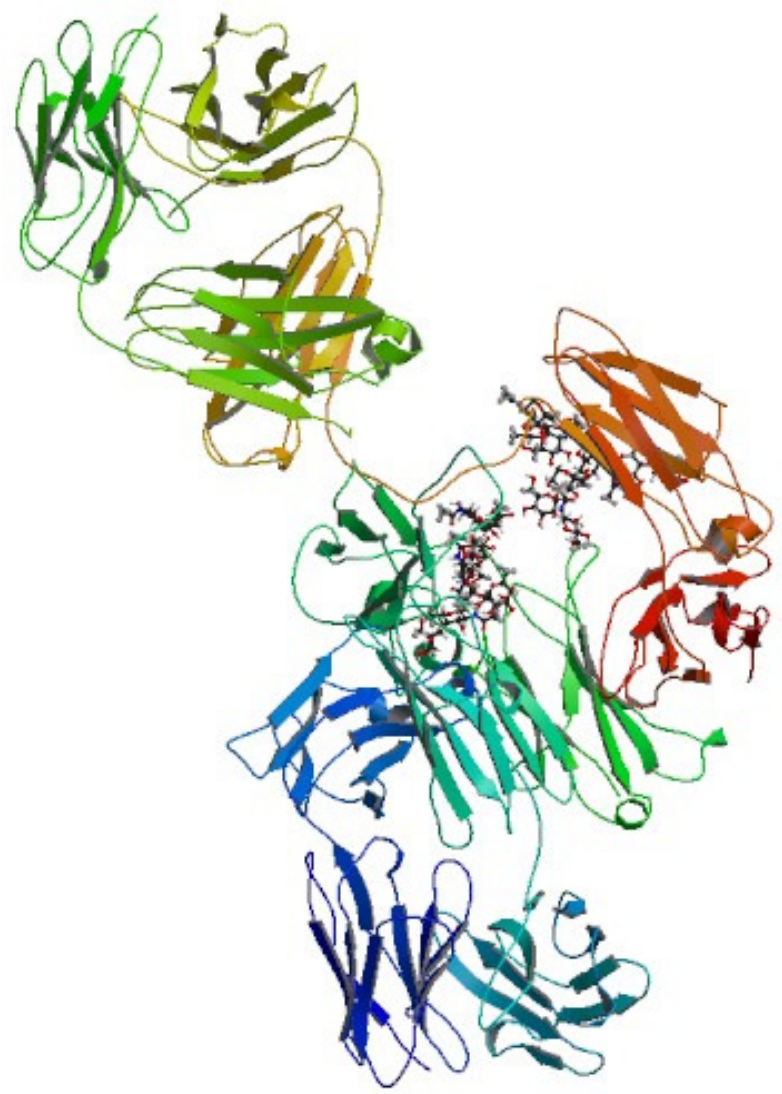


Figure 2 displays adalimumab (https://www.drugbank.ca/drugs/DB00051). Adalimumab comprises 1330 amino acids. One amino acid comprises approximately 20 atoms. The adalimumab molecule is around 700 times larger than the omeprazole molecule. The 3D-structure of most proteins is relatively unstable. It may e.g. aggregate (molecules form clusters) and denature (molecules unfold). If it does so, it will usually loose its desired pharmacological function.

While small molecules may usually be administered orally using tablets, it is necessary to administer protein based products parenterally, usually sub-cutaneously. Consequently, it is necessary to formulate protein based products as a solution that can be injected.

If a protein such as adalimumab is dissolved in water, it will denature over time. It is therefore necessary to add excipients to the solution that stabilise adalimumab.

Using adalimumab as an example, it is also necessary to manage the pH of the solution, because adalimumab is only dissolvable above and below its isoelectric

point, which is around pH 8. As it is not desirable to administer a solution with a pH over 8 to the human body, pH needs to be set to a point below 8.

Moreover, it is desirable to formulate an adalimumab solution so that it is isotonic, i.e. has the same osmolality as the body. If it has not, injection of the solution will hurt and may damage the cells around the injection point. Also, the excipients used in a formulation need obviously to be safe when administered to patients.

When formulating a solution comprising adalimumab, it is consequently relevant to target a solution that (i) has a pH below 8, (ii) is isotonic and safe to administer to patients and (iii) stabilises the protein.

Many different excipients may be used to pursue these targets – some excipients may only be used in the pursuit of one of the targets, others may be used to simultaneously address all targets, and others again may positively affect one or two targets while being to the detriment of one of both other targets. The number of possibilities when combining excipients is close to infinite.

3.2 Please review Manning (exhibit X) and explain the key teachings that you would expect 'a person skilled in the art' to take away, both in terms of which technical features that seem to have a positive effect when applied in adalimumab formulations and in terms of which technical features that seem to have a negative effect when applied in adalimumab formulations

Conclusion

Manning presents and tests a large number of different adalimumab formulations in which Manning tests different combinations of excipients. In the context of specific embodiments, Manning explains that use of particular excipients should preferably be avoided. In other specific embodiments, Manning suggests the use of the same excipients. This makes it clear that in many instances, it is not possible to conclude that the use of one particular excipient is good or bad. It very much depends on which other excipients are used – and in which concentrations. When reviewing Manning's experiments, it becomes obvious that the effects of the applied excipients are interlinked, but Manning's experiments do not systematically teach how. It therefore seems difficult to draw any general conclusions on how to formulate optimal formulations other than perhaps those that Manning himself set out in his concluding remarks on page 107 et seq., where Manning, in my resumé, teaches the 'person skilled in the art' that when aiming at formulating adalimumab formulations with long term stability:

1) Do use a pH of 5.2 +/- 0.2.
2) When using a buffer, use histidine alone or histidine-succinate in combination. Do not use a combination of citrate and phosphate.

3) Do use arginine and/or glycine as stabilisers/tonicity modifiers. They both work better than mannitol. Mannitol in concentrations exceeding 150 mM, preferably exceeding 200mM works well. Sorbitol and trehalose appear to work about as well as mannitol. Be cautious to use NaCl as a stabiliser/tonicity modifier. If you use NaCl, do so in concentrations that do not exceed 75-100 mM.
4) Use PS 80 instead of other surfactants such as PS 20 and F-68.

Observations

As also observed by Frøkjær, page 4, paragraph 15, Manning explains in the opening paragraph on page 1, line 3-7, that the patent application presents an invention that relates to aqueous pharmaceutical compositions suitable for long-term storage of adalimumab.

On page 2, Manning presents a summary of the invention. This is done by presenting multiple particular embodiments of the invention.

By way of example and as also observed by Frøkjær, page 4, paragraph 17, Manning presents a "first embodiment" (page 2, line 23-30) by observing:

"In a first embodiment, the invention provides a stable aqueous pharmaceutical composition comprising adalimumab; a stabilizer comprising at least one member selected from the group consisting of a polyol and a surfactant; and a buffer selected from the group consisting of citrate, phosphate, succinate, histidine, tartrate and maleate, wherein said composition has a pH of about 4 to about 8 and preferably about 5 to about 6, and wherein said buffer does not comprise a combination of citrate and phosphate, and preferably does not comprise any citrate buffer. In this embodiment, the stabilizer preferably comprises both polyol and surfactant."

This first embodiment comprises a combination of a stabiliser and a buffer. Manning suggests to positively consider a number of possible particular stabilisers and buffers – and to avoid both citrate and phosphate in combination and preferably to avoid citrate.

Manning then moves on to suggest multiple further embodiments where one gets the impression that Manning suggests formulations that are defined using a combinatorial approach. By way of example, on page 3-4, line 2, Manning presents as the "second embodiment" a solution with a single buffer; as the "third embodiment" a buffer free solution; as the "fourth" and "fifth" embodiment, solutions that are surfactant and polyol free, respectively.

On page 4, line 3-20, Manning observes that each of the foregoing five embodiments may comprise a further "stabilizer selected from the group consisting of an amino acid, a salt, ethylenediaminetetraacetic acid (EDTA) and a metal ion". Manning also observes that preferably, the solution should not comprise citrate and

phosphate in combination and most preferably, should be free or substantially free of citrate buffer. Manning also observes that preferably the solution should not comprise NaCl in concentrations above 100 mM. Manning also observes that preferably the solution should comprise arginine and/or glycine. Manning also observes that preferably, when the stabiliser includes a polyol, this should be mannitol in concentrations exceeding 150 mM.

Manning then moves on to present further specific embodiments on page 4, line 21 – page 7, line 5.

On page 7, line 30-33, Manning provides as a general observation that "We have discovered a distinct and surprising thermal stabilization advantage in selecting PS 80 instead of PS 20."

On page 8-25, Manning then moves on with a more detailed presentation of the various embodiments of the invention.

On page 26-107, Manning presents and tests a large number of different solutions where Manning uses different combinations of excipients. In the context of specific embodiments, Manning explains that use of particular excipients should preferably be avoided. In other specific embodiments, Manning suggests the use of the same excipients. This makes it clear that in many instances, it is not possible to conclude that the use of one particular excipient is good or bad. It very much depends on which other excipients are used – and in which concentrations. When reviewing Manning's experiments, it becomes obvious that the effects of the applied excipients are interlinked, but Manning's experiments do not systematically teach how. It therefore seems difficult to draw any general conclusions on how to formulate optimal formulations other than perhaps those that Manning himself set out in his concluding remarks on page 107 et seq., where Manning observes:

"SUMMARY OF FINDINGS FOR BLOCKS A THROUGH H
The formulation studies in Blocks A through H evaluated adalimumab formulations stored at elevated temperature and held for either one week at 40° C or for two weeks at 25° C. The stability was monitored using SEC, RP HPLC, clEF and CE-SDS.

The optimal pH appears to be 5.2 ± 0.2. Of all of the buffer compositions tested, the citrate-phosphate combination is inferior to nearly any other buffer system evaluated, hence an important aspect of the present invention is the avoidance of this combined buffer system altogether. The best single buffer appears to be His, while a His-succinate buffer also offers very good stability. Even buffer-free systems, which rely on the ability of the protein to buffer the formulation, appear to have acceptable stability profiles under accelerated stress conditions.

Of all of the stabilizers/tonicity modifiers evaluated, both Arg and Gly elicit very good stabilization of adalimumab. They both work better than mannitol. Mannitol does appear to be a stabilizer, however we have discovered that if used it should be at the highest possible concentrations, but in any event exceeding about 150 mM, a[n]d most preferably at or exceeding about 200 mM. By comparison, NaCl is clearly a destabilizer, especially when the concentrations exceed 75-100 mM; hence, NaCI, if present should be controlled to levels below about 75 mM. Other polyols, such as sorbitol and trehalose, appear to work about as well as mannitol and therefore may be substituted for mannitol if desired.

Surprisingly, polysorbate 80 (PS 80) provides significant protection against thermal stress. While the mechanism of stabilization is not known, it appears that other surfactants tested (PS 20 and F-68), do not appear to be nearly as effective as PS 80. Hence the selection of PS 80 versus PS 20 is a preferred feature of the present invention. Formulations according to the present invention preferably contain contain at least 0.04% (w/v) PS 80.

Based on the findings in the formulation studies of Blocks A through H, the following are particularly preferred adalimumab formulations according to the present invention.

TABLE M

SELECTED FORMULATIONS

Form No	pH	His (mM)	succinate (mM)	Gly (mM)	Arg (mM)	mannitol (mM)	NaCl (mM)	PS 80 (wt %)
A	5.2	30	0	240	0	0	0	0.1
B	5.2	30	0	240	0	0	0	0.02
C	5.2	30	0	0	0	240	0	0.1
D	5.2	30	15	0	0	220	0	0.1
E	5.2	30	0	90	0	150	0	0.1
F	5.2	30	0	240	0	0	0	0
G	5.2	20	0	0	0	240	0	0
H	5.4	30	0	240	0	0	0	0.02
I	5.2	30	0	120	80	0	0	0.1
J	5.2	30	15	90	80	0	0	0.1
K	5.2	30	0	0	0	240	0	0.1
L	5.2	30	0	0	50	160	0	0.1
M	5.2	30	0	90	100	0	0	0.1
N	5.2	20	0	120	90	0	0	0.1
O	5.4	30	0	120	80	0	0	0.1
P	5.2	30	0	120	0	0	50	0.01
Q	5.2	30	0	0	0	240	0	0.02

When ‘a person skilled in the art’ reviews Manning, the above summary of findings, in my opinion, teaches which respective technical features that seem to have a positive or a negative effect on long term stabilisation when applied in adalimumab formulations. In my summary, the ‘person skilled in the art’ is provided with the following take away:

1) Do use a pH of 5.2 +/- 0.2.

2) When using a buffer, use histidine alone or histidine-succinate in combination. Do not use a combination of citrate and phosphate.
3) Do use arginine and/or glycine as stabilisers/tonicity modifiers. They both work better than mannitol. Mannitol in concentrations exceeding 150 mM, preferably exceeding 200mM works well. Sorbitol and trehalose appear to work about as well as mannitol. Be cautious to use NaCl as a stabiliser/tonicity modifier. If you use NaCl, do so in concentrations that do not exceed 75-100 mM.
4) Use PS 80 instead of other surfactants such as PS 20 and F-68.

I would like to make the following supplementary observations:

- Frøkjær observes on page 6, paragraph 25, that the 'person skilled in the art' when reading Manning, page 57, will conclude that "sorbitol og trehalose er, hvis ikke bedre end mannitol, så i hvert fald mindst lige så gode som mannitol" [in English: sorbitol and trehalose are if not better than mannitol, then at least as good as mannitol]. I do not agree that the 'person skilled in the art' will draw this general conclusion based on Manning, page 57.

  On page 57, Manning discusses particular experiments made in the context of Block D. All experiments in Block D regard formulations that comprise citrate and/or phosphate buffers. In the context of Block D it is concluded that such buffer choice is sub-optimal – this is actually one essential teaching of Manning. Using these sub-optimal citrate/phosphate buffers, Manning in Block D tests formulations comprising mannitol, sorbitol or trehalose, and Manning observes on page 57, line 17, that "Both sorbitol and trehalose display better stability profiles than mannitol when used as the sole tonicity agent in <u>these formulations</u>" [my emphasis]. Manning's wording makes clear that the finding regarding sorbitol and trehalose is specific for the formulations tested there. In Manning's general conclusion on page 108, line 1-3, he notes that sorbitol and trehalose "appear to work about as well as mannitol" [in Danish: ser ud til at fungere omtrent så godt]. It seems clear to me that Manning's specific observation on page 57 is not the same as his general conclusion on page 108. I therefore disagree with Sven Frøkjær when he on page 6, paragraph 26, observes that Manning's general conclusions on page 108 are "i overensstemmelse med" [in English: in agreement with] Manning's formulation-specific observations on page 57.

- Stating "Som jeg forklarede ovenfor" [in English: As I explained above], i.e. on page 6, paragraph 25-26, Frøkjær states on page 12, paragraph 46, that the 'person skilled in the art' when reading Manning will conclude that the three sugar alcohols – mannitol, sorbitol and trehalose - can replace each other in a "1:1" concentration. I disagree that Manning offers this general conclusion.

On page 7, line 6-9, Manning observes that "in certain embodiments" "sorbitol and trehalose are discovered to be significantly better stabilizers of adalimumab formulations, unless mannitol is used at concentrations in excess of about 200-300 mM in which case the three are generally equivalent". In the cited observations, Manning thus teaches that "in certain embodiments" sorbitol, trehalose and mannitol are "generally equivalent" if mannitol is used in concentrations in excess of about 200-300 mM. Manning makes a similar observation in the context of the formulations discussed in Block D. Manning does not observe that mannitol, sorbitol and trehalose – in these "certain embodiments" or generally - can replace each other in a 1:1 concentration.

- Frøkjær observes on page 7, paragraph 27 in the end, that Manning in the context of Block H does not identify any particular formulation as clearly better or worse than others. I do not agree. Manning, page 94, line 4-20, identifies formulation 12 as the most stable formulation. As the overall objective of Manning is to identify most stable formulations (see e.g. Manning, page 2, line 21-22), it will be clear to the 'person skilled in the art' that Manning on page 94 identifies formulation 12 as the best formulation of those tested in Block H. pH data identifies all but formulation 1, 4 and 5 as acceptable; SEC and RP HPLC data identifies formulation 7 and 12 as best; CE-SDS data identifies formulation 12 as best. Consequently, among the formulations tested in Block H, formulation 12 appears to stand out as the superior formulation. The 'person skilled in the art' will see that formulation H12 is a formulation that reflects the general suggestions provided in Manning's conclusion and set out above: Formulation 12 has a pH of 5.2; comprises a combined histidine-succinate buffer; and as stabilisers/tonicity modifiers comprises arginine and glycine instead of mannitol and NaCl.

- Frøkjær observes on page 7, paragraph 28, of his declaration that Manning on page 107 identifies the combination of histidine and acetate buffer as a very good combination. I take this to be a mis-transcription, and that Frøkjær agrees that Manning points to the combination of histidine and succinate as very good.

3.3 If a 'person skilled in the art' was tasked with modifying formulation 11 from Table H (Manning page 88) with a view to provide a viable formulation that allows for fewer excipients, what would (not simply could) the 'person skilled in the art', in your expectation, do in the light of his general technical knowledge and the particular technical teachings identified in your answer to the above question 0? In particular, would the 'person skilled in the art' remove mannitol and NaCl and replace with sorbitol or trehalose? In particular, would the 'person skilled in the art' replace PS 80 with PS 20?

If a 'person skilled in the art' - with formulation H11 as the starting point - was asked to develop a viable formulation allowing for fewer excipients, the 'person

skilled in the art' would - using his general technical knowledge - identify two overall strategies:

1) Reduce the number of excipients by removing one or more excipients – and possibly then adjust the concentration of the remaining excipients
2) Reduce the number of excipients by removing two or more excipients and adding fewer yet new excipients – and possibly then adjust the concentration of the excipients used

When considering how to pursue these two strategies, the 'person skilled in the art' would, in my expectation, consider Manning's four teachings (1-4) set out in my answer to question 0 above. When doing so, the 'person skilled in the art' would naturally take note of Manning's identification of the 17 formulations in Table M as being preferred, and the 'person skilled in the art' would observe that apart from formulation J in Table M, all formulations comprises fewer excipients as compared to formulation H11, and thus represent a viable formulation with fewer excipients thereby solving the task.

The 'person skilled in the art' would obviously also consider whether he could identify and use any further teachings pertaining to the particular experiments performed in Block H. As already explained in the paragraph immediately over question 0, the particular teaching in section H is that formulation H12 – which, except for the concentration of the buffer, is similar to formulation J in Table M - is the better solution. The 'person skilled in the art' would take note that the difference between formulation H11 and H12 is that (i) citrate is substituted with succinate, and (ii) that mannitol and NaCl are substituted by arginine and glycine. In my expectation, the 'person skilled in the art' would be motivated to consider options having these teachings in mind.

Re removal of excipients

Manning points the 'person skilled in the art' to remove citrate because histidine functions well by itself. Manning also points to the removal of NaCl. Based on these pointers, the 'person skilled in the art' would, in my expectation, try formulations that do not comprise citrate and/or NaCl. Formulation C in Table M – which formulation comprises fewer constituents than H11 – indicates that a formulation aligned with Manning's teachings work well.

Re substitution of excipients

Manning suggests that succinate is a preferred buffer to combine with histidine and that glycine and arginine are superior to mannitol. Based on these pointers together with Manning's observations on excipients that may be removed (citrate and NaCl and possibly also mannitol), the 'person skilled in the art' would, in my expectation, try formulations where citrate and/or NaCl and possibly also mannitol

are removed – and where succinate, glycine and/or arginine are added. Formulations A, B, C, D, E, F, G, H, I, K, L, M, N, O, and Q in Table M – which formulations all comprise fewer constituents than H11 – indicate that formulations aligned with Manning's teachings work well.

In the below table, I have tried to illustrate some of the main variations that the 'person skilled in the art', in my expectation, would formulate based on his own general knowledge and the teachings of Manning if tasked with providing viable formulations that allow for fewer excipients. Had the person been tasked to provide viable formulations with same or more excipients, the number of possible variations that could be devised using the person's general knowledge in combination with Manning's teachings would rise exponentially.

The illustrated 24 formulations that allow for fewer excipients are all variations of formulation H11. Table M comprises yet other examples, none of which are set out below. Manning's teachings point to many more formulations.

The below table is based on Table H in Manning, page 88. The columns are the same as in Table H – with the addition of a far left column with numbers, and a far right column that counts the number of excipients. Further columns – and thereby variations – could obviously be added. The below variation possibilities are not adjusted as to their isotonicity.

		Protein	Citrate	Phosphate	Succinate	Histidine	Acetate	Glycine	Arginine	Mannitol	NaCl	PS 80	Number of constituents
	H11	50	10			10				65	100	0.1	6
1	Delete one (citrate)	50				10				65	100	0.1	5
2	Delete one (NaCl)	50	10			10				65		0.1	5
3	Delete two (citrate and NaCl)	50				10				65		0.1	4
4	Delete two, add one	50			+	10				65		0.1	5
5	Delete two, add one	50				10		+		65		0.1	5
6	Delete two, add one	50				10			+	65		0.1	5
7	Delete two, add one	50				10		+			100	0.1	5
8	Delete two, add one	50				10			+		100	0.1	5
9	Delete three, add one	50				10		+				0.1	4
10	Delete three, add one	50				10			+			0.1	4
11	Delete three, add two	50				10		+	+			0.1	5

		Pro-tein	Cit-rate	Pho sph ate	Su cci nat e	Histi-dine	Ac-e-tate	Gly cin e	Argi-nine	Man-nitol	NaCl	PS 80	Num-ber of constit-uents
12	Delete three, add two	50			+	10		+				0.1	5
13	Delete three, add two	50			+	10			+			0.1	5
	Less NaCl												
14	Delete one (cit-rate)	50				10				65	75	0.1	5
15	Delete two, add one	50				10		+			75	0.1	5
16	Delete two, add one	50				10			+		75	0.1	5
17	More mannitol												
18	Delete one (cit-rate)	50				10				150	100	0.1	5
19	Delete one (NaCl)	50	10			10				150		0.1	5
20	Delete two (cit-rate and NaCl)	50				10				150		0.1	4
21	Delete two, add one	50			+	10				150		0.1	5
22	Delete two, add one	50				10		+		150		0.1	5
23	Delete two, add one	50				10			+	150		0.1	5
	Less NaCl, more mannitol												
24	Delete one (cit-rate)	50				10				150	75	0.1	5

<u>The concentration used of each excipient is a balancing act</u>

As indicated in the above table, the concentration of the excipients used is a separate variable. When working with formulations, it is clear to the 'person skilled in the art' that the actual concentration used of the different excipients is sometimes important. It is usually a balancing act, because the used excipients are functionally related meaning that they are likely to impact the functionality of each other. Moreover, the total concentration of the excipients used should result in an isotonic solution, as I have explained in paragraph 0 above. The art is to optimally balance the concentration in which each excipient is used. To this end, Manning points the 'person skilled in the art' to use a larger concentration of mannitol and a lower concentration of NaCl as compared to what is used in formulation H11, thus providing an alternative to H11. This notion is similarly evidenced by the formulations in Table M which all comprise concentrations of excipients that are different from the concentrations used in formulation H11.

***

Would the 'person skilled in the art' remove mannitol and NaCl and replace with sorbitol or trehalose?

If a 'person skilled in the art' - with formulation H11 as the starting point - was asked to develop a viable formulation allowing for fewer excipients, the 'person skilled in the art' would identify the above two overall strategies. When considering the 2nd main strategy where one or more excipients are removed and fewer, yet new excipients are added, the 'person skilled in the art' will know from his own general knowledge that a large number of potentially relevant stabilisers exists, including but not limited to particular buffers, polyols, salts and surfactants. In Manning, some of these well-known excipients are identified and analysed. It will be clear to the 'person skilled in the art' that a close to infinite number of combinatorial variations exists. Among these is certainly a possibility that mannitol and NaCl are replaced with sorbitol or trehalose, and of course the 'person skilled in the art' could choose this particular formulation as well as any other particular formulation out of the close to infinite combinatorial variations that uses other well known excipients.

When it comes to the question whether the 'person skilled in the art' would choose this alteration (remove mannitol and NaCl and replace with sorbitol or trehalose), I note that the 'take away' message provided by Manning – both the general teachings set out above (1-4), as supported by Table M, and the particular teachings of Block H - does not suggest so. There is no indication that in the context of formulation H11 – or other formulations of Block H or Table M – that replacement of mannitol and NaCl with sorbitol or trehalose will result in similar or better formulations. In the context of a replacement of mannitol and NaCl, Manning as a first step points the 'person skilled in the art' to choose glycine or arginine – because according to Manning, both are better. Manning also teaches the possibility to remove NaCl and use the "highest possible concentration" of mannitol. This is another option that Manning points to. Moreover, Manning identifies sorbitol and trehalose as polyols that "appear" only to "work about as well" as mannitol. This preference for mannitol over sorbitol and trehalose is evidenced by Table M that comprises many formulations with only mannitol, but none with sorbitol or trehalose. As explained above, I therefore expect that a 'person skilled in the art' would try to replace mannitol and NaCl with glycine and/or arginine – or replace NaCl and higher the concentration of mannitol. The possibility to replace NaCl and mannitol with sorbitol or trehalose is just a combinatorial possibility among a close to infinite number of combinatorial possibilities. I therefore agree with Frøkjær's observation on page 12, paragraph 46, that the 'person skilled in the art' indeed "may" perform such substitution with sorbitol or trehalose (although not necessarily in a 1:1 concentration), but based on Manning, I cannot see why the 'person skilled in the art' would perform such substitution. If realistically considering whether a skilled, yet non-creative, person was asked to review Manning and in turn modify

H11 with a view to define a viable formulation allowing for fewer constituents, the person would not try a formulation where he removed mannitol and NaCl and replaced with sorbitol or trehalose, unless somebody explicitly asked him to do so.

Would the 'person skilled in the art' replace PS 80 with PS 20
Based on Manning's very clear suggestion that PS 80 works better than PS 20, the 'person skilled in the art' would, in my expectation, be consciously clear on not replacing PS 80 with PS 20. While the replacement option is obviously a combinatorial possibility, the 'person skilled in the art' would have learned from Manning that this theoretical option is not a good path to go. I therefore disagree with Frøkjær's observations (see page 11, paragraph 42(l), and also page 13, paragraph 50) that the 'person skilled in the art' from the teaching of Manning would replace PS 80 with PS 20. Manning explicitly and generally advises against such substitution, moreover observing that the mechanism of stabilisation is not known:

"The method may further comprise the selection of PS 80 as a surfactant based on empirical data indicating that PS 80 imparts better thermal stability to the adalimumab formulation than other surfactants, including PS 20." (Manning, page 6, line 15-18)

"We have discovered a distinct and surprising thermal stabilization advantage in selecting PS 80 instead of PS 20." (Manning, page 6, line 15-18)

"Surprisingly, polysorbate 80 (PS 80) provides significant protection against thermal stress. While the mechanism of stabilization is not known, it appears that other surfactants tested (PS 20 and F-68), do not appear to be nearly as effective as PS 80." (Manning, page 108, line 4-7)"

Michael Bech Sommer har i erklæring af 4. marts 2019 bl.a. anført:

1. PREAMBLE
In the context of the Maritime and Commercial High Court case no. BS-39398/2018-SHR, Jakob Krag Nielsen and Rasmus Vang have as attorneys for Fresenius Kabi Deutschland GmbH asked me to answer the below questions in my capacity as European patent attorney.

I understand that I have been retained to answer the below questions with a view to assist the Maritime and Commercial High Court in considering whether the technology defined in claim 1 of UM '70 and claim 1 of UM '71, respectively, does not go beyond the content of the application as filed, and further is novel and involves a creative step when compared to formulation H11 in Manning, page 88. In my understanding the defendants have identified formulation H11 as closest prior art. Please appreciate that my below observations are provided within this context and with a view to be used only in the context of the Maritime and Commercial High Court's decision in the above matter. I am not aware of Fresenius' position

with respect to what is to be considered as the "closest prior art", or how the technology defined in claim 1 of UM '70 and claim 1 of UM '71, in Fresenius' view may differ from such.

I am a European patent agent. My professional experience is described in the attached CV (exhibit MBS 1). I work with AWA Denmark A/S and note that other patent attorneys from AWA Denmark A/S than me are providing advice to Fresenius in other aspects of this case.

I have been provided with copies of the below documents which I have reviewed before providing my answers to the below questions:

- DK 201800070 Y4 ("UM '70") (exhibit 16)
- DK 201800071 Y4 ("UM '71") (exhibit 17)
- EP 3 403 646 A1 ("'646") (exhibit H)
- EP 14 169754 ("'754") (exhibit I)
- Application for EP '510 (exhibit V)
- WO 2017/039903 A2 ("Manning") (exhibit X)
- Formule du medicament, Imraldi® (exhibit AB)
- Assessment report, Imraldi® (exhibit AE)
- Appeal re UM '70 (exhibit AN)
- Appeal re UM '71 (exhibit AN)
- Declaration of professor Sven Frøkjær of 8 February 2019 (exhibit AO)
- Defence filed in BS-39398/2018-SHR
- Declaration of professor Anette Müllertz 4 March 2019

2. ALLEGED ADDED MATTER

2.1 Please review the defence and provide your assessment on whether the technical features of claim 1 of UM '70 and claim 1 of UM '71 have basis in EP 3 403 646 ('646). Please also provide your assessment on whether claim 1 of UM '70 and claim 1 of UM '71 can claim priority from EP 14 169754 ('754)**.**

The utility models in suit '70 and '71 are branched off from pending European patent application EP 3 403 646 ('646). EP '646 in turn is a divisional application from EP 3 148 510 ('510), the "parent". Thus, the utility models, the divisional and the parent have the same filing date, 15 May 2015.

Both UM '70 and '71, the divisional '646 and the parent '510 claim and share the same priority, namely from EP 1 4 169754 ('754) having a priority date 23 May 2014.

In the instant case, I am not aware of the existence of any differences between the content of the parent '510 and the priority application '754. The defendants do not identify any differences and observe that the documents are "almost identical", see citation from page 64 of the defence below. I therefore take it that the parties agree that at least, no relevant differences exist. Since the subject matter of the priority application and the '510 document as filed is the same, all subject matter of the '510 document as well as UM '70 and UM '71 can benefit from the priority date of 23 May 2014.

In the defence, page 43-64, the defendants allege that the technical features of claim 1 of UM '70 and claim 1 of UM '71 do not have adequate basis in parent '510/divisional '646. If that is the case, the technical features of the claims that lack basis simply have no priority, because they are not described in the application as filed.

In legal terms, the relevant question therefore is whether the issued claim 1 of UM '70/UM '71, respectively, comprises 'added matter'. If so, the relevant UM claim is invalid due to unlawful added matter. The fact that the features of such claim in the case at hand would also lack priority is of no legal relevance as the utility right in question would be invalid due to unlawfully added matter. The defendants seem to share this perspective in the defence, page 64, where they state:

"10. No right to priority
The Priority Application is almost identical to the application for EP '510. Therefore, the subject-matter claimed in the Utility Models cannot be found in the Priority Application either. For the reasons described in section 9 above relating to added subject-matter, no priority can be claimed either for the Utility Models."

In conclusion, if the technical features of UM '70, claim 1, or UM '71, claim 1, lack adequate basis, claim 1 of the issued UM in question will, in the case at hand, also lack priority. On the other hand, if the technical features of UM '70, claim 1, or UM '71, claim 1, do have adequate basis, no priority problem exists.

ooOOoo

The legal basis for the discussion regarding "added matter" is section 18 of the Danish Utility Models Act, which reads:

"§ 18. En ansøgning om brugsmodelregistrering må ikke ændres således, at brugsmodelregistrering søges for noget, som ikke fremgik af ansøgningen, da denne blev indleveret."

Section 18 corresponds to article 123(2), EPC.

When assessing allowability of the claims of a Danish utility model application under section 18, the DKPTO applies the same standard as when the EPO assesses a patent application under article 123(2), EPC. As also suggested by the defendants in the defence on e.g. page 43-44, the practice of the EPO is therefore relevant. I will perform my below assessment on this basis.

When determining whether a claim lacks "basis" – which is the same as saying that the claim has "added subject matter" – the question is whether the claim in question comprises any technical feature that cannot be derived directly and unambiguously from the application as filed. The Guidelines make it clear that literal support for a claim (amendment) is not a requirement under the EPC, cf. Guidelines H-V-2.2:

"Under Art. 123(2), it is impermissible to add to a European application subject-matter which the skilled person cannot derive directly and unambiguously, using common general knowledge and also taking into account any features implicit to a person skilled in the art in what is expressly mentioned in the document, from the disclosure of the application as filed. Literal support is, however, not required by the wording of Art. 123(2) (see T 667/08)."

New claims may thus be formulated, or existing claims modified, using information which is available in the application as filed.

In the case at hand, the applications leading to UM '70 and UM '71 comprised a complete translation of the divisional '646 which in turn comprised a complete copy of the parent '510 application as filed. When assessing basis for claim 1 of UM '70 and UM '71, the legal requirement is that all features of the claims can be found in parent '510 application as filed and published (exhibit V). It is of absolutely no relevance, whether claim 1 of UM '70 and/or UM '71 differ from the claims of divisional '646 or parent '510 application as filed, or parent '510 as granted. The whole point in being able to file divisional and branched of applications – such as UM '70 and UM '71 – is that by doing so, one may claim subject matter that differs from the subject matter claimed in the parent '510 as well as divisional '646. The defendants' observations on how claim 1 of UM '70 and UM '71 differ from the claims of '510 as filed are therefore without any relevance to the assessment of added matter.

In the following, basis for all the claim elements of UM '70 and UM '71 respectively will be discussed with reference to the '510 application as filed and published (represented by exhibit V).

Feature	**UM '070 as granted**	**UM '071 as granted**	**EP '510 as granted**	**Basis in the text of '510 as filed and published**
1.	An aqueous pharmaceutical composition comprising:	An aqueous pharmaceutical composition comprising:	An aqueous pharmaceutical composition comprising:	[00122] provides basis for claiming an "aqueous" pharmaceutical composition.
2.	(a) adalimumab;	(a) adalimumab;	(a) adalimumab;	Aspects of the invention described in each of [0011], [0014] and [00194] provide a framework of the claim by reciting a combination of adalimumab, a histidine buffer system, sugar stabiliser, and surfactant.
3.	(b) a histidine buffer or histidine buffer system;	(b) a histidine buffer or histidine buffer system;	(b) a histidine buffer or histidine buffer system;	
4.a	(c) sugar stabiliser selected from the group including trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol; and		(c) sugar stabiliser selected from the group including trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol; and	This list of sugar stabilisers is derived from [00111] but with 'mannitol' deleted – this is a so-called "shrinking of a generic group" rather than "singling out", and is thus allowable, see EPO case-law of the boards of appeal (8th ed.), II-E-1.4.2): "In T 615/95 there were three independent lists of sizeable length specifying distinct meanings for three residues in a generic chemical formula in a claim. One originally disclosed meaning was deleted from each of the three independent lists. The board stated that the present deletions did not result in singling out a particular combination of specific meanings, i.e. any hitherto not specifically mentioned individual compound or group of compounds, but maintained the remaining subject-matter as a generic group of compounds differing from the original group only

Feature	UM '070 as granted	UM '071 as granted	EP '510 as granted	Basis in the text of '510 as filed and published
				by its smaller size. Such a shrinking of the generic group of chemical compounds was not objectionable under Art. 123(2) EPC 1973, since these deletions did not lead to a particular combination of specific meanings of the respective residues which was not disclosed originally or, in other words, did not generate another invention (see also T 948/02, which refers in detail to this case law and which did not allow the amendment of a generic chemical formula; see also T 659/97, T 894/05, T 888/08). In T 1506/13 the board, referring to T 948/02, summarised that a deletion of genes from a list of specific genes was allowable if it fulfils two conditions: First, the deletion must not result in singling out any hitherto not specifically mentioned individual compound or group of compounds, but maintains the remaining subject-matter as a generic group of compounds differing from the original group only by its smaller size. Second, the deletion does not lead to a particular combination of a specific meaning which was not disclosed originally, i.e. it does not generate another invention, or in other words it merely restricts the required protection but does not provide any technical contribution to the originally disclosed subject-matter." (https://www.epo.org/law-practice/legal-texts/html/caselaw/2016/e/clr_ii_e_1_4_2.htm)
4.b		(c) sugar stabiliser selected from the group including trehalose, sucrose, mannitol, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol; and		This list of sugar stabilisers is derived from [00111].
5.a	(d) from 0.05 mg/ml to 2 mg/ml of surfactant chosen from		(d) from 0.05 mg/ml to 2 mg/ml of surfactant chosen from	Surfactant concentration derived from [00163], [00166] and [00170]. As per T 1241/03, specific concentrations of par-

Feature	UM '070 as granted	UM '071 as granted	EP '510 as granted	Basis in the text of '510 as filed and published
	Polysorbate 20 andPolysorbate 80;		Polysorbate 20 and Polysorbate 80;	ticular compounds need not have literal basis in a single package in combination with the other claimed features.
5.b		(d) Polysorbate 20;		Surfactant individualised to 'polysorbate 20', but this is not a list selection because it was disclosed as a specific embodiment in [00168] due to the use of the word "or" in the sentence 'polysorbate 80 or polysorbate 20' (which is not a list).
	wherein the composition:	wherein the composition:	wherein the composition:	
6.	has a pH between 5.0 and 6.7;		has a pH between 5.0 and 6.7;	The pH range is derived from [00102]. pH is measured with a defined scale of 0-14. In [00102] it is stated that pH should be at least 5.0 – thereby defining the range between 5.0 and 14. In [00102] it is also stated that pH should be less than or equal to 6.7 – thereby defining the range between 0 and 6.7. Combination of end points of such ranges is not violating 123(2) as per established case law, see e.g. T2001/10, reasoning 10.
7.	is either free of amino acids other than histidine or comprises one or more amino acids other than histidine in a (collective) concentration of at most 0.1 mM; and	is either free of amino acids other than histidine or comprises one or more amino acids other than histidine in a (collective) concentration of at most 0.1 mM; and	is either free of amino acids other than histidine or comprises one or more amino acids other than histidine in a (collective) concentration of at most 0.1 mM; and	The aspects described in each of [0014] and [00131] provide basis for low/no amino acids but histidine.
8.	is either free of phosphate buffering agents or comprises a phosphate buffer system in a concentration of at most 0.1 mM;	is either free of phosphate buffering agents or comprises a phosphate buffer system in a concentration of at most 0.1 mM;	is either free of phosphate buffering agents or comprises a phosphate buffer system in a concentration of at most 0.1 mM;	The aspects described in [00148] provide basis for low/no phosphate.
9.	wherein the composition further comprises a citrate buffer and	wherein the composition further comprises a citrate buffer and	Claim 9 of EP '510 as granted	Citrate buffer finds basis in [0062] and [0063] alone (citric acid and sodium citrate form a citrate buffer) and also read in conjunction with [0096] et seq.

Feature	UM '070 as granted	UM '071 as granted	EP '510 as granted	Basis in the text of '510 as filed and published
10.	wherein the composition includes the sugar stabiliser in a concentration of 50 to 400 mM.	wherein the composition includes the sugar stabiliser in a concentration of 50 to 400 mM.	Claim 4 of EP '510 as granted	The aspects described in [00118] provide basis for sugar stabiliser concentration. See also T1241/03 that verifies that combining amounts with the respective constituents does not constitute added subject matter.

3. VALIDITY – NOVELTY AND CREATIVE STEP

3.1 In your opinion, are UM '70, claim 1, and UM '71, claim 1, novel over formulation H11 (Manning, page 88)? In your answer, please comment on the assessment made by Frøkjær and in the defence.

UM '70

Claim 1 of UM '70 is, in my opinion, novel over Manning because Manning does not in one single embodiment disclose all the features of claim 1.

Formulation H11 (Manning, page 88) does not comprise any of the sugar stabilisers of claim 1. It is further noted that NaCl is present in the H11 formulation.

With respect to Frøkjær, I note that Frøkjær has reviewed Manning and observes on page 12, paragraph 44, that in his analysis formulation H11 "indeholder hvert af de træk, der fremgår af [UM '70] krav 1, bortset fra, at den indeholder mannitol som sukkerstabilisator" (in English: "comprises each of the features of UM '70, claim 1, except for the feature that it comprises mannitol as sugar stabiliser").

To me, Frøkjær seems to acknowledge that claim 1 of UM '70 is novel over Manning. Biogen explicitly acknowledges the same in its complaint to The Board of Appeal for Patents and Trademarks ("BAPT") (exhibit AN) where it is stated on page 6, 3rd last paragraph:

"…selvom Manning ikke eksplicit beskriver én enkelt formulering kendetegnet ved samtlige træk ifølge kravene ifølge BR'070, så ville læren ifølge Manning i sig selv uden tvivl tilskynde fagmanden til at fremstille en formulering, der falder indenfor kravene ifølge BR'070" [In my English translation: in spite of the fact that Manning does not disclose one particular formulation characterised by all features of the claims of UM'70, the teaching of Manning would in itself motivate the person skilled in the art to manufacture a formulation that is covered by the claims according to UM'70]

In the defence, page 69-70 (paragraph 12.2.3), I have taken note that it is alleged that claim 1 of UM '70 lacks novelty over formulation H11. This observation is contrary to Frøkjær's assessment and the defendants' own complaint to BAPT, exhibit AN. It seems to me that the defendants mix arguments against novelty and inventive step. Replacing excipients of formulation H11 is not a matter of novelty but rather creative step.

UM '71

Similarly, claim 1 of UM '71 is, in my opinion, novel over Manning because Manning does not in one single embodiment disclose all the features of claim 1.

Formulation H11 (Manning, page 88) comprises PS 80 and not, as claim 1 defines, PS 20. It is further noted that NaCl is present in the H11 formulation.

With respect to Frøkjær, I note that Frøkjær on page 13, paragraph 48, observes that in his analysis formulation H11 "adskiller sig kun fra krav 1 i BM '71 ved at formulering H11 indeholder polysorbate 80 og ikke polysorbate 20 som det overfladeaktive stof" (in English: "differs only from claim 1 of UM '71 by that formulation H11 comprises polysorbate 80 and not polysorbate 20 as surfactant").

To me, Frøkjær seems to acknowledge that claim 1 of UM '71 is novel over Manning. Biogen explicitly acknowledges the same in its complaint to the BAPT (exhibit AN) where it is stated on page 6, 2nd last paragraph:

"…selvom Manning ikke eksplicit beskriver én enkelt formulering kendetegnet ved samtlige træk ifølge kravene ifølge BR'071, så ville læren ifølge Manning i sig selv uden tvivl tilskynde fagmanden til at fremstille en formulering, der falder indenfor kravene ifølge BR'071" [In my English translation: in spite of the fact that Manning does not disclose one particular formulation characterised by all features of the claims of UM '71, the teaching of Manning would in itself motivate the person skilled in the art to manufacture a formulation that is covered by the claims according to UM'71]

In the defence, page 72-75 (paragraph 12.2.6), I have taken note that it is alleged that claim 1 of UM '71 lacks novelty over formulation H11, page 88, of Manning. Also this observation is contrary to Frøkjær's assessment and the defendants' own complaint to BAPT, exhibit AN. Again, it seems to me that the defendants' mix arguments against novelty and inventive step. Replacing excipients of formulation H11 is not a matter of novelty but rather creative step

3.2 The defendants submit that UM '70, claim 1, does not involve a creative step over formulation H11 of Manning. In your opinion, does UM '70, claim 1, involve a creative step over formulation H11 of Manning?

When assessing inventive/creative step the DKPTO applies the problem-solution approach in conformity with the practice of the EPO. I will therefore in the following use the problem-solution approach as it is applied by the DKPTO/EPO.

<u>Step 1 – identification of closest prior art</u>
The first step is to identify the closest prior art. I understand that the defendants have identified formulation H11 of Manning as closest prior art.

The formulations of Block H focus on assessing (i) variations in protein concentrations, (ii) formulations with no buffers, and (iii) formulations with various buffer combinations. The Block H study focuses on the long-term stability of the formulations.

<u>Step 2 – defining an objective technical problem, claim 1, UM '70</u>
Having formulation H11 as the starting point, the difference to claim 1 of UM '70 is that claim 1 formulations stipulate a sugar stabiliser other than mannitol and that NaCl is not a requirement. The effect of this difference is that viable adalimumab

formulations are provided. Thus, an objective technical problem may be formulated as how to provide a viable formulation that allows for fewer excipients. This problem is in line with the subjective problem defined on page 3, line 4-17, of UM '70:

> Med hensyn til den fysiske og kemiske stabilisering af Adalimumab, ser den komplekse række bestanddele i de førnævnte handelsformuleringer ud til at klare sig dårligere end forventet, navnlig i lyset af det store antal bestanddele. Selv om denne særlige kombination af excipienser utvivlsomt repræsenterer en "delikat balance" (i betragtning af samspillet mellem forskellige tekniske faktorer) og var resultatet af omfattende forskning og udviklingsarbejde, er det i lyset af den tilsyneladende risiko for dårligere ydelse tvivlsomt, hvorvidt et sådant højt antal af forskellige excipienser er berettiget, specielt i betragtning af at dette uundgåeligt forøger fremstilling- og omkostningsbyrderne, toxicitetsrisici og risikoen for skadelige samvirkninger mellem bestanddele, som kan kompromittere formuleringen. Selv hvis den overordnede funktion af handelsformuleringerne ikke skulle kunne overgås, ville en alternativ formulering med sammenlignelig funktion men indeholdende færre bestanddele repræsentere en højst ønskelig erstatning for formuleringerne i handlen af i hvert fald de førnævnte grunde.

The solution of claim 1 of UM '70 solves the above problem in that the formulation defined in claim 1 allows for one less excipient than the H11 formulation; it does not require NaCl; it requires a sugar stabiliser not including mannitol. I also note that it seems plausible that the technical effect of providing a viable formulation is achieved. I base this on the fact that according to the assessment of Imraldi® (exhibit AE, page 22, 3rd paragraph), the stability of Imraldi® is comparable to EU Humira®. In this context it is noted that is not a requirement that the effect of a creation is documented with examples in the application as filed. Such documentation may be post-produced or -filed. In the case at hand, Imraldi® therefore adequately documents the technical effect.

Step 3 – determining whether the skilled person (i) presented with the above objective technical problem, and (ii) with the outset in the closest prior art chosen, would have arrived at the creation of claim 1, UM '70

Manning focuses on finding formulations that have long-term stability. This is the technical problem that Manning seeks to solve. With this problem in mind, Manning discusses and investigates a large number of formulations in order to identify formulations that have such long-term stability.

Manning does not identify the above problem of providing viable formulations that allow for fewer excipients. Using the vocabulary of the EPO/DKPTO, Manning does not provide the person skilled in the art with any 'explicit pointers' or 'hints' that guide him in the direction of solving the above problem of providing viable formulations that allow for fewer excipients. The 'explicit pointers' and 'hints' that Manning provide are directed towards solving the problem of providing formulations with long-term stability.

However, as explained by professor Anette Müllertz, the skilled person finds viable variations of the H-formulations having the same or fewer number of excipients, and on page 94, line 3-20, he is given some guidance on variations to H11. For example, he learns that formulations 2, 3, 6, 7, 8, 9, 10 and 12 appear to have similar or better stability as compared to formulation H11. Of these, formulation H2 and H3 comprise fewer excipients. None of these formulations correspond to the solution of UM '70, claim 1.

The skilled person also learns from page 107-109 in 'Summary of findings for Blocks A through H' (including table M) that a number of preferred formulations have been deduced from the experiments. Most of the formulations in table M have fewer excipients; formulation J has the same number of excipients. None of the formulations in table M correspond to the solution of UM ´70, claim 1.

In my conclusion, starting from formulation H11 and tasked with the objective problem stipulated above, the general knowledge and Manning will guide the skilled person towards solutions as explained above and in further details by professor Anette Müllertz.

Thus, from the teaching of Manning the skilled person would not change the formulation H11 in such a way that he would arrive at the solution claimed in UM ´70, claim 1. Consequently, claim 1 involves an inventive step. I note that DKPTO evaluates creative step as requiring less than inventive step. Thus, having established that there is an inventive step, it is even more clear that a creative step is involved.

3.3 The defendants submit that UM '71, claim 1, does not involve a creative step over formulation H11 of Manning. In your opinion, does UM '70, claim 1, involve a creative step over formulation H11 of Manning? In your answer, please comment on the assessment made by Frøkjær and in the defence

The above considerations regarding creative step in respect of UM '70, claim 1, equally applies to the assessment of the creative step in respect of UM '71, claim 1. I add the below particular observations.

<u>Step 1 – identification of closest prior art</u>
Also, in respect of UM '71, claim 1, I understand that the defendants have identified formulation H11 of Manning as closest prior art.

<u>Step 2 – defining an objective technical problem, claim 1, UM '71</u>
Having formulation H11 as the starting point, the difference to claim 1 of UM '71 is that claim 1 formulations stipulate PS 20 as surfactant instead of PS80 and that NaCl is not a requirement. The effect of this difference is that viable adalimumab formulations are provided. Again, an objective technical problem may be formulated as how to provide a viable formulation that allows for fewer excipients. This problem is in line with the subjective problem defined on page 3, line 4-17, of UM '71, see above.

The solution of claim 1 of UM '71 solves the above problem in that the formulation defined in claim 1 allows for one less excipient than the H11 formulation; it does not require NaCl; it requires PS 20. Again, it seems plausible that the technical effect of providing a viable formulation is achieved. It follows from the assessment

for Imraldi® (exhibit AE, page 22, 3rd paragraph) that the stability of Imraldi® is comparable to EU Humira®.

Step 3 – determining whether the skilled person (i) presented with the above objective technical problem, and (ii) with the outset in the closest prior art chosen, would have arrived at the creation of claim 1, UM '71

As explained above, Manning does not provide the person skilled in the art with any 'explicit pointers' or 'hints' that guide him in the direction of solving the above problem.

However, as explained by professor Anette Müllertz, the skilled person finds viable variations of the H-formulations with the same or fewer excipients, and on page 94, line 3-20, he is given some guidance on variations to H11. For example, he learns that formulations 2, 3, 6, 7, 8, 9, 10 and 12 appear to have similar or better stability as compared to formulation H11. Of these, formulation 2 and 3 are also simpler (comprise fewer excipients). None of these formulations correspond to the solution of UM '71, claim 1.

The skilled person also learns from page 107-109 in 'Summary of findings for Blocks A through H' (including table M) that a number of preferred formulations have been deduced from the experiments. Most of the formulations in table M comprise fewer excipients; formulation J comprises the same number of excipients as H11s. None of the formulations in table M correspond to the solution of UM ´71, claim 1.

Out of the close to infinite number of possible variations, should the skilled person for some reason specifically choose to replace the surfactant, PS 80, with another surfactant, Manning teaches him against choosing PS 20. As pointed out by professor Anette Müllertz, Manning on page 108, line 4-7, explains that PS 80 provides significant protection as compared to PS 20, and that the mechanism of stabilisation is not known. Therefore, the skilled person would look for another solution than the one provided in claim 1 of UM '71.

Thus, from the teaching of Manning the skilled person would not change the formulation H11 in such a way that he would arrive at the solution claimed in UM ´71, claim 1. Consequently, claim 1 involves an inventive step and so much more also a creative step."

Michael Bech Sommer har i erklæring af 4. marts 2019 bl.a. anført:

"…
This is a supplement to my declaration of the same date regarding validity related matters. I refer to the preamble of said further declaration.

2. PATENT PROTECTION OF PROTEIN FORMULATIONS

2.1 Have there been any attempts to patent the formulation of Humira® or other adalimumab biosimilar formulations, and if so have any patents been granted? You are requested to give an illustrative rather than complete answer.

I have made a simple search for patents owned by AbbVie mentioning adalimumab, and I found i.a. EP 1528933 B1 (A1) and EP 2359856 B1 (A2) protecting specific formulations.

Further, I made a quick search using the search terms "adalimumab" and "formulation" and among the results, I identified the following patent rights relating to various adalimumab formulations:

- EP 3 156 071 B1 (A3)
- EP 3 212 667 B1 (A4)
- US 9,821,059 B2 (A5)

2.2 In the defence, page 19-24, the defendants list a number of antibody based pharmaceutical products. The table and pertaining text is inserted in copy below. Have there been any attempts to patent a formulation of the below formulations or the active ingredients in other formulations, and if so have any patents been granted? You are requested to give an illustrative and not necessarily a complete answer. Please set out your answer in the grey column to the right.

Similar to the above, I have made a simple search using the term "formulation" and then combined with each of the actives given below.

"The table below shows formulations of other authorised antibodies and is adapted from tables published in the literature in 2010/2011. Antibodies are listed in order of decreasing concentration in the approved formulation.
…"

Sven Frøkjær har i erklæring af 3. april 2019 bl.a. anført:

"…
Introduction

2. I have been asked on behalf of Samsung Bioepis UK Limited ("SB") and Biogen (Denmark) Manufacturing ApS and Biogen (Denmark) A/S (together "Biogen") to provide this declaration in these proceedings pending before the Maritime and Commercial High Court [note: Case no. BS-39398/2018-SHR.]. I provide this declaration further to a declaration that I provided in the context of administrative appeal proceedings relating to the Utility Models DK 2018 00070 Y4 ("UM '070") and DK 2018 00071 Y4 ("UM '071") (together the "Utility Models") that are pending before the Danish Patent and Trademark Board of Appeal (my "First Declaration"). I understand that my First Declaration has also been filed in these proceedings. I repeat and build upon that declaration with my further opinions set out below.

3. For the purpose of preparing this declaration, I was provided with and have read a copy of the patent application WO 2014/039903 A2 ("Manning").

4. I have also been provided with and have read copies of the Utility Models. The Utility Models are registered in the name of Fresenius Kabi Deutschland GmbH. I understand that they relate to alternative formulations of adalimumab to those found in Humira® (the original adalimumab product).

5. I have considered whether the claims of the Utility Models contribute any technical teaching that I do not find in Manning or that is only distinguishable from Manning in a manner that is obvious ("nærliggende") to a person skilled in the art.

6. The questions I was asked in connection with the preparation of this declaration relate to what a notional "skilled person" would have done, or the considerations that the skilled person would have had, as of 23 May 2014. I have been asked to assume that the skilled person in this case is a formulation chemist or a protein chemist with an interest in the formulation of proteins, including antibodies, for therapeutic use. I have understood that the skilled person would have the "common general knowledge" ("CGK") of someone working in this field and would have access to all relevant literature. I was furthermore told that the skilled person would have knowledge of common methods in the field and access to carry out routine work and perform common experiments. Moreover, I was told that in this connection the skilled person would not have inventive skills, but would have a routine approach to his work.

Summary

7. In my opinion, the experiments presented in the Utility Models test formulations containing standard excipients, all of which were well known in the protein formulation field well before 2014. There is nothing unusual or surprising to me about any of the excipients tested. The methods used to screen and test stability were all routine methods. The formulations that are concluded to be best are not formulations that would be covered by the claims of UM '070 or UM '071 due to the requirement for inclusion of a surfactant and a citrate buffer stated in the claims. Moreover, even for the best performing of the formulations tested in the Utility Models, no improvement over Humira® was demonstrated.

8. At a high level the claims of the Utility Models concern aqueous formulations including the following constituents: (a) **adalimumab** antibody, (b) a **combination of histidine and citrate buffers**, (c) a **sugar stabiliser** selected from a given list at a concentration between 50 and 400 mM, (d) a specified **surfactant**, and (e) the **pH range** 5.0 – 6.7 (in claim 1 of UM '070 and claim 2 of UM '071). The claims also require that the formulations are free of (or contain only low levels of) phosphate buffer and amino acids other than histidine.

9. I discuss the disclosure of Manning in more detail further below, however in summary in Manning I find that for (a)-(e) above it teaches the following:

Antibody: The focus of Manning is only on aqueous adalimumab formulations.
Buffer: Tested formulations include a number of buffers (histidine, citrate, phosphate, succinate, tartrate, maleate and acetate). A number of buffer combinations are also tested, including the combination of histidine and citrate.
Sugar: Most of the tested formulations contain a sugar stabiliser, and the most commonly employed is mannitol. It is indicated that sorbitol and trehalose are at least as good stabilisers as mannitol and are readily substitutable. In the vast majority of formulations tested, the sugar was present at a concentration of between 50 and 400 mM.
Surfactant: The most commonly used surfactant in Manning is polysorbate 80. However, the Block G results would suggest to the skilled person that other surfactants, including polysorbate 20, are also suitable.

pH: the vast majority of formulations in Manning were held at pH 5.2, and that is a suitable pH.

10. In any event, in my opinion it would be obvious for the skilled person to substitute (i) mannitol for sorbitol or trehalose and/or (ii) polysorbate 80 for polysorbate 20 in an aqueous adalimumab formulation based on the data and teaching in Manning and their common general knowledge and experience of protein formulation.

The technical field and state of the art

11. I have been provided with the Statement of Defence that has been submitted by Biogen and SB in the present proceedings relating to an application by Fresenius for the grant of a preliminary injunction (the "Statement of Defence").

In section 7, the Statement of Defence discusses the relevant technical field, the person skilled in the art, the technical background of the alleged inventions (*frembringelser*) of the Utility Models and the descriptions of the Utility Models. I fully agree with the statements set out in in that section regarding the technical background to the case. Many of the statements regarding formulation of antibodies for therapeutic use are reflected in the 2013 edition of my textbook, and I have been informed that page 155 of that book has been submitted in the proceedings as Exhibit J and Chapter 8 of that book as Exhibit Æ. A further excerpt of that book is enclosed as Annex 2 to this declaration (excerpts from Chapter 6). Particularly, I would like to point to the sections of this textbook on pages 123-124 regarding the use of sucrose, trehalose, mannitol and sorbitol as stabilizers; on pages 155-157 regarding buffers; and on pages 167-170 regarding surfactants.

12. I have also been shown and have read the declaration of Professor Anette Müllertz dated 4 March 2019. I have commented on parts of this declaration below. However, where I have not commented on a particular part of Professor Müllertz's declaration, that does not necessarily mean that I agree with it.

13. In section 3.1 of her declaration, Professor Müllertz discusses what the considerations of the person skilled in the art would have been if he/she had been asked to formulate a protein-based pharmaceutical such as adalimumab. In doing so she quotes from my textbook as referred to above. I agree with her comments in this section. One small clarification I would make is that, whilst it is important to formulate isotonic solutions for injection, non-isotonic solutions can be administered by infusion and similarly if the product is to be delivered by infusion there may be more flexibility as to the pH of the formulation.

14. In the final sentence of the section, Professor Müllertz comments that "*[t]he number of possibilities when combining excipients is close to infinite*". In my view this is a mathematical formalism. In reality the person skilled in the art would take a more practical approach, based upon their common general knowledge and experience of formulating other proteins, including looking at the excipients which were commonly used in approved protein based pharmaceuticals, including the approved formulation of Humira itself. This more practical approach would lead to a much more manageable number of formulations [note: Furthermore, by 2014 formulation stability testing could be automated, allowing a large number (hundreds to thousands) of formulations to be tested in parallel, e.g. in 96-well plates].

As demonstrated by the approved formulations listed in the table at paragraph 7.8 of the Statement of Defence, in fact there were only a limited number of classes of excipients and a limited number of commonly used excipients within each of those classes. The person skilled in the art would have chosen combinations of those commonly used excipients as their starting point for a new formulation. Moreover, the skilled person would have known that there are likely to be many acceptable formulations and that typically one would have considerable latitude to substitute one excipient with another similar excipient from the same class.

The Utility Models

15. The Utility Models are concerned with the development of alternative formulations of adalimumab to that of AbbVie's Humira.

16. The therapeutic activity of an antibody depends on maintaining its three-dimensional structure and therefore the formulation of an antibody is intended to protect against chemical and/or physical destabilisation / degradation. This is reflected on page 3 of the specification of the Utility Models which explains that: "*the primary goal of formulation development is to provide a pharmaceutical composition that will support the stability of a biopharmaceutical protein during all stages of its production, storage, shipping and use*," and that this is important for the safety, efficacy and ultimately the commercial success of any biopharmaceutical.
The performance of antibody therapeutics can be impacted by a number of different factors that compromise protein stability, including temperature, mechanical stress (shear/shaking), light stress [note: In my experience, in early screening it is not standard practice to do light stress testing. Typically light stress is less of a concern in achieving satisfactory shelf-life provided product is adequately packaged.], pH and protein concentration. Physical instability of proteins involves changes in the secondary and higher order structures of the protein. Such instability can present itself in a number of different ways, including the formation of aggregates, changes in viscosity and turbidity, changes in pH and/or chemical modification of the protein, and may cause the protein to precipitate or adsorb to interfaces. Measuring changes in the amount of aggregation of the antibody (expressed as the amount of high molecular weight aggregates formed relative to the total amount of antibody – "%HMW") is a common indicator for physical stability of a formulation [note: Protein aggregation is a particular concern and needs to be prevented to the extent possible, as it can negatively impact upon biological activity, is implicated in immunogenicity and can ultimately lead to precipitation and the clogging of needles. Measuring protein aggregation is the most commonly used indicator of formulation stability]. The greater the amount of aggregation (typically measured as %HMW), the less physically stable the formulation is considered to be. Chemical instability of proteins involves chemical modifications such as the breakage of covalent bonds within the protein, leading to *e.g.* fragmentation of the original polypeptide chain or changes to individual amino acid side chains. This can be assessed by techniques such as (but not limited to) capillary electrophoresis and isoelectric focusing.

The Utility Models describe the preparation of a number of different formulations of adalimumab having different salt concentrations, pH, stabilisers and surfactant levels. These formulations were tested to determine their stabilisation of the antibody by exposing them to different physical stresses including heat, freeze/thaw

and mechanical agitation. The physical stability of the formulation was then studied, including by measuring the level of high molecular weight aggregates present by HPLC. The Utility Models describe these experiments as follows [note: English language version of the text included here and elsewhere in this declaration in connection with references to the descriptions or claims of the Utility Models is taken from the corresponding paragraphs of the description or claims of European Patent EP 3 148 510.]:

"*Thermal stress tests were performed by simply heating a sample of the relevant formulations at the stipulated temperature for the stipulated amount of time (typically 2 weeks or 4 weeks/1 month).*" (page 75)
"Mechanical stress tests were performed by simply mechanically shaking a sample of the relevant formulations at room temperature at 200rpm for the stipulated period of time (typically 24 hours or 48 hours)." (page 75)
"Light stress tests were performed by simply exposing a sample of the relevant formulations to 765W/m² light (in accordance with ICH Q1B guidelines of the European Medicines Agency in relation to photostability testing of new active substances and medicinal products) for 7 hours." (page 75)
"Isoforms profiles, aggregates and sub-visible particular of the three DoE2 formulations have been determined before and after freeze-thawing cycles (-80°C → room temperature) in order to assess whether the surfactant exerts any impact." (page 81 of UM '070 and page 80 of UM '071)

17. Companies aiming to launch a biopharmaceutical product, whether a new molecule or a biosimilar such as in the present case, need to satisfy the relevant regulatory authorities, including the EMA and FDA, that the product remains safe and efficacious during its approved shelf-life [note: The shelf-life is the period of time from the manufacturing date that a product is required to remain within its approved product specification while stored under defined conditions.] (which needs to be long enough for the product to be commercially viable – typically around two years) [note: For a biosimilar drug the stability would be expected to be similar to that of the reference product]. Maintaining physical and chemical stability of the protein during bulk processing and production of the drug product and its storage is an important part of this assessment. While the stability of new products will be assessed in long term storage, it is also common to perform "accelerated" stability studies in which product is stored under stressed conditions, at which product degradation and aggregation would be expected to be more rapid. Testing at elevated temperature (e.g. 40^{0}C and above) is common, as is stressing the product's stability in other ways such as mechanical agitation and exposing it to successive freeze-thaw cycles. Accelerated stability testing along the lines of the experiments described in the Utility Models is routinely used to provide an indication (in the short-term) of how the product is likely to perform under long-term storage.

18. Claim 1 of UM '070 and claim 1 of UM '071 are slightly different. Both require an aqueous formulation of adalimumab in which certain excipients are present/absent as follows:

- a histidine buffering agent or histidine buffer system,
- a citrate buffer,
- a sugar stabiliser, selected from a list, at a concentration of 50 to 400 mM,
- free of amino acids other than histidine or that these are included at a collective concentration of at most 0.1 mM, and

- free of a phosphate buffer or include a phosphate buffer at a concentration of at most 0.1 mM.

19. The differences between claim 1 of UM '070 and claim 1 of UM '071 are as follows:

- the list of sugar stabilisers in UM '071 expressly includes mannitol, whereas in UM '070 it does not,
- whilst both require the presence of a surfactant, UM '071 requires this to be polysorbate 20 (with no concentration specified), whereas UM '070 requires "*0.05 mg/ml to 2 mg/ml surfactant selected from polysorbate 20 or polysorbate 80*", and
- UM '070 has an additional requirement in claim 1 that the composition has a pH of between 5.0 and 6.7 and whilst this is not a requirement of claim 1 of UM '071 I note that it is the basis for claim 2 of UM '071.

20. Thus, these claims describe an adalimumab formulation containing as excipients a "*histidine buffering agent or histidine buffering system*", a "*citrate buffer*", a "*sugar stabiliser*" and a "*surfactant*" and having a pH between 5.0 and 6.7 (for UM '070). It was in 2014, and still is, very common to prepare an aqueous formulation of an antibody (or other proteins) including a buffer system, a stabiliser and a surfactant. The particular excipients mentioned in the claims of the Utility Models are (and were in 2014) amongst the most commonly used excipients for stabilising antibodies in aqueous solution. With reference to the statement in the Utility Models regarding the allegedly large number of excipients in Humira®, I note that the number of excipients in this formulation is comparable to those of other antibody products (see for example those listed in the table at paragraph 7.8 of the Statement of Defence and to those claimed by the Utility Models [note: Of the approved formulations listed in Table 7.8 of the Statement of Defence, Campath® and Simulect® share the same number of excipients as Humira® (they each have 5 excipients, counting the acid and base components of a buffer as a single excipient). Formulations according to the Utility Models also have the same number of excipients if NaCl is present as per the subsidiary claims in each.]).

21. The claims list a number of ''sugars stabilisers'', including trehalose, sucrose, sorbitol, and other sugars (including mannitol, in the case of UM '071 but not UM '070) that were widely used in the formulation of biopharmaceuticals, including antibodies, in 2014.

The Utility Models define the "sugar stabiliser" as a component that "*facilitates maintenance of the structural integrity of the biopharmaceutical drug, particularly during freezing and/or lyophilisation and/or storage (especially when exposed to stress)*", on page 23. This is fully in line with the definition of "stabiliser" on page 14, which lists amino acids such as histidine and sugar stabilisers such as sorbitol as examples of "*typical stabilisers*". The description on page 15 goes on to describe stability as the "*physical stability and/or chemical stability and/or biological stability of a component… during preservation/storage.*" Furthermore, page 23 describes a stable formulation as a formulation that performs "*particularly well in stress tests, especially in relation to aggregation, fragmentation and protein unfolding, which can be important indicators of stability and drug product viability*."

22. Further guidance on the stability targets set by the Utility Models is set out on pages 36-40 under the heading "*Other Parameters relating to the invention*". For example, it is stated that for thermal stress testing (28 days at 40^0C) the quantity of aggregates "*increases by no more than a factor of 4…, suitably by no more than a factor of 3, suitably by no more than a factor of 2.5, suitably by no more than a factor of 2.2*". Similar thresholds are set for other stress tests and protocols.

23. Protein aggregation is a complex phenomenon and as noted in a 2005 review article I published with Professor Daniel Otzen [note: Protein drug stability: a formulation challenge. Nat Rev Drug Discov 2005 Apr 4 (4) 298-306.] "*the prevention of aggregation remains largely empirical due to a lack of insight into the molecular details of the aggregation process*" although various qualitative relationships are recognized. Protein aggregation and the impact of sorbitol (or any other potential stabiliser) thereupon depends largely upon the particular protein under study, but also upon other factors including the other excipients present, the pH, contaminants and impurities etc [note: This is consistent with Professor Müllertz' observations at page 6 of her declaration that the performance of a formulation depends upon the interaction between different excipients: "*It very much depends on which other excipients are used and in which concentrations…It becomes obvious that the effects of the applied excipients are interlinked…*"]. I note that, none of the formulations tested in the Utility Models included sorbitol. The molecules identified as stabilisers in the formulations tested in the Utility Models were instead: trehalose dihydrate, lysine hydrochloride, mannitol and arginine monohydrochloride + aspartic acid [note: Additionally, polysorbate 80 was included in the formulations tested in Screening Experiment 2.].

24. In section 2.1 of her declaration, Professor Müllertz discusses the role of sorbitol as a stabilising agent. In particular she refers to comments in my First Declaration (repeated in this declaration at paragraph 54 below) that the skilled person would conclude from Manning that mannitol, sorbitol and trehalose have similarly good stabilising ability in the adalimumab formulations tested. She also refers to the fact that in the Statement of Defence it is observed that sugars such as sorbitol "may assist in stabilising proteins" and to the 2013 edition of my textbook which gives sorbitol as an example of a cosolvent that "can stabilise proteins in solutions because the cosolvent is preferentially excluded from surface interaction with the protein". Indeed, by 2014 it was well known that sorbitol can act as a stabiliser of a protein due to so-called "preferential exclusion" [note: This refers to the phenomenon that some stabilising small molecules are found at slightly lower concentrations in the region very close to the protein than in the bulk solution.] but whether or not it would in fact act as a stabiliser in any particular formulation would depend among other things on the particular protein and the other excipients present. For example, some proteins are inherently more stable than others and for such inherently stable proteins sorbitol may well not contribute further stability.

Accordingly, it cannot be said that sorbitol will always act as a stabiliser in the same way as it will inherently always act as a tonicity agent, as pointed out by Professor Müllertz at the end of her section 2.1 and with which I agree.

25. As regards the stability of formulations tested in the examples described in the Utility Models, only minimal differences were observed between the formulations for the majority of the stability tests in the two formulation screens (Screening Experiments 1 and 2). Moreover, there are a number of inconsistencies/oddities in the

results, which in the absence of any indication that the experiments have been repeated (let alone any statistical analysis carried out) leads me to doubt whether the differences observed are meaningful or simply the result of experimental error and/or variability. For example, the Utility Models report the following unlikely findings:

- in Figure 1 the data suggest that in a number of cases (6 out of 11) the concentration of adalimumab present in the formulation had increased after 4 weeks storage at 40^0C;
- In Figure 3 the amount of adalimumab fragments present in Formulation #20 appears to have increased between 0 and 2 weeks at 40^0C and then decreased again between 2 and 4 weeks; and
- In Figure 11 the amount of adalimumab fragments present in Formulation DoE2-9 appears to have decreased and then increased again within the space of 48 hours.

26. I think that it is difficult to draw any conclusions from Screening Experiment 1. In particular, I do not see the experimental basis for the conclusion that "*somewhat unexpectedly, formulations containing trehalose dihydrate as the sole stabilizer performed extremely well, especially in terms of fragmentation inhibition, unfolding inhibition and pH maintenance…*" (on which basis trehalose containing formulations were singled out for "fine-tuning" in Screening Experiment 2). Leaving to one side my concerns about how the experiments were conducted and whether or not the results obtained are within the margin of experimental error, I do not see anything in the results of Screening Experiment 1 (Figures 1-4) that makes the trehalose containing formulations (#s 18, 23 and 25) stand out from those containing other stabilisers. In fact the non-trehalose formulations (#s 19-22) were superior to the trehalose-containing formulations with regards to aggregation (Figure 2).

27. Screening Experiment 2 modifies Formulation 25 by adding the surfactant polysorbate 80. Three samples are tested, numbered Formulation 7 (no PS80), Formulation 8 (0.5 mg/mL PS80) and Formulation 9 (1 mg/mL PS80) [note: In addition, whilst the NaCl concentration of Formulation 25 in Experiment 1 was 100 mM, each of Formulations 7-9 in Experiment 2 only included 50 mM NaCl. No explanation is provided in the Utility Models for this discrepancy.].

Thermal, mechanical and light stress tests were performed and the impact on the formulation was investigated by analysis of protein content, aggregation, fragmentation, protein unfolding, pH screening and iso-form profile change versus the Humira® reference samples [note: In some experiments Humira® was included as a control/comparison, but in many of the experiments it was not.]. In addition, the effect of surfactant on freeze-thawing cycles was tested, about which it is concluded that *"there is no added value in adding a surfactant with the aim of preventing particles and aggregates formation/protein degradation in the course of freeze-thawing cycles. This highlights the effectiveness of the novel formulations irrespective of surfactant"* (page 81).

28. The conclusions for Screening Experiment 2 are that formulations 7, 8 and 9 show (i) comparable performance to Humira® when thermal stress is applied, (ii) minimal increase in aggregation upon mechanical shaking and (iii) increased degradation and isoforms profile change with respect to Humira® due to susceptibility of histidine to light and degradation products from PS80. Formulation 7 (without PS80) is concluded to have been slightly worse than the Humira® reference

samples *"but remarkably better than the others in histidine + Polysorbate 80 (0.5 or 1.0 mg/mL)"* (page 82).

29. The overall conclusion of the Utility Models, at page 82 , lines 22-28 (UM '070) / lines 15-20 (UM '071), is that "*the best composition, showing comparable or even improved characteristics with respect to Humira® upon different stressing conditions (thermal, mechanical, light) has been identified as:* [50 mg/mL adalimumab, 10 mM histidine, 200 mM trehalose dihydrate, 50 mM sodium chloride and WFI and sodium hydroxide q.b. to adjust pH to 6.4]". In light of Professor Müllertz's comments on these excipients in sections 3.2 and 3.3 of her declaration it is noteworthy that this formulation includes sodium chloride and does not include a surfactant. In my view there is nothing in the data to indicate that the formulations tested have any improved characteristics with respect to Humira®. In fact, Fig. 5 suggests that DoE2-8 and -9 perform worse than Humira® US (and also worse than Humira® EU at 2 weeks). DoE2-7 (without surfactant) performs slightly better than Humira® but shows higher fragmentation (Fig. 6), although this is (without additional documentation) ascribed to a contamination problem.

30. In my view the experiments described in both Screening Experiment 1 and Screening Experiment 2 are problematic, for a number of reasons, in particular:

- Multiple changes to excipients were made in several of the experiments (rather than following a systematic design in which only one excipient is changed in each experiment, and the effect monitored, or performed as a factorial design experiment), so it is very difficult to draw any conclusions as to the cause of any differences that were observed (even if assumed to be a "real" difference).

- The authors noted discrepancies in the results that were "unexplained" and considered that the samples may have been "contaminated" (see pages 76f lines 27-1 (UM '070), page 76, lines 20-25 (UM '071), page 77, lines 13-14 (UM '070), respectively page 77, lines 6-7 (UM '071) and page 77, lines 24-25 (UM '070), page 77, lines 18-19 (UM '071)). However, no steps were taken to confirm this possibility and to repeat the experiments. This compromises the results and makes it difficult to draw any conclusions from the data reported in the Utility Models.

- On top of the serious problems with the experimental design one simply does not know whether any apparent differences in physical stability are the result of differences in the composition of the relevant formulations or an artefact caused by contamination.

- The experiments are limited in scope, do not appear to have been repeated and therefore there are no error bars or statistical analysis to suggest that the (often very small) differences recorded were statistically significant. I have highlighted above a few examples of where it would appear clear that the differences between the different formulations are within the margin of experimental error, but it seems likely that this is a more far-reaching problem.

31. Thus, based on the experiments performed and the results obtained it is not in my opinion possible for the skilled person to draw conclusions as to the impact (if any) that the various excipients, either alone or in combination, may have on the physical stability of the tested formulations. The Utility Models do not adequately

address the impact of these different excipients on protein stability (e.g. by testing stability in the presence and absence (and at different concentrations) of a particular excipient while keeping all other components unaltered).

32. It is not clear to me how the conclusions that are drawn in the specification of the Utility Models relate to the claims of either UM '070 or UM '071. As set out above, claim 1 of both UM '070 and UM '071 requires the inclusion of a surfactant: UM '071 requiring polysorbate 20 and UM '070 requiring 0.05 – 2 mg/ml of either polysorbate 20 or polysorbate 80. None of the formulations in Screening Experiment 1 contained any surfactant and therefore none of those formulations fall within the claims. Further, the conclusion drawn from Screening Experiment 2 is that the PS80 containing formulations are inferior to those that do not contain any surfactant. As a result, the formulation which is finally concluded to be the best of all of those tested does not include a surfactant. I also note that, although UM '071 is limited to polysorbate 20, polysorbate 20 is not tested at all in the examples of the Utility Models (where only PS80 is tested).

33. Similarly, it is surprising to me that claim 1 of both Utility Models requires citrate buffer to be present in addition to histidine buffer when none of the formulations tested in the experiments include this combination. In fact, all of the formulations tested include histidine as the sole buffer (except for the instances where Humira® is included as a control) and on page 9 it is stated that the invention *"most suitably comprises one buffering agent only and an acid/base conjugate thereof"* (consistent with the stated objective of keeping the number of excipients to the minimum necessary). Citrate is merely included as an example in a list of possible buffers included in the definition of the term "buffer" or "buffer solution" on page 9.

34. The pH range that is singled out in the Utility Models also seems to have little in common with the pH ranges tested in the experiments. Claim 1 of UM '070 and claim 2 of UM '071 both include the requirement that the formulation is in the range of pH 5.0 to 6.7. However, all of the experiments use formulations with a much narrower pH range between 6.0 and 6.4 and no data is presented for the majority of this range from pH 5.0 to 6.0. The focus on this narrowed sub-range being preferred is further highlighted in numerous paragraphs in the description of the Utility Models, for example:

"*In a particular embodiment, especially where the buffering agent is an histidine buffering agent, the liquid pharmaceutical composition has a pH between 6.0 and 6.6. In a particular embodiment, the liquid pharmaceutical composition has a pH between 6.3 and 6.5. In a particular embodiment, the liquid pharmaceutical composition has a pH of about 6.4*" (page 22);
"*… Furthermore, liquid pharmaceutical compositions whose histidine buffer system maintains a steady pH 6.4 perform particularly well*" (page 23); and
"*At pH > 6.0 and in presence of sugar/polyols, all the formulas, including the references, are comparable…*" (page 70).

35. In addition, the "best" formulation according to the specification of the Utility Models (see the formulation in the penultimate paragraph on page 82 of both Utility Models) includes sodium chloride, whereas this is not a requirement of claim 1 of either Utility Model (although it is specified in a later claim in both cases).

36. In conclusion, in my opinion the experiments presented in the Utility Models test formulations containing standard excipients, all of which were well known in the protein formulation field well before 2014. There is nothing unusual or surprising to me about any of the excipients tested. The methods used to screen and test stability were all also routine methods. However, as I have described, I do not believe that it is possible to place any weight on these data alone to allow any meaningful conclusions to be drawn. Further, even if one were to rely on the conclusions drawn by the authors of the Utility Models themselves, the formulations that are concluded to be best are not formulations that would be covered by the claims of UM '070 or UM '071 due to their requirement for inclusion of a (particular) surfactant and a citrate buffer. Moreover, even for the best performing of the formulations tested in the Utility Models, no improvement over Humira® was demonstrated.

Manning

37. I understand that Manning was published on 13 March 2014. Manning is entitled "*Stable Aqueous Formulations of Adalimumab*" and, as the document explains on page 1, it relates to pharmaceutical compositions suitable for long-term storage both of adalimumab itself and biosimilar products. Manning is the surname of one of the named inventors.

38. The first section of Manning (from pages 1 to 26) describes the background to the claimed invention and introduces various "embodiments" of it. In the second section of Manning, from pages 26 to 109, there is a description of the various experiments undertaken, the data obtained, and the conclusions on the experiments are discussed.

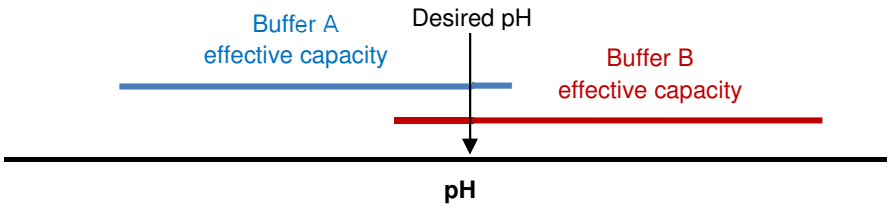
Description (pages 1-26)

39. A number of "*Embodiments of the Invention*" are described. For example, Embodiment I on page 17, describes a formulation which preferably comprises a polyol and a surfactant (polysorbate 20, polysorbate 80 and pluronic F-68 are given as examples). In addition, the formulation can comprise "*one, or any combination of two or more buffers*" from citrate, phosphate, succinate, histidine, tartrate and maleate (but not the specific combination of phosphate and citrate [note: The Humira® formulation used a combination of phosphate and citrate.]), and a pH preferably between about 5 to 6. As the skilled person would have known, the pH of the Humira® formulation was 5.2 so this pH range is entirely expected.

40. As such, the main excipients of an antibody formulation which I believe the skilled person would usually expect to see are present in Embodiment I on page 17 – buffer, stabiliser, surfactant and formulated to a standard pH range.

41. A more specific embodiment of this type is found on pages 5-6, which describes an adalimumab formulation comprising histidine buffer, mannitol (or sorbitol or trehalose) and polysorbate 80. As such, it contains all the classes of components from page 17 but with more precision (e.g. polysorbate 80 specifically, rather than "*a surfactant*"). The top of page 6 indicates this embodiment also includes the option of combining histidine with citrate, acetate, phosphate, maleate and/or tartrate buffers.

42. In general, most formulations comprise one buffer, and the list of buffers given on page 6 and in Embodiment I on page 17 is quite standard, although the skilled person would recognise that tartrate and maleate are less common. However, it was and is well known in the art that there are circumstances where using two buffers may be advantageous, and the skilled person would be aware that the Humira® formulation itself employed two buffers. One reason for using two buffers may be if the desired pH is towards the limit of the effective buffering capacity of one buffer, in which case another buffer can be added to provide overlapping buffering capacity at the desired pH, and so "reinforce" the buffering capacity of the formulation at the critical point. This is illustrated schematically below:



As shown in the above, using two buffers also increases the overall effective range of buffering capacity of the formulation.

43. I agree with Professor Müllertz's comments at section 2.1 of her declaration that citrate "*is a good buffer at pH levels around its pKa at e.g. 5.2*" and her reference to the above illustration (which is also included in the First Declaration) as demonstrating how *"[b]y combining these two buffers [*histidine and citrate*], the pH 5.2-5.3 of Imraldi is placed at a point where the buffers used have overlapping buffer capacity*".

44. Using a combination of citrate and histidine to maintain a pH of around 5.2 is advantageous as it provides for good buffering capacity if the pH were to fluctuate in either direction (i.e. with histidine having the greater buffering capacity if the pH rises and with citrate having the greater buffering capacity if the pH drops (in both cases from a starting point of pH 5.2)). In addition, and as noted by Professor Müllertz in her section 2.1, "*histidine also has a protein stabilising effect – beyond the stabilising effect that is a result of its buffering property, see to this end Manning, page 96, line 18, where it is specifically observed that histidine is found to be a stabiliser in the tested adalimumab formulations*". Further, by 2014 it was known that citrate could cause injection site pain [note: See for example Sek D, European Pharmaceutical Review (2012) issue 3, 10 July 2012: "*Breaking old habits: moving away from commonly used buffers in pharmaceuticals*". This review article by David Sek (from Pfizer) describes citrate as "*one of the most commonly used buffers*" in injectable formulations, but notes also the issue of short duration injection site pain associated with this excipient and that alternative buffers such as histidine may be advantageous in this respect.] and the use of the combination of the two buffers has the additional benefit of allowing less citrate to be used. For all these reasons I consider the combination of histidine and citrate to be a good choice of buffer at pH 5.2 and a combination that the skilled person would expect to work well (including in the light of Manning's Block H experiments considered further below).

45. Manning also recites various other embodiments that are described in the introductory pages. For example, Embodiment II on page 17 is specific to using single buffers not combinations, Embodiment III on page 19 is buffer free, Embodiment

IV excludes the surfactant etc. In broad terms, these other embodiments all appear to be variations on Embodiment I which includes all of the basic and familiar excipients of an antibody formulation.

Experiments (pages 26-109)

46. The experiments in Manning are divided into "Blocks" labelled A to H. Broadly, each block appears to have been intended to test a different aspect of the formulation (or several different aspects simultaneously). For example, as stated at the top of page 32, the Block A studies examined different buffer systems using Humira®, Block B repeated the Block A experiments using a proprietary biosimilar to Humira®, and so on. As such there is a logical design to the manner in which the experiments were carried out in Manning.

47. At the end of most of the Blocks, and in a Summary of Conclusions starting on page 107, Manning draws various conclusions on the relative performance of different formulation components and conditions. As a general comment on the experiments, I note that in most of the blocks the formulations were "stress tested" by measuring the level of aggregation and pH stability after (i) one week at 40°C and (ii) two weeks at 25°C. The vast majority of the formulations tested in Blocks A to H show a monomer content of >98% (indicating aggregation of less than 2%) on testing, and only very minor pH variation. While this makes it difficult to draw robust conclusions about the significance of these changes it indicates that the formulations are providing stable conditions for adalimumab and is a preliminary indication that a stable formulation can be achieved. The absence of major changes in stability between the different formulations tested in Manning suggests that there is plenty of scope to formulate adalimumab in a number of different, equally satisfactory, ways using a standard approach and a variety of the commonly used excipients (as described above). The data in Manning suggests that adalimumab is a fairly robust antibody and not very sensitive to significant changes in stability upon switching between the different excipients tested.

48. I note that each experiment was only conducted once, and the tests that the formulations were subjected to could have been more extensive; *e.g.* by conducting studies for longer than two weeks, or at higher temperatures than 40°C, or using a greater number of freeze/thaw cycles. I believe the skilled person would prefer to see the experiments repeated before endorsing the conclusions drawn in Manning regarding differences between different formulation components and conditions. However, in my opinion, it remains the case that the skilled person would recognise that the vast majority of formulations screened in Manning show very encouraging results and demonstrate good stability. Based on the excipients used by Manning and the way in which they have been combined, which was consistent with the common general knowledge in the field (including e.g. the Humira® formulation and the other approved formulations mentioned in the Table in section 7.8 of the Statement of Defence), the results are not surprising to me.

49. In section 3.2 of her declaration Professor Müllertz comments that "*it seems difficult to draw any general conclusions* [from Manning] *as to how to formulate optimal formulations other than perhaps those Manning himself set*[s] *out in his concluding remarks on page 107 et seq*". I note that Professor Müllertz refers to "optimal" formulations but does not comment on whether the majority of the formulations, would, nevertheless, be expected to have good stability, sufficient to enable pharmaceutical use. I note that elsewhere in her declaration Professor Müllertz uses the term "viable".

However Professor Müllertz does not explain what she means by "viable" nor is it clear whether or not she is seeking to draw a distinction between formulations that are "viable" or "optimal". To me, the small changes in the percentages between the performance of the different formulations disclosed in Manning suggest that if the "preferred" formulations are considered "viable", then so too would many other formulations tested in Manning. As explained above, in my view, many of the formulations tested (and not just those selected by Manning in his summary from page 107), would be expected to have satisfactory stability, e.g. to have similar stability to Humira® or for that matter, to the formulations tested in the Utility Models and discussed above.

As there is a large number of Blocks, I have been asked in particular to comment on Blocks D, G and H.

Block D

50. Block D comprises sixteen formulations "*designed to evaluate other stabilizers as alternatives to mannitol, such as sorbitol and trehalose*". The formulations are shown in Table D on page 47, and I note that formulations D1, D7 and D8 are the same as each other, except that they contain mannitol, sorbitol and trehalose respectively (at 65mM). Equally formulations D10, D11 and D12 are the same as each other, except that they contain mannitol, sorbitol and trehalose respectively (at 240mM). In my experience, and I believe that of the skilled person, both of these sugar concentrations are well within the range of what would ordinarily be expected.

BLOCK D STUDY DESIGN

Form No.	API	citrate	phosphate	sorbitol	trehalose	mannitol	NaCl	PS 80
1	Adalimumab biosimilar	8	18	0	0	65	100	0.1
2	Adalimumab biosimilar	8	18	0	0	65	100	0
3	Adalimumab biosimilar	20	0	0	0	65	100	0.1
4	Adalimumab biosimilar	20	0	0	0	65	100	0
5	Adalimumab biosimilar	0	20	0	0	65	100	0.1
6	Adalimumab biosimilar	0	20	0	0	65	100	0
7	Adalimumab biosimilar	8	18	65	0	0	100	0.1
8	Adalimumab biosimilar	8	18	0	65	0	100	0.1
9	Adalimumab biosimilar	0	20	65	0	0	100	0.1
10	Adalimumab biosimilar	0	10	0	0	240	0	0.1
11	Adalimumab biosimilar	0	10	240	0	0	0	0.1
12	Adalimumab biosimilar	0	10	0	240	0	0	0.1
13	Adalimumab biosimilar	10	0	0	0	0	150	0.1
14	Adalimumab biosimilar	10	0	0	0	0	150	0
15	Adalimumab biosimilar	0	10	0	0	0	150	0.1
16	Adalimumab biosimilar	0	10	0	0	0	150	0

51. The results of the various experiments set out in Block D show that the formulations containing sorbitol, trehalose and mannitol all perform well. With respect to pH stability, all the formulations were described as "*quite good*". Manning also concludes that "*both sorbitol and trehalose display better stability profiles than mannitol when used as the sole tonicity agent*", but mannitol does appear stabilising at "*levels preferably above 150* [mM]*"* (page 57). Further similar comments are made elsewhere in Manning.

52. In my opinion any differences between the sets of similar formulations containing sorbitol or trehalose compared to mannitol is very marginal. For example, below is an extract from Table D-2:

Form No.	API	citrate	phosphate	sorbitol	trehalose	mannitol	NaCl	PS 80	t0	t1	t2
1	Adalimumab biosimilar	8	18	0	0	65	100	0.1	99.28	98.21	98.96
7	Adalimumab biosimilar	8	18	65	0	0	100	0.1	99.30	98.19	98.94
8	Adalimumab biosimilar	8	18	0	65	0	100	0.1	99.28	98.14	98.85
10	Adalimumab biosimilar	0	10	0	0	240	0	0.1		97.93	98.54
11	Adalimumab biosimilar	0	10	240	0	0	0	0.1	99.32	98.65	99.00
12	Adalimumab biosimilar	0	10	0	240	0	0	0.1	99.32	98.53	98.96

53. There appear to be no differences between formulations D1, D7 and D8, but perhaps, arguable, there could be a very small potential difference between formulations D10, D11 and D12, with D10 slightly lower (although the t0 value being missing for D10 makes it difficult to draw any reliable conclusions in respect of that formulation). The absence of standard deviations makes it even more difficult to make any firm conclusions as to significant differences between the different measurements.

54. Overall, I believe from this that the skilled person would at least conclude that sorbitol and trehalose, if not better than mannitol, are at least as good as mannitol and so the three sugars have similarly good stabilising ability in the adalimumab formulations tested and are substitutable with each other at a 1:1 concentration (albeit swapping trehalose for sorbitol or mannitol at the same concentration would impact the tonicity of the formulation) [note: While sorbitol and mannitol are both monosaccharides (they are isomers of each other), trehalose is a disaccharide (made up of two glucose units). Accordingly, at the same mass concentration (g/L) sorbitol and mannitol would have twice the molar concentration (mol/L) as trehalose and thus exert twice the osmotic pressure of trehalose. This is because osmotic pressure of a compound in solution is proportional to the molar concentration of that compound.]. I do not believe that the skilled person would find this conclusion surprising, considering all three compounds are well-known stabilisers (and tonicity modifiers) that have been used in antibody formulations for some time.

55. In addition, this is also in accordance with the statement made in the Summary of Conclusions in Manning, which states on page 108 that "*other polyols, such as sorbitol and trehalose, appear to work about as well as mannitol and therefore may be substituted for mannitol if desired*", and with an embodiment described on page 5 which treats mannitol, sorbitol and trehalose as alternatives stating that the formulation

comprises "*mannitol (or sorbitol or trehalose)*", and several other indications in Manning (e.g. on page 3, lines 25-26; page 7, lines 6-9 and lines 22-29; page 18, lines 15-17; and page 22, lines 1-3) suggesting sugar substitution.

56. In section 3.2 of her declaration (page 10), Professor Müllertz comments that Manning's conclusions on page 57 in respect of sorbitol and trehalose displaying "*better stability profiles than mannitol*" would be taken as limited to the specific formulations tested in the Block D experiments and disagrees with my view that this is in accordance with his general conclusion on page 108 that sorbitol and trehalose "*appear to work as well as mannitol*". However, I consider these conclusions to be very closely aligned and believe that the skilled person would have drawn the conclusion that sorbitol and trehalose work at least as well as mannitol for the formulations tested in the different blocks of experiments in Manning.

57. Professor Müllertz goes on (page 11) to comment that "*Manning does not observe that mannitol, sorbitol and trehalose – in these "certain embodiments" [*in Block D*] or generally – can replace each other in a 1:1 concentration*". As explained above, in my view there is sufficient data in Manning to support the conclusion that for adalimumab formulations, mannitol, sorbitol and trehalose are substitutable with each other at a 1:1 concentration, in particular (as noted above) formulations D1, D7 and D8 provide a suitable comparison (each sugar being included at a concentration of 65 mM), as do formulations D10, D11 and D12 (each sugar being included at a concentration of 240 mM), the level of protein aggregation being similar in all cases.

Block G

58. One of the aims of Block G, as explained on page 75, was to evaluate two alternative surfactants to polysorbate 80 – namely polysorbate 20 and pluronic F-68 (both of which the skilled person would have been very familiar with).

59. In the Block G studies, pluronic F-68 was tested only at 0.1% w/w (1 mg/ml), but polysorbate 20 and 80 were each tested at 0.01% (0.1 mg/ml), 0.05% (0.5 mg/ml) and 0.1% (1 mg/ml) concentrations. In my opinion the tables over the following pages show almost all the formulations displaying good pH stability, and low aggregation (i.e. monomer content above around 98%).

60. The discussion on the results of Block G on page 86 state "*there appears to be some preference in terms of polysorbates over F-68 in terms of stability*", although noting that the difference is "*relatively small*". In addition, page 86 states that some results suggest polysorbate 20 is "*the best stabiliser at 0.1% for the Humira® formulation*", but otherwise again the differences are "*too small and variable*" to draw conclusions.

61. I believe the skilled person would agree, and recognise that there is little difference in the stability of the formulations employing the different surfactants tested – which all performed well.

62. I note that the Summary of Conclusions in Manning on page 108 states "*polysorbate 80 … provides significant protection against thermal stress … hence the selection of PS80 versus PS20 is a preferred feature*", and page 7 also refers to a "*distinct and surprising thermal stabilization advantage*" in selecting polysorbate 80 over 20 (and Professor Müllertz has also highlighted these passages). However, it is not apparent to me which data are said to support that conclusion, as little explanation is given.

63. In section 3.3 (page 17) Professor Müllertz states that "*[b]ased on Manning's very clear suggestion that PS 80 works better than PS20, the 'person skilled in the art' would, in my expectation, be consciously clear on not replacing PS80 with PS20*." I do not agree with this conclusion. Whilst, as noted above, Manning does draw a conclusion in this regard, the skilled person would have looked at the underlying data (in particular the stability data from Block G and Block H) to seek to understand this conclusion (which Manning himself describes as surprising) and would have found it to have no apparent basis. As a result, the skilled person would have expected formulations with PS20 to be stable (based both on the data in Manning and also on his/her knowledge that PS20 is one of the most commonly used surfactants in antibody formulations). Nothing in Manning would dissuade the skilled person from testing PS20. Accordingly, I disagree with Professor Müllertz's conclusion that the skilled person would have been deterred from pursuing such formulations.

Block H

64. As explained on page 87, the Block H experiments had three aims, one of which was to test different combinations of buffers. Table H on page 88 shows that the following combinations were tested:

a. Phosphate and citrate (as used in Humira® - the original adalimumab product)
b. Histidine and acetate
c. Histidine and succinate
d. Histidine and phosphate
e. Histidine and citrate
f. Succinate and acetate
g. Succinate and citrate
h. Buffer free

65. The following pages then show the testing of the formulations, and again the results are promising. The results of Block H are discussed on page 94, which states that the pH stability was acceptable for all the tested formulations, except the buffer free formulations. In addition, it is stated that "*in general, the best buffer combination appears to be His*[tidine]-*succinate*", but no clear "best" or "worst" is identified. I believe this reflects the fact that the skilled person would conclude that all the combinations tested show good stability and promise. I also consider the skilled person would observe that, whilst citrate was identified as the least-well performing single buffer in the Block A experiments, the histidine/citrate and succinate/citrate combinations appear to perform as well as the other combinations in Block H.

66. At the end of section 3.2 of her declaration (page 11) Professor Müllertz comments that she does not agree with my view that Manning, in the context of Block H, does not identify any particular formulation as clearly better or worse than the others. In her opinion formulation 12 is identified as the most stable formulation. I do not agree that the skilled person would reach such a conclusion. As noted above (and in the First Declaration) on page 94 Manning comments that *"[i]n general, the best buffer combination appears to be His-succinate (Formulations 7 and 12)*" in relation to the Table H-2 data. In my view, the skilled person would have reviewed the data in each of the Block H Tables and would have come to the same conclusion that I reached, namely that no clearly "best" or "worst" formulation is identified

[note: Table H-5 ("percentage of main bands seen in the cIEF profile of formulations in Block H") does not even include formulation 12.]. As noted above, the absence of standard deviations makes it even more difficult to identify any clear and significant differences.

67. I note that in the Summary of Conclusions on page 107, it is stated that, if a single buffer is used, then histidine appears best, with the histidine-succinate buffer [note: At the end of section 3.2 of her declaration (bottom of page 11), Professor Müllertz pointed out that in the First Declaration I had stated this to be "histidine-acetate" which I confirm was a typographical error.] combination also showing "*very good stability*".

Comparison of Manning to the Utility Models

68. I have been asked to consider whether the two Utility Models would have taught the skilled person reading either of them anything more than Manning.

69. At a high level the claims of the Utility Models concern aqueous formulations including the following constituents: (a) **adalimumab** antibody, (b) a **combination of histidine and citrate buffers**, (c) a **sugar stabiliser** selected from a given list at a concentration between 50 and 400 mM, (d) a specified **surfactant**, and (e) the **pH range** 5.0 – 6.7 (cf. claim 1 of UM '070 and claim 2 of UM '071). The claims also require that the formulations are free of (or contain only low levels of) phosphate buffer and amino acids other than histidine.

70. As such, below I first briefly summarise my opinion of what Manning would teach the skilled person about these aspects, then consider if either Utility Model teaches anything further.

Analysis in respect of Manning

71. As regards Manning I find it teaches the following for each of the key elements:

Antibody: The sole focus is aqueous adalimumab formulations.
Buffer: A number of buffers are considered including histidine, citrate, phosphate, succinate and acetate, and a number of combinations are also tested. As I noted, from the Block H results, the various buffer combinations (including the combination of histidine and citrate) show good results.
Sugar: Most formulations contain a sugar stabiliser, and the most commonly employed is mannitol. I do not believe this would be of any surprise to the skilled person as it was a common and well-known component of many formulations at the time. However, as I explained above the Block D results, and other statements in Manning, indicate that sorbitol and trehalose are at least as good at stabilising these adalimumab formulations as mannitol and are readily substitutable (on a 1:1 basis). In the vast majority of formulations tested, the sugar was present at a concentration of between 50 and 400 mM.
Surfactant: The most commonly used surfactant in Manning is polysorbate 80. Again I do not believe this would be of any surprise to the skilled person. In line with what the skilled person would expect, in my opinion the Block G results would suggest to the skilled person that other surfactants would also be suitable, including polysorbate 20. I commented above that I believe the skilled person would not identify any significant differences in the contributions of PS80 and

PS20 to adalimumab stability, and if developing a new adalimumab formulation he/she would certainly have considered both surfactants.
pH: The vast majority of formulations in Manning were held at pH 5.2, and that is a suitable pH [note: I assume that Manning has focused on pH 5.2 because that is the pH of Humira®. The only other pH tested in Manning is pH 3.5, tested in the Block E experiments.].

72. If the skilled person looked at the teaching of Manning as a whole then I believe they would be encouraged to see that many formulations are tested, and the vast majority show promising stability. I believe that the skilled person would take this as an indication that adalimumab is a relatively resilient antibody and amenable to being formulated using common buffers, sugar stabilisers and surfactants, to obtain an alternative to the Humira®-formulation.

73. As I have explained above, I do not agree with Professor Müllertz's comment that "*it seems difficult to draw any general conclusions [*from Manning*] as to how to formulate optimal formulations other than perhaps those Manning himself set[*s*] out in his concluding remarks on page 107 et seq*". As I have noted the skilled person would have been impressed by how resilient adalimumab appears to be, in the sense of having broadly similar stability across many of the formulations tested by Manning. Whilst not necessarily "optimal", many of the formulations tested (and not just those selected by Manning in his summary from page 107 and Table M), would be expected to have satisfactory stability for the purposes of pharmaceutical use. The skilled person would simply have regarded the Table M formulations as the particular formulations that Manning had himself chosen to work with and would not have viewed this as excluding the many other formulations which had been shown to have good stability in the various Blocks of experiments.

74. Further, as I have described above at paragraphs 15 to 36, the Utility Models themselves do not allow any conclusions to be drawn regarding "optimal" adalimumab formulations and the claims do not require any particular level of stability to be achieved. In fact, as I have explained, the Utility Models do not even test any formulations which would fall within their own claims, as neither citrate nor PS20 are present in any of the formulations tested. Furthermore, the teaching of the Utility Models is that PS80 containing formulations are inferior to those that do not contain any surfactant and none of the formulations that were tested had a pH of less than 6.0.

In section 3.3 of her declaration Professor Müllertz responds to the question of how the skilled person would modify formulation 11 from Table H of Manning "*with a view to provide a viable formulation that allows for fewer excipients*"[note: I note that in this context she has been asked to deal with "viable" formulations rather than the "optimal" formulations she has referred to elsewhere in her declaration when considering the teaching of Manning.].

In my experience, reducing the number of excipients is a secondary consideration in the development of biological pharmaceuticals. Developing a stable formulation with the necessary shelf life is the primary objective and reducing the number of excipients only becomes of potential interest if all other considerations are equal between the formulations being selected from. A formulation having an inferior performance in any way (e.g. physical or chemical stability or side effect profile) would not be preferred simply because it had fewer excipients. In the case of adalimumab the skilled person would be well aware of the composition of the

Humira® formulation by the priority date of the Utility Models (as set out in the Statement of Defence) and would not have considered it to contain an unusual number of excipients. As set out above, the Utility Models do not report tests on any formulation prepared according to the claims of either Utility Model (neither citrate nor PS20 are included in any of the formulations tested). Accordingly, the experiments in the Utility Models do not demonstrate that a formulation made according to their claims, can have fewer excipients than Humira®, yet still achieve comparable or improved properties.

75. Professor Müllertz explains that in her view, the skilled person would consider what she refers to as Manning's "four teachings". As set out in my own summary of the key teachings of Manning at paragraph 71 above, I agree with her that it teaches the use of a pH of around 5.2 (her teaching (1)), which is the pH of the Humira®-formulation. In her teaching (2) Professor Müllertz singles out the use of either histidine alone or histidine-succinate as a buffer. As I have explained above, in my view the experimental results in the Utility Models teach that all of the buffers tested resulted in "viable" formulations. A skilled person developing an alternative formulation of adalimumab would not be deterred from proceeding with any of the commonly used buffers tested in Manning, and he/she would proceed with any of those buffers, based upon the common general knowledge and any individual preference. As mentioned in paragraphs 43 – 44 above, Professor Müllertz and I agree that the combination of citrate and histidine is a good choice of buffer for an adalimumab formulation at pH 5.2 and, as also noted above, this choice of buffer combination appeared to work as well as the other buffers tested by Manning in the Block H experiments.

76. Professor Müllertz's teaching (3) is that arginine and/or glycine should be used as stabilisers/tonicity modifiers as both work better than mannitol (which works well at concentrations exceeding 150mM, preferably exceeding 200mM) and that sorbitol and trehalose appear to work about as well as mannitol. As I have set out above, most of the formulations in Manning contain sorbitol, trehalose or mannitol and the vast majority of those formulations are found to be stable, formulations. Manning's experiments make it difficult to directly compare the impact of glycine, arginine and the various sugars tested (mannitol, trehalose and sorbitol). In experiment C Formulations 3, 4 and 6 are identical, except for the inclusion of 65mM mannitol (Formulation 3), 65mM glycine (Formulation 4) or 65mM arginine (Formulation 6). The differences in stability that are reported between these different formulations are very small. In Table C-2 the monomer content after 2 weeks at 25^0C is marginally lower for the mannitol containing formulation (Formulation 3) than for the glycine or arginine-containing formulations (Formulations 4 and 6). Conversely in Table C-3, the percent purity after 2 weeks at 25^0C is marginally higher for the mannitol containing formulation. I disagree that one can conclude based on the data in Manning that either glycine or arginine are better stabilisers of adalimumab formulations than mannitol (or sorbitol or trehalose).

77. Further Professor Müllertz also comments that the skilled person would be cautious about using NaCl in an adalimumab formulation and that, if NaCl is used, it should be at concentrations that do not exceed 75-100 mM. I agree that by 2014 it was well known that high concentrations of NaCl could have a negative effect on protein stability. Therefore the skilled person would have been motivated to avoid high concentrations of NaCl, preferring to use other tonicity agents. Accordingly if, as Professor Müllertz suggests, the goal of the formulator was to try to reduce

the number of excipients, then the skilled person would, on the basis of their common general knowledge, immediately consider removing NaCl and increasing the concentration of sugar in order to adjust the tonicity to the target level. However, I note that all of the formulations tested in the Utility Models include NaCl and it is expressly included (at a concentration between 25 and 100 mM) in claim 8 of UM '070 and claim 9 of UM '071.

78. As I have explained above, I do not agree with Professor Müllertz's teaching (4) in relation to the use of PS80 instead of other surfactants such as PS20 and F-68. In my view the skilled person would consider using both PS80 and PS20, based on the teaching of Manning.

79. Professor Müllertz goes on to explain that in her view the skilled person would focus on the formulations in Manning's Table M as well as formulation 12 from Table H. I do not agree that the skilled person would have this particular focus for the reasons I have given above.

80. In her sections "Re removal of excipients" and "Re substitution of excipients" Professor Müllertz comments that the skilled person would, in her view, based on the teachings in Manning "*try formulations where citrate and/or NaCl and possibly also mannitol are removed – and where succinate, glycine and/or arginine are added*".

81. As I have explained above, I do not agree that the skilled person would strive to achieve a formulation with fewer excipients than Humira® unless all other factors, in particular the stability profile, were equal. Further, I do not agree that the skilled person would take this approach based on the teachings in Manning. As I have already explained, in my opinion the main teaching of Manning is the vast majority of the formulations tested were stable so that the skilled person would have been encouraged to conclude that adalimumab is a robust antibody which could be formulated with standard excipients to achieve stable formulations.

Analysis with respect to UM '070

82. With respect to Manning, I have explained that the vast majority of the formulations tested show good results. I believe the skilled person would consider that there are a large number of promising formulations in Manning which could be selected for further investigation. One of these, is formulation H11 on page 88. That formulation meets every criteria of claim 1 above, except that it employs mannitol as the sugar stabiliser:

Form No.	API	protein	citrate	phosphate	succinate	HIS	ACETATE	Gly	Arg	mannitol	NaCl	PS80
Form No.	API	protein	citrate	phosphate	succinate	HIS	ACETATE	Gly	Arg	mannitol	NaCl	PS80

This formulation comprises 50 mg/ml adalimumab, 10 mM citrate, 10 mM histidine, 65 mM mannitol, 100 mM sodium chloride (not relevant to claim 1) and 0.1% (1 mg/ml) polysorbate 80. Table H-1 on page 89 confirms the pH of formulation was 5.2. It also positively states there is no phosphate, or glycine or arginine (two other commonly used amino acid stabilisers).

83. As I explained above, Manning contains teaching supported by data that either sorbitol or trehalose (both of which are listed in part (c) of claim 1 above) could be

substituted for mannitol at a 1:1 concentration. Making such a substitution is more than a mere suggestion, with Manning positively stating that sorbitol and trehalose "*may be substituted"* for mannitol if desired.

84. In any event, in my opinion it would be obvious for the skilled person that such a substitution could be made based on the data and teaching in Manning and their knowledge and experience of formulation.

Analysis with respect to UM '071

85. With respect to claim 1 of UM '071, formulation H11 in Manning shown above differs from claim 1 of UM '071 only in that formulation H11 uses polysorbate 80 and not polysorbate 20 as the surfactant.

86. I have explained that polysorbate 80 and 20 were both well-known and widely used in antibody formulation by 2014, and that the skilled person would have been experienced with working with both. I have noted there is some suggestion in Manning that polysorbate 80 should be preferred due to advantages with respect to thermal stability. However, that is secondary to the primary role of a surfactant, and as I have explained I believe the skilled person would be skeptical that Manning provides sufficient evidence to show there is a meaningful difference. In addition, on page 86 Manning identifies an instance where polysorbate 20 performs better than polysorbate 80, and I believe that this would reinforce to the skilled person that the two are likely to be comparable in their performance.

87. Therefore, in my opinion, as both polysorbate 80 and 20 perform the same role, are chemically closely related compounds, and were both very well known in antibody formulation (and two of a very small number of commonly used surfactants), the skilled person would consider it obvious and entirely routine to switch between the two and so either could be used to produce a viable formulation of adalimumab for pharmaceutical use. As I have explained above I do not agree with Professor Müllertz's suggestion that the skilled person would be "consciously clear" on not replacing PS80 with PS20.

Conclusion

88. The Utility Models use standard approaches to test formulations containing excipients that were well known and commonly used in other commercial antibody formulations in 2014. Given my concerns over the way in which the experiments described in the Examples were performed, one cannot place much weight on the results or the conclusions drawn in the Utility Models. However, even if taking the data at face value, they do not amount to anything that is in any way out of the ordinary or unexpected. Even for the best performing of the formulations tested in the Utility Models (which as I have noted would not appear to fall within the scope of the claims in any event), no improvement over the Humira® formulation was demonstrated. Formulations containing polysorbate 20 or the combination of citrate and histidine, as required by the claims of the Utility Models, were not even tested in the Examples.

89. Manning is very similar in its general scope to the Utility Models – as I have explained above, Manning discloses a number of promising formulations some of which match those that are claimed in the claims of the Utility Models. To the extent that there are differences between the particular formulations in Manning that

I have highlighted above and the formulations with which the Utility Models are concerned (aqueous formulations of: (a) adalimumab, (b) a combination of histidine and citrate buffers, (c) a sugar stabiliser selected from a given list at a concentration between 50 and 400 mM, (d) a specified surfactant, and (e) the pH range 5.0 – 6.7 (cf. claim 1 of UM '070 and claim 2 of UM '071)), the difference is trivial. To switch from one excipient to the other would be routine formulation work based on the data and teaching in Manning and the skilled person's knowledge and experience of protein formulation."

Anette Müllertz har i erklæring af 11. april 2019 anført bl.a.:

"…
I have been provided with copies of the following additional documents which I have reviewed before providing my answers to the below questions:

- Rejoinder of 4 April 2019
- Declaration of Sven Frøkjær of 3 April 2019 (exhibit AV). According to paragraph 2 of Sven Frøkjær's supplementary declaration "*I [i.e. Sven Frøkjær] repeat and build upon that declaration [exhibit AO] with my further opinions set out below*".
- Patent application WO 2014/068029 A1 (Rast) (exhibit W)
- Patent application WO 2012/121754 A1 (Dai) (exhibit Y)
- Patent application WO 2010/129469 A1 (Fraunhofer) (exhibit Z)
- Application for EP '510 (exhibit V)
- Wang (1999), *Instability, stabilization, and formulation of liquid protein pharmaceuticals* (exhibit 26)
- Wang (2007), *Antibody Structure, Instability, and Formulation* (exhibit 27)
- NHS (2018), *Update on development of biosimilar versions of adalimumab with particular focus on excipients and injection site reactions* (exhibit 28)
- Frøkjær (2013), *Pharmaceutical Formulation Development of Peptides and Proteins*, page 168 (exhibit 29)
- Sek (2012), Breaking old habits: Moving away from commonly used buffers in pharmaceuticals (exhibit 30)

2. ORIGINAL DECLARATION
2.1 Upon having reviewed the above documents, please advise whether you would like to modify any of your observations set out in your original declaration of 4 March 2019.

I maintain the observations set out in my original declaration.

3. Further on manning vs UM '70 and UM '71
3.1 In paragraph 7 of Sven Frøkjær's supplementary declaration, Sven Frøkjær explains that the utility models-in-suit regard adalimumab formulations that comprise "*standard excipients, all of which were well known in the protein formulation field well before 2014*". Sven Frøkjær elaborates this observation in i.a. paragraphs 20 et seq. In paragraph 20, Sven Frøkjær observes that the claims in the utility models-in-suit "*describe an adalimumab formulation containing as excipients a "histidine buffering agent or histidine buffering system", a "citrate buffer", a "sugar stabiliser" and a "surfactant" and having a pH between 5.0 and 6.7 (for UM '070). It was in 2014, and still is, very common to prepare an aqueous formulation of an antibody (or other proteins) including a buffer system, a stabiliser and a surfactant. The particular excipients mentioned in the claims of the*

***Utility Models are (and were in 2014) amongst the most commonly used excipients for stabilising antibodies in aqueous solution.*" In paragraph 36, Sven Frøkjær concludes "*in my opinion the experiments presented in the Utility Models test formulations containing standard excipients, all of which were well known in the protein formulation field well before 2014. There is nothing unusual or surprising to me about any of the excipients tested.*"**

Do you agree with Sven Frøkjær?

I agree that on the priority date, the individual excipients used in the adalimumab formulations of the utility models-in-suit were all well known in the general context of protein formulations. Most if not all of the individual excipients mentioned in the utility models-in-suit are also mentioned in Manning. However, to my knowledge, the utility models-in-suit regard a new and creative combination of already known excipients – in both qualitative and quantitative terms.

As I have explained in my original declaration of 4 March 2019, the qualitative selection and in turn the quantitative determination of concentration of excipients to be used in a particular protein formulation is a balancing act. A formulation that works for one protein may not work for another. It is an art to develop a formulation that works for a particular protein. As a good example, I point to Sven Frøkjær and Daniel Otzen's article discussed in paragraph 23 of Sven Frøkjær's supplementary declaration where it is observed that ""*the prevention of aggregation remains largely empirical due to a lack of insight into the molecular details of the aggregation process" although various qualitative relationships are recognized. Protein aggregation and the impact of sorbitol (or any other potential stabiliser) thereupon depends largely upon the particular protein under study, but also upon other factors including the other excipients present, the pH, contaminants and impurities etc.*[10]" The cited footnote 10 is a reference to my original declaration. Sven Frøkjær's footnote 10 reads: "*This is consistent with Professor Müllertz' observations at page 6 of her declaration that the performance of a formulation depends upon the interaction between different excipients: "lt very much depends on which other excipients are used and in which concentrations ... lt becomes obvious that the effects of the applied excipients are interlinked ...""*. Sven Frøkjær offers a further example in *Pharmaceutical Formulation Development of Peptides and Proteins*, page 168 (2013) (exhibit 29):

> Surfactants are well known to prevent the denaturation and aggregation of insulin (Kerwin, 2009; Lougheed et al., 1983; Sato et al., 1984). However, the choice of surfactant and the final concentration optimal for stabilization is quite dependent on a variety of factors, including other formulation ingredients (e.g., sugars), protein concentration, headspace in the container, the type of container, and test methodology.

Sven Frøkjær's observations are also backed by Wang (1999) and Wang (2007).

3.2 In paragraph 9 of Sven Frøkjær's supplementary declaration, Sven Frøkjær explains:

"*9. I discuss the disclosure of Manning in more detail further below, however in summary in Manning I find that for (a)-(e) above it teaches the following:*

***Antibody**: The focus of Manning is only on aqueous adalimumab formulations.*

***Buffer**: Tested formulations include a number of buffers (histidine, citrate, phosphate, succinate, tartrate, maleate and acetate). A number of buffer combinations are also tested, including the combination of histidine and citrate.*
***Sugar**: Most of the tested formulations contain a sugar stabiliser, and the most commonly employed is mannitol. lt is indicated that sorbitol and trehalose are at least as good stabilisers as mannitol and are readily substitutable. ln the vast majority of formulations tested, the sugar was present at a concentration of between 50 and 400 mM.*
***Surfactant**: The most commonly used surfactant in Manning is polysorbate 80. However, the Block G results would suggest to the skilled person that other surfactants, including polysorbate 20, are also suitable.*
***pH**: the vast majority of formulations in Manning were held at pH 5.2, and that is a suitable pH.*"

Sven Frøkjær elaborates the above observations in paragraph 71 of his supplementary declaration.

Do you agree that Manning offers the above teachings?

In my opinion, there is a difference between what Manning describes and what Manning teaches.

I agree that Manning describes "aqueous adalimumab formulations", and that Manning describes different formulations that comprise different buffers, sugars, surfactants and exhibit different pH levels.

However, when it comes to Manning's general teachings, these are set out in Manning, page 107-109, including Table M. In paragraph 3.2 of my original declaration, I have tried to explain what I would expect 'a person skilled in the art' to take away from Manning, both in terms of which technical features that seem to have a positive effect when applied in adalimumab formulations and in terms of which technical features that seem to have a negative effect when applied in adalimumab formulations in the context of Manning.

In respect of the above citation from Sven Frøkjær's supplementary declaration, I note the following:

- Re 'Buffer': I agree that Manning tests H11 that among other excipients comprises a histidine and citrate buffer combination. After having tested this formulation and many other formulations, Manning on page 107 concludes that histidine is the best single buffer, that histidine and succinate is the best combination buffer and that the combination of citrate and phosphate should be avoided.
- Re 'Sugar': I disagree that Manning concludes that "*sorbitol and trehalose are at least as good stabilisers as mannitol*". On page 108, line 3-4, Manning concludes that "*sorbitol and trehalose appear to work about as well as mannitol*". In my understanding, "*about as well*" is "omtrent så godt", i.e something that is less than equally good. That this is not pure semantics is backed by the PLS analyses that Manning presents on page 94-107. On page 108, Manning clearly does not suggest that sorbitol and trehalose are at least as good as mannitol.
- Re 'Surfactant': I agree that Manning in Block G tests formulations that comprise different stabilisers and surfactants. After having tested the formulations in Block G and many other formulations, Manning on page 108 concludes that "*Surprisingly, polysorbate 80 (PS 80) provides significant protection against thermal stress. While the mechanism of stabilization is not known, it appears that other surfactants*

tested (PS 20 and F-68), do not appear to be nearly as effective as PS 80. Hence the selection of PS80 versus PS 20 is a preferred feature of the present invention."

In my opinion, it is important to appreciate that Manning displays and tests multiple different formulations. In the context of Manning's tests of particular formulations, Manning draws a number of specific observations linked to the particular tests in questions, namely those of Blocks A-H. A 'person skilled in the art' cannot draw any general teachings from these specific observations. The general teachings that a 'person skilled in the art' can take away from Manning are those set out on page 107 et seq. These teachings are backed by the PLS model A-C analyses that Manning explains in details on pages 94-107.

3.3 In paragraph 3.2 of your original declaration, you explain that Manning provides the 'person skilled in the art' with four particular teachings. In paragraphs 75 et seq. of Sven Frøkjær's supplementary declaration, it is suggested that these four teachings are yours rather than Manning's teachings. Please advise whether you agree.

The four teachings set out in paragraph 3.2 of my original declaration represents a resumé of the general teachings that Manning provides on page 107-108. So just for clarification, the teachings are Manning's, not mine.

3.4 In the defendants' rejoinder, paragraph 3.1, the defendants state as follows:
"As a starting point Professors Frøkjær and Müllertz appear to agree as to what kind of competences to expect from the relevant skilled person/team in the technical field of the Utility Models. Also, the experts would appear to agree that when embarking on the task of formulating a formulation comprising adalimumab at the priority date of the Utility Models (i.e. 23 May 2014 ("Priority Date")), a skilled person would have found it relevant to target a solution that

1. ***includes a buffer system ensuring an appropriate pH;***
2. ***is preferably isotonic;***
3. ***includes one or more stabilisers; and***
4. ***includes a surfactant.***

In the context of doing so Professors Frøkjær and Müllertz also appear to agree that the skilled person would have known that of the different excipients which could be used to pursue these targets, some may have more than one function.

Furthermore, there seems to be agreement between the experts that even if many excipients could theoretically have been used in an adalimumab formulation, certain excipients were more commonly used at the Priority Date, both in approved protein-based pharmaceuticals in general and in known adalimumab formulations, including Humira® itself. It also seems to be common ground that the skilled person would have chosen as his/her starting point for a new formulation, a formulation with combinations of those commonly used excipients.

As regards buffers, the experts seem to agree that the combination of histidine and citrate would, in the eyes of the skilled person, have presented itself as a good choice of buffer in an adalimumab formulation at pH 5.2 at the Priority Date. The formulation of Humira® was already known to be pH 5.2.

It also seems to be acknowledged by all experts that histidine would, at the Priority Date, have been expected by the skilled person to be capable of acting as a stabiliser of protein formulations."

Do you agree to the above factual points?

I have taken no position as to the 'person skilled in the art'
I have not been asked to consider who the 'person skilled in the art' is. In my understanding, this is a legal question, and I have been asked by Fresenius to base my assessment on the defendants' suggestion that the 'person skilled in the art' is a "*formuleringskemiker" [formulation chemist] or "proteinkemiker" [protein chemist] "med interesse for formulering af proteiner, herunder antistoffer til terapeutisk brug" [with an interest in the formulation of proteins, including antibodies, for therapeutic use]*". Please see the preamble in my original declaration of 4 March 2019.

Adalimumab formulations need not incorporate the alleged four characteristics
In respect of the above four suggested characteristics of an adalimumab formulation I note the following: I believe that proteins for therapeutic use may be formulated in many different ways. By way of example, whereas Manning describes aqueous formulations, Rast describes non-aqueous liquid formulations, and Dai describes lyophilised formulations. The formulations in Rast and Dai and some of the formulations in Manning do not combine the four alleged characteristics. It appears to me that Sven Frøkjær does not agree with the above points either, as he in paragraph 13 of his supplementary declaration explains that *"whilst it is important to formulate isotonic solutions for injection, non-isotonic solutions can be administered by infusion and similarly if the product is to be delivered by infusion there may be more flexibility as to the pH of the formulation*."

A particular excipient may have more than one function in an adalimumab formulation
I agree that the excipients available to the 'person skilled in the art' may have more than one function. By way of example I take note that Sven Frøkjær and I agree that histidine works both as a buffer and as a protein stabiliser beyond the buffering effect, cf. Sven Frøkjær's supplementary declaration, paragraph 44, where he observes:

> 44. Using a combination of citrate and histidine to maintain a pH of around 5.2 is advantageous as it provides for good buffering capacity if the pH were to fluctuate in either direction (i.e. with histidine having the greater buffering capacity if the pH rises and with citrate having the greater buffering capacity if the pH drops (in both cases from a starting point of pH 5.2)). In addition, and as noted by Professor Müllertz in her section 2.1, "*histidine also has a protein stabilising effect – beyond the stabilising effect that is a result of its buffering property, see to this end Manning, page 96, line 18, where it is specifically observed that histidine is found to be a stabiliser in the tested adalimumab formulations*". Further, by 2014 it was known that citrate

Many different excipients may be used in the context of pharmaceutical protein formulations
In respect of the paragraph starting with "*Furthermore, there seems…*", I am not sure exactly which facts that the defendants believe are agreed to by me and Sven Frøkjær. I hope the following points clarifies my position:

- I agree that on the priority date, many specific excipients could have been used in pharmaceutical protein formulations.

- I also agree that on the priority date, it seems – as a statistical phenomenon - plausible that some particular excipients were more commonly used than others in approved pharmaceutical formulations. However, it seems to me that in practice there are no 'common denominators' when it comes to the choice of specific excipients actually used in approved pharmaceutical products. To illustrate, I refer to the list of approved products in paragraph 7.8 of the defence. I moreover refer to the list set out in Table 1 in Wang (exhibit 26 and 27). Also for a number of approved adalimumab formulations (other than Humira®) published after the priority date, quite different excipients are used, see (exhibit 28).

<u>On the priority date, the 'person skilled in the art' had no basis for considering the combination of histidine and citrate to be a good choice of buffer in an adalimumab formulation</u>

In the paragraph starting with "*As regards, …*", the defendants observe that "*the experts seem to agree that the combination of histidine and citrate would, in the eyes of the skilled person, have presented itself as a good choice of buffer in an adalimumab formulation at pH 5.2 at the Priority Date.*" This is certainly not my opinion:

- In paragraph 2.1 of my original declaration, I have explained the buffer function of histidine and citrate shown to be present in Imraldi®. The model used by Sven Frøkjær in paragraph 20 of his original declaration and likewise paragraph 42 of his supplementary declaration is illustrative.
- In paragraph 3.2 of my original declaration, I observe that if a 'person skilled in the art' on the priority date was furnished with Manning, the 'person skilled in the art' would be taught to as a buffer (i) to use histidine alone or to use a combination of histidine and succinate, and (ii) to refrain from using a combination of citrate and phosphate.
- For the sake of completeness, I note that Sven Frøkjær in footnote 16 of this supplementary declaration cites an article from 2012 (exhibit 30) that explicitly cautions against using citrate as a buffer in formulations for subcutaneous use - particularly where patients will invariably self-administer, as per adalimumab formulations:

Citric acid

Citric acid is one of the most commonly used buffers (Table 1). It is a trivalent buffer containing three carboxylic acids with pKa of 3.1, 4.8 and 6.4 (Table 2) offering a wide buffering range5. According to the FDA's Inactive Ingredient Database, citrate is found in over 100 approved, injectable products, giving it a large history of use and proving its safety.

Table 2. Molecular Properties of Buffers Used in Parenteral Products

	pKa	Buffering Range	pH Shift during Freezing	
			pH at 25°C	Δ pH at = -20°C
Phosphoric acid	2.1, 7.2, 12.3	Neutral-Basic	7.2	-1.8[8]
Citric acid	3.1, 4.8, 6.4	Acidic-Neutral	6.2	-0.2[9]
Acetic acid	4.8	Acidic	5.6	+0.5[9]
Histidine	1.8, 6.1, 9.2	Neutral	5.4	+0.8[9]
Lactic acid	3.9	Acidic	N/A	N/A
Tromethamine	8.1	Neutral-Basic	7.2	+2.1[8]
Gluconic acid	3.6	Acidic	N/A	N/A
Aspartic acid	2.1, 3.9, 9.8	Acidic	N/A	N/A
Glutamic acid	2.1, 4.1, 9.5	Acidic	N/A	N/A
Tartaric acid	3.2, 4.9	Acidic	5.0	-0.3[41, 42]
Succinic acid	4.2, 5.6	Acidic-Neutral	5.6	+0.3[9]
Malic acid	3.4, 5.1	Acidic-Neutral	5.0	-0.3[41, 42]
Fumaric acid	3.0, 4.4	Acidic	N/A	N/A
α-Ketoglutaric	2.5, 4.7	Acidic-Neutral	N/A	N/A

N/A – Data not available

However, studies comparing subcutaneous injections of citrate-buffered formulations against com parable formulations buffered with phosphate or histidine have established that citratebuffered solutions induced more pain upon subcutaneous injection[18-20]. While this pain was relatively short in duration (less than two minutes), it raises concerns of patient compliance with self-administering injections containing citrate[18]. When formulating with citric acid, the target product profile and intended route of administration should be noted. When frequent subcutaneous injections are intended, another buffering agent may be more appropriate.

(Red square added to emphasise)

3.5 In Sven Frøkjær's supplementary declaration, paragraph 73, Svend Frøkjær i.a. observes that a 'person skilled in the art' based on Manning would be "*impressed by how resilient adalimumab appears to be, in the sense of having broadly similar stability across many of the formulations tested by Manning. Whilst not necessarily "optimal", many of the formulations tested (and not just those selected by Manning in his summary on page 107 and Table M), would be expected to have satisfactory stability for the purposes of pharmaceutical use. The skilled person would simply have regarded the Table M formulations as the particular formulations that Manning had himself chosen to work with and would not have viewed this as excluding the many other formulations which had been shown to have good stability in the various Blocks of experiments*". Do you agree?

No, I do not agree.

On page 94, line 21, - 107, line 12, Manning deploys three PLS analyses. PLS is a tool used to identify trends in large data sets, such as the results of the experiments made in Block A-H.

Manning's teachings on page 107 et seq. are based on the PLS analyses, and the formulations set out in Table M comprise different combinations of the excipients that Manning has found to be promising when formulating adalimumab formulations

that allow for long term storage which is the problem that Manning seeks to solve. In my opinion, Manning's teachings on page 107 et seq. are based on sound science, and not merely something Manning has chosen himself out of the blue, as suggested by Sven Frøkjær in paragraph 73 of his supplementary declaration.

I note that the formulations described by Manning in Tables A-H have generally been subjected to a relatively light stress tests. I thus agree with the observations made by Sven Frøkjær in paragraph 48 of his supplementary declaration, where it is explained that the experiments in Manning were "*only conducted once, and the tests that the formulations were subjected to could have been more extensive, e.g. by conducting studies for longer than two weeks, or at higher temperatures than 40°C or using a greater number of freeze/thaw cycle.*" Nonetheless, these initial stress tests provide an early negative indication of which particular formulations that do not seem to stabilise adalimumab. The stress tests are probably inadequate when it comes to positively identifying which particular formulations, if any, that are viable for the often required two years shelf-life (see below) but they are certainly good enough to see which formulations would not work. If it is concluded already after one week that a particular formulation does not adequately stabilise adalimumab, there would be no point in continuing down that path.

3.6 At the end of paragraph 3.2 of your original declaration, you observe that within the context of Block H, Manning identifies formulation 12 as the most stable formulation. Sven Frøkjær criticises this observation in paragraph 66 of his supplementary declaration. Please advise whether you maintain your observation, and in the affirmative why.

In Block H, Manning tests 12 particular formulations, nos. 1-12. In the commentary on page 94, Manning explains that in terms of pH, formulations 4 and 5 do not perform acceptable. As far as pH is concerned, Manning observes a "*slight rise in pH*" for formulation 1. This observation reflects that also formulation 1 is less promising.

On page 94, Manning further explains that based on SEC and RP HPLC analyses (that measure the monomer content), formulations 1, 4 and 5 underperform. In terms of monomer content, formulations 7 and 12 stand out as the best.

Manning further explains that based on CE-SDS (that in my words measures the 'intactness' of the antibody), formulation 12 stands out as the best. Formulation 7 stands out as the least good.

In sum: Formulations 1, 4, 5 and 7 perform relatively poorly in one or more of the tests. Formulations 2, 3, 6, 8, 9, 10 and 11 seem to work relatively satisfactory. Formulation 12 performs relatively well in the SEC, RP HPLC and CE-SDS analyses, and does not underperform in the pH analysis.

Based on the above observations, I maintain that Manning in Block H identifies formulation 12 as the best of the tested formulations in that block. As I also noted in paragraph 3.3 of my original declaration, formulation H12 is a formulation that reflects the general suggestions provided in Manning's conclusion (page 107-108): Formulation 12 has a pH of 5.2; comprises a combined histidine-succinate buffer; and as stabilisers/tonicity modifiers comprises the amino acids arginine and glycine instead of the sugar polyol, mannitol and the salt, NaCl.

3.7 In paragraph 49 of Sven Frøkjær's supplementary declaration, Sven Frøkjær observes that you do not explain what you mean when you use the respective terms 'viable' and 'optimal' formulations. Please explain.

I have used the two terms as synonyms in the contexts to which Sven Frøkjær refers. As Sven Frøkjær explains in paragraph 17 of this supplementary declaration, "*Companies aiming to launch a biopharmaceutical product, whether a new molecule or a biosimilar such as in the present case, need to satisfy the relevant regulatory authorities, including the EMA and FDA, that the product remains safe and efficacious during its approved shelf-life (which needs to be long enough for the product to be commercially viable - typically around two years)*."

When developing a formulation for e.g. adalimumab, the task is to find a formulation that is viable in the sense that Sven Frøkjær explains. The formulation needs to provide for a shelf-life of around two years, and obviously the formulation needs to be safe in use to satisfy the relevant regulatory authorities. Not least in the context generic and biosimilar products, a further consideration is to develop a formulation that is cost-effective in production.

3.8 If a 'person skilled in the art' was tasked with modifying formulation 11 from Table H (Manning page 88) with a view to provide ~~a viable~~ an alternative formulation that allows for fewer excipients, what would (not simply could) the 'person skilled in the art', in your expectation, do in the light of his general technical knowledge and the particular technical teachings identified in your answer to the above question 3.1 of your original declaration? In particular, would the 'person skilled in the art' remove mannitol and NaCl and replace with sorbitol or trehalose? In particular, would the 'person skilled in the art' replace PS 80 with PS 20?

The above re-formulation of the question I was asked as question 3.3 in my original declaration does not change my answer set out in paragraph 3.3 of my original declaration.

If a 'person skilled in the art' was tasked with modifying formulation 11 from Table H (Manning page 88) with a view to provide an alternative formulation that allows for fewer excipients, the 'person skilled in the art' would realistically focus on developing viable formulations in the sense explained by Sven Frøkjær in paragraph 17 of his supplementary declaration, please see above. If the 'person skilled in the art' – in a theoretical scenario – was tasked to look for mere alternatives – including non-viable alternatives – the list of combinatorial possibilities would be even larger and include non-viable formulations. This would not make any sense to me.

3.9 In paragraph 14 of Sven Frøkjær's supplementary declaration, Sven Frøkjær criticises your observation in paragraph 3.1. of your original declaration where you observe that the number of possibilities when combining excipients is close to infinite. What are your comments hereto?

My observations in paragraph 3.1 reflect that in general, there exists a close to infinite combinatorial possibilities. If tasked with developing a formulation for a particular protein, one would obviously start by reviewing relevant literature with a view to narrowing down which specific excipients that seem relevant to use and

combine. Whereas a literature review may often entail a cut in the number of relevant excipients to be used, the number of combination possibilities often remains close to infinite. To develop a viable formulation, one would therefore need to go to the lab.

In paragraph 3.3 of my original declaration, I observe that if a 'person skilled in the art' was tasked with modifying formulation 11 from Table H (Manning page 88) with a view to provide a viable formulation that allows for fewer excipients, the 'person skilled in the art' could define a close to infinite number of different formulations.

4. SUGAR STABILISERS - SORBITOL

4.1 Claim 1 of UM '70 and UM '71 i.a. requires that the aqueous pharmaceutical composition comprises a "*sukkerstabilisator valgt fra gruppen der indbefatter trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol*". Please advise how the 'person skilled in the art', in your expectation, would understand the term 'sukkerstabilisator' [sugar stabiliser] as used in the context of UM '70 and UM '71.

In the view of a protein chemist, the term 'sukkerstabilisatorer' [sugar stabiliser] is a generic term that denotes a group of specific compounds that are frequently used in pharmaceutical protein formulations. The group comprises multiple compounds, including those mentioned in claim 1, feature (c), of UM '70 and UM '71.

I have reviewed UM '70 and UM '71 and taken note of the following paragraph on page 14, where the documents read as follows:

> En "stabilisator" refererer til en bestanddel, som letter opretholdelse af den strukturelle integritet af det biofarmaceutiske lægemiddel, særligt under frysning og/eller frysetørring og/eller lagring (navnlig under udsættelse for belastninger). Dense stabiliserende virkning kan opstå af allehånde grunde, dog kan sådanne stabilisatorer typisk optræde som osmolytter, som beskytter mod proteindenaturering. Typisk indbefatter stabilisatorer aminosyrer (dvs. frie aminosyrer, der ikke indgår i et peptid eller protein – f.eks. glycin, arginin, histidin, asparaginsyre, lysin) og sukkerstabilisatorer såsom en sukkerpolyalkohol (f.eks. mannitol, sorbitol) og/eller et disaccharid (f.eks. trehalose, sukrose, maltose, laktose), selv om de væskeformige farmaceutiske sammensætninger ifølge frembringelsen indbefatter en stabilisator, hvoraf mindst én er en sukkerstabilisator (dvs. enten en sukkeralkohol eller et disaccharid). Fortrinsvis er den mindst ene sukker stabilisator et ikke-reducerende sukkerstof (de være sig en sukkeralkohol eller et disaccharid).

The corresponding paragraph in EP '510 reads as follows:

> **[0033]** Herein, a "stabiliser" refers to a component which facilitates maintainance of the structural integrity of the biopharmaceutical drug, particularly during freezing and/or lyophilization and/or storage (especially when exposed to stress). This stabilising effect may arise for a variety of reasons, though typically such stabilisers may act as osmolytes which mitigate against protein denaturation. Typical stabilisers include amino acids (i.e. free amino acids not part of a peptide or protein - e.g. glycine, arginine, histidine, aspartic acid, lysine) and sugar stabilisers, such as a sugar polyol (e.g. mannitol, sorbitol), and/or a disaccharide (e.g. trehalose, sucros, maltose, lactose), though the liquid pharmaceutical compositions of the invention include a stabiliser, at least one of which is a sugar stabiliser (i.e. either a sugar polyol or a disaccharide). Most suitably the at least one sugar stabiliser is a non-reducing sugar (be it a sugar polyol or a disaccharide).

When the 'person skilled in the art' reads the above paragraph, the person will understand that compounds that work as a 'stabiliser' "*typical[ly] […] include[s]*" compounds from two particular groups of compounds denoted 'amino acids' and 'sugar stabilisers'. The generic group 'sugar stabilisers' is further broken down in two generic sub-groups, denoted 'sugar polyol[s]' and 'disaccharide[s]'.

The 'person skilled in the art' is thus provided with the below hierarchy:

Generic group	amino acids	sugar stabilisers						
Generic sub-group	N/A	sugar polyol[s]			disaccharide[s]			
Specific group member	glycine arginine histidine aspartic acid lysine	mannitol	sorbitol		Trehalose	sucrose	maltose	lactose

The 'person skilled in the art' will note that particular compounds belonging to the group of 'amino acids' and the group of 'sugar stabilisers' (including the sub-groups 'sugar polyol[s]' and 'disaccharide[s]') typically will work as a stabiliser in adalimumab formulations in one way or the other.

The cited technical feature of claim 1 of UM '70 and UM '71 reads: "*sukkerstabilisator valgt fra gruppen der indbefatter trehalose, sucrose, mannitol, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol".*

When reading this wording, the 'person skilled in the art' will recognise all the specifically mentioned compounds as belonging to the group of compounds called 'sukkerstabilisatorer' (in English: 'sugar stabilisers').

The cited technical feature does not define what exact functionalities the adding of any of the mentioned sugar stabilisers will entail in an adalimumab formulation.

In my expectation, the 'person skilled in the art' will understand that the term 'sugar stabilisers' is used to identify a group of compounds without defining exactly which technical function the adding of any member from the group in an adalimumab formulation will entail.

Likewise, had the cited technical feature defined the use of an 'amino acid', 'sugar polyol' or 'disaccharide', the 'person skilled in the art' would, in my expectation, understand that the use of such term merely identifies a group of compounds without defining exactly which technical function the adding of any member from such group in a adalimumab formulation would entail.

4.2 The defendants submit as a matter of fact "*that sorbitol does not function as a stabiliser in Imraldi*®" (rejoinder, page 22, last paragraph). The defendants have not provided any evidence to substantiate this factual submission. Please provide your opinion on whether sorbitol does function as a stabiliser in Imraldi®.

The first part of the above-cited paragraph from page 14 of the utility models-in-suit explains what is meant by the term 'stabiliser'. It is explained that the term "*"stabiliser" refers to a component which facilitates maintainance of the structural integrity of the biopharmaceutical drug, particularly during freezing and/or lyophilization and/or storage (especially when exposed to stress). This stabilising effect may arise for a variety of reasons, though typically such stabilisers may act as osmolytes which mitigate against protein denaturation."* As it can be seen, a compound may be considered as a 'stabiliser' for a variety of reasons, including because the compound may "*act as osmolytes which mitigate against protein denaturation*".

The term 'osmolyte' denotes a compound that affects the 'osmolarity' which is the same as the 'tonicity' of a formulation. As effectively also explained on page 14, line 31, of the utility models, the terms 'tonicity modifier' and 'tonicifier' are synonyms with the term 'osmolyte' in that a 'tonicity modifier'/'tonicifier'/'osmolyte' "*contributes to (or increases) the overall osmolality and osmolarity of the composition*":

En "tonicitetsmodifikator" eller et "toniseringsmiddel" refererer til et middel, hvis medtagelse i en sammensætning på passende vis bidrager til (eller forøger) sammensætningens overordnede osmolalitet og osmolaritet.

In agreement with me, Sven Frøkjær states in paragraph 24 of his supplementary declaration that sorbitol "*will inherently always act as a tonicity agent*". Therefore, it must follow that sorbitol is considered a 'stabiliser' in the context of the utility models.

For the sake of completeness, I add that Figure 6 of Manning illustrates that sorbitol shows a positive effect on adalimumab stability. The same follows from Table 11 (page 49) and Example 7 in Fraunhofer, page 64.

Michael Bech Sommer har i erklæring af 11. april 2019 anført bl.a.:

"…
2. ADDED SUBJECT MATTER
2.1 In paragraph 2 of the rejoinder, including Appendix 1, the defendants argue that the utility models-in-suit are invalid because they contain added subject matter. What are your comments hereto?

The criteria applied by the EPO/DKPTO when assessing the question of added subject matter
It follows from EPC article 123(2) and the Danish Utility Models Act, section 18, that a patent/utility model may not contain subject-matter which extends beyond the content of the application as filed.

The criteria for the assessment of added subject matter is elaborated in the EPO's guidelines:

2.2 Content of the application as "originally" filed – general rules

Under **Art. 123(2)**, it is impermissible to add to a European application subject-matter which the skilled person cannot derive directly and unambiguously, using common general knowledge and also taking into account any features implicit to a person skilled in the art in what is expressly mentioned in the document, from the disclosure of the application as filed. Literal support is, however, not required by the wording of **Art. 123(2)** (see **T 667/08**).

(https://www.epo.org/law-practice/legal-texts/html/guidelines/e/h_iv_2_2.htm)

The referenced Boards of Appeal decision T 667/08 explains:

It is an undisputed principle in the jurisprudence of the Boards of Appeal of the EPO that an amendment is allowable under Article 123(2) EPC if the subject-matter resulting from the amendment is directly and unambiguously derivable from the original application documents i.e. the description, the claims and the drawings, using common general knowledge. Thereby it is not necessary that the subject-matter resulting from the amendment was explicitly disclosed in the original application.

It is therefore essential, when deciding on issues of added subject-matter, to identify the actual teaching conveyed by the original disclosure, i.e. the technical information that the skilled person reading the original disclosure would have derived from its content (description, claims, drawings) considered in its entirety.

This approach might lead to the identification of subject-matter which has not been explicitly revealed as such in the application as filed, but nevertheless derives directly and unambiguously from its content. Literal support is not required by the wording of Article 123(2) EPC. An amendment can therefore be allowable if it combines information which has not been disclosed in one and the same section of the original disclosure, but results, for instance, from information gathered from various embodiments possibly associated with general statements regarding the information derivable from the introductory section of the application.

If this were not the case, the original disclosure would be deprived of a part of the information it actually contains, namely the technical teaching that the skilled person would retrieve from the application but which may typically extend beyond a mere literal interpretation of the original text.

In paragraph 2.1 of my original declaration, I have examined in detail whether the technical features of claim 1 of UM '70 and UM '71 can be derived from the application as filed. As explained in the framework on pages 4-7 of my original declaration, the technical features of claim 1 of UM '70 and UM '71 have basis in the application as filed. They are all derived directly and unambiguously from the description of the application as filed. I have taken note that also the DKPTO in its statement of 29 March 2019 (exhibits 31 and 32) finds that the utility models-in-suit are not subject to any unallowable added subject matter. Also, by way of example, the subject matter of claim 1 of UM '70 corresponds to claim 9 (dependant on claim 4, dependant on claim 1) of EP '510 which the EPO upon examination found to be in compliance with EPC article 123(2).

Shrinking of a generic group

I have taken note that the defendants refer to T 615/95 in support of their submission that the shrinking out of mannitol in UM '70 constitutes unallowable added

subject matter. In this regard, I observe that T 615/95 relates to removal of residues in 3 positions in a generic Markush formula, which was not seen as unallowable added subject matter. The rationale is explained in the EPO's Case Law text book:

> In **T 615/95** there were three independent lists of sizeable length specifying distinct meanings for three residues in a generic chemical formula in a claim. One originally disclosed meaning was deleted from each of the three independent lists. The board stated that the present deletions did not result in singling out a particular combination of specific meanings, i.e. any hitherto not specifically mentioned individual compound or group of compounds, but maintained the remaining subject-matter as a generic group of compounds differing from the original group only by its smaller size. Such a **shrinking of the generic group** of chemical compounds was not objectionable under **Art. 123(2) EPC 1973**, since these deletions did not lead to a particular combination of specific meanings of the respective residues which was not disclosed originally or, in other words, did not generate another invention (see also **T 948/02**, which refers in detail to this case law and which did not allow the amendment of a generic chemical formula; see also **T 659/97**, **T 894/05**, **T 888/08**).

(https://www.epo.org/law-practice/legal-texts/html/caselaw/2016/e/clr_ii_e_1_4_2.htm)

T 615/95 relates to added subject matter under EPC article 123(2) and not, as the defendants seem to suggest, novelty of claimed subject matter under EPC article 54(2).

3. PATENTABILITY

3.1 Novelty

3.1.1 In the rejoinder, page 7, paragraph 4.1 and 4.2, the defendants maintain their submission that both UM '70 and UM '71 lack novelty over Manning and Dai and criticise your observation in paragraph 3.1 of your original declaration that the assessment of novelty turns upon whether all technical features of a claimed creation are disclosed in the prior art. Please provide your comments to the defendants' criticism.

The criteria applied by the EPO/DKPTO when assessing novelty

The basic novelty requirement for the grant of a patent/utility model follows from EPC article 54(2) and the Danish Utility Models Act, section 5.

The criteria for the assessment of novelty is elaborated in the EPO's guidelines:

"An invention is considered to be new if it does not form part of the state of the art. For a definition of "state of the art", see G-IV, 1. It is to be noted that in considering novelty (as distinct from inventive step, see G-VII, 8), it is not permissible to combine separate items of prior art together. It is also not permissible to combine separate items belonging to different embodiments described in one and the same document, unless such combination has specifically been suggested (see T 305/87). For the specific case of selection inventions see G-VI, 8." (https://www.epo.org/law-practice/legal-texts/html/guidelines/e/g_vi_1.htm)

The above same criteria are reflected in the DKPTO's guidelines for both patents and utility models:

"Når spørgsmålet om nyhed behandles (til forskel fra væsentlig adskillelse, se Kombination af modhold), er det ikke tilladt at kombinere enkeltdele af kendt teknik med hinanden. Det er heller ikke tilladt at kombinere enkeltdele, der tilhører forskellige udførelsesformer beskrevet i et og samme dokument, medmindre e"n sådan kombination specifikt er foreslået (EPO T 305/87, OJ 8/1991, 429)." (http://paguidelines.dkpto.dk/aa/betingelser-for-patenterbarhed/nyhed.aspx)

"Når spørgsmålet om nyhed behandles (til forskel fra tydelig adskillelse), er det ikke tilladt at kombinere enkeltdele af kendt teknik med hinanden. Det er heller ikke tilladt at kombinere enkeltdele, der tilhører forskellige udførelsesformer beskrevet i et og samme dokument, medmindre en sådan kombination specifikt er foreslået." (http://bmguidelines.dkpto.dk/aa/behandling-af-brugsmodelansoegninger/proevning-af-brugsmodelansoegning-foer-registrering/registrerbarhedsvurdering/nyhed.aspx)

As set out in the guidelines, when considering novelty, the key question is whether a particular prior art embodiment comprise all features of the claimed invention/creation. If confronted with a prior art document, the key question is whether that document comprises one single embodiment that comprises all features of the claimed invention/creation. If the prior art document describes multiple embodiments, it is – in the context of the novelty assessment – not allowed to combine the technical features of the particular embodiments, unless the document specifically suggest to do so. Using H11 in Manning as an example, Manning does not explicitly suggest to combine formulation H11 with other technical features. Therefore, in the context of assessing novelty, formulation H11 reprsents an embodiment with a fixed set of technical features.

The phrase "*directly and unambiguously*" is used by the EPO in different contexts. In the context of novelty, the phrase is according to EPO's guidelines used in situations where it is considered whether a particular piece of prior art discloses a technical feature implicitly. In such situation, it is in the context of a novelty assessment required that the implicit feature in question can be derived "directly and unambiguously" from the disclosure. EPO's guidelines read:

"A document takes away the novelty of any claimed subject-matter derivable directly and unambiguously from that document including any features implicit to a person skilled in the art in what is expressly mentioned in the document, e.g. a disclosure of the use of rubber in circumstances where clearly its elastic properties are used even if this is not explicitly stated takes away the novelty of the use of an elastic material. The limitation to subject-matter "derivable directly and unambiguously" from the document is important. Thus, when considering novelty, it is not correct to interpret the teaching of a document as embracing well-known equivalents which are not disclosed in the documents; this is a matter of obviousness." (https://www.epo.org/law-practice/legal-texts/html/guidelines/e/g_vi_2.htm)

In sum: When the EPO/DKPTO consider novelty under EPC article 54(2)/The Utility Models Act, section 5, it is assessed whether a particular prior art embodiment comprise all features of the claimed invention/creation. When confronted with a prior art document, the key question is whether that document comprises one single embodiment that comprises all features of the claimed invention/creation. If the prior art document describes multiple embodiments, it is – in the context of the novelty assessment – not allowed to combine the technical features of the particular embodiments, unless the document specifically suggest to do so. A particular

embodiment is considered to disclose all its explicit technical features. Implicit features are considered as disclosed only if they are "*directly and unambiguously*" derivable from the embodiment in question.

For the sake of clarity I note that the guidelines of the EPO/DKPTO do not in the context of novelty assessment use a criterion denoted "*whole contents approach*" as suggested by the defendants.

Novelty over H11 of Manning

As explained in paragraph 3.1 of my original declaration, H11 of Manning does not disclose all technical features of neither UM '70, claim 1 nor UM '71, claim 1.

Manning does not specifically suggest to combine H11 with any features that lead to either of the creations of UM '70, claim 1 or UM '71, claim 1.

All excipients in formulation H11 are explicitly disclosed. H11 does not comprise any implicit technical features, and there exists thus no question of whether any implicit technical features are "*directly and unambiguously*" derivable from H11.

Whether Manning points the person skilled in the art to modify H11 so that it leads to either of the creations of UM '70, claim 1 or UM '71, claim 1, is a question of creative step.

I have taken note that the DKPTO in its statements of 29 March 2019 (exhibits 31 and 32) seems to be in line with the above observations.

I have also taken note that the defendants in the rejoinder observe that claim 1 of both UM '70 and UM '71 differs from H11 of Manning, see pages 17 and 18 of the rejoinder:

- UM '070

In relation to UM '070, and when considering Manning H11 as the starting point, the only difference is that Manning H11 comprises a sugar, mannitol, which is not explicitly mentioned in the list of sugar stabilisers in claim 1. The technical effect of the sugars mentioned in claim 1 is to contribute to the stabilisation of the

- UM '071

In relation to UM '071 and when taking Manning H11 as the starting point, the only distinguishing feature is that Manning H11 comprises PS80 instead of PS20.

Sven Frøkjær makes the same observation in his supplementary declaration:

Analysis with respect to UM '070

82. With respect to Manning, I have explained that the vast majority of the formulations tested show good results. I believe the skilled person would consider that there are a large number of promising formulations in Manning which could be selected for further investigation. One of these, is formulation H11 on page 88. That formulation meets every criteria of claim 1 above, except that it employs mannitol as the sugar stabiliser:

Analysis with respect to UM '071

85. With respect to claim 1 of UM '071, formulation H11 in Manning shown above differs from claim 1 of UM '071 only in that formulation H11 uses polysorbate 80 and not polysorbate 20 as the surfactant.

Novelty over Dai

Dai regards particular non-aqueous formulations. I can see that the defendants believe that formulation Sd_2, Form-6, described in example 7 is novelty destroying.

Sd_2, Form-6 does not comprise adalimumab. Dai does not on page 18 specifically suggest to combine Sd_2, Form-6 with adalimumab. Alone for this reason, Dai is not novelty destroying relative to claim 1 of UM '70 or claim 1 of UM '71.

Further, Sd_2, Form-6 does not comprise PS 20, and also for this reason Dai is not novelty destroying for UM '71 or UM '70, claims 7/9-10.

I have taken note that the defendants have not submitted to the PTAB that Dai is novelty destroying for UM '71 or UM '70.

The presence of NaCl in formulation H11 of Manning does not impact the novelty assessment

As explained in my original declaration, paragraph 3.1, and as further elaborated above, neither Manning nor Dai destroys the novelty of the utility models-in-suit. I did not and do not base this assessment on the fact that H11 of Manning comprises NaCl, whereas the presence of this excipient is not required in claim 1 (or 7/9-10) of UM '70 or claim 1 of UM '71.

3.2 Creative step

3.2.1 In paragraph 5 of the rejoinder, the defendants criticise the assessment you perform of creative step in paragraph 3.2 of your original declaration. Please provide your comments hereto.

The presence of NaCl in formulation H11 of Manning

When assessing novelty, my conclusion is not based on the absence of NaCl in claim 1 of UM '70/ UM '71.

When assessing creative step, I believe a difference between the technology defined in claim 1 (or 7/9-10) of UM '70 or claim 1 of UM '71 also includes that NaCl may be excluded. UM '70 and UM '71 provide a technology that does not necessitate the presence of NaCl, whereas H11 contains NaCl e.g. for the purpose of obtaining the required osmolarity (same as tonicity) of that specific formulation.

H11 of Manning as closest prior art

I have not performed any separate assessment of what is the closest prior art. My assessment of creative step is based on this as a given fact, please see the formulation of question 3.1 in my original declaration.

For the sake of completeness, I note that in the defendants' appeal to the PTAB, the defendants explicitly identify Manning as closest prior art, and argues that both utility models-in-suit are invalid over H11 of Manning. To this end, the defendants

submitted Sven Frøkjær's original declaration that substantiates the identification of H11 as closest prior art in paragraphs 44 and 48. In the DKPTO's statement to the PTAB of 29 March 2019 (exhibits 31-32), the DKPTO explicitly states that H11 of Manning is the closest prior art. (In the context of the DKPTO's original decision to grant UM '70 and UM '71, the DKPTO identified Parshad as closest prior art. In the DKPTO's statement of 29 March 2019, the DKPTO now identifies and applies – in conformity with the defendants' submission – H11 of Manning as the closest prior art.) Based on my own review of the prior art documents (Manning, Dai, Fraunhofer and Rast) filed by the defendants in the case at hand, I have no reason to disagree that H11 of Manning is the closest prior art. I therefore agree that the question of inventive step may be assessed with H11 of Manning as the starting point.

H11 of Manning is the basis for the formulation of the objective problem

I have taken particular note of the following observations made by the defendants:

> In section 3.3. of her declaration (Exhibit 21), Professor Müllertz was asked what a skilled person "*with a view to provide a viable formulation that allows for fewer excipients*" would do and accordingly, Professor Müllertz concludes that the compositions in Table M of Manning provide a better starting point than composition Manning H11.
>
> Since the precondition of the objective technical problem set out by Mr Sommer is fundamentally flawed, it follows that it is erroneous to conclude that because the compositions in Table M comprise fewer excipients than Manning H11, they provide a better starting point than Manning H11.

In my reading, it seems like the defendants think that I have based the formulation of the objective problem on a misconceived reading of Anette Müllertz declaration. This is not the case.

In paragraph 3.3 of Anette Müllertz declaration, Anette Müllertz addresses what a person skilled in the art would do if tasked with modifying formulation H11 of Manning with a view to provide a viable formulation that allows for fewer excipients, i.e. the objective problem formulated by me in section 3.1 of my original declaration. Anette Müllertz observed that the formulations in Table M would be among the solutions that the person skilled in the art would suggest. Anette Müllertz does not – as alleged by the defendants - suggest that "*the compositions in Table M of Manning provide a better starting point than composition Manning H11*". In fact, Anette Müllertz has not provided any opinion hereon, and obviously the observations made in my original declaration are not based hereon either. As explained above, I have no reason to disagree that formulation H11 is a good starting point and therefore the closest prior art. My formulation of the objective technical problem is based on H11 as being the closest prior art.

Formulation of the objective technical problem

With reference to the more detailed observations in paragraph 3.2 of my original declaration, I agree with the defendants that the differing feature between H11 and claim 1 of UM '70 is that H11 comprises mannitol, whereas claim 1 of UM '70 comprises a sugar stabiliser chosen from a set list that does not comprise mannitol. Further the formulation defined in claim 1 allows for fewer excipients than H11.

I also agree that the differing feature between H11 and claim 1 of UM '71 is that H11 comprises PS 80, whereas claim 1 of UM '71 comprises PS 20. Further the formulation defined in claim 1 allows for fewer excipients than H11.

In my opinion, if using H11 as the starting point, the objective technical problem is to formulate a viable adalimumab formulation that allows for fewer excipients.

The term viable reflects that the formulation should be useful in the context of a pharmaceutical product, as also explained in paragraph 17 of Sven Frøkjær's supplementary declaration. (It is not clear to me whether the starting point, H11, is actually viable, though. Already after a light stress test, H11 stands – among the formulations tested in Block H - out as the least stable formulation in terms of aggregation (Manning, page 90, Table H-2). Similarly, in Manning, page 91, Table H-3, H11 is one of out of the three formulations with the lowest percent purity.)

The inclusion of the wording "*that allows for fewer excipients*" reflects that the creations comprised by claim 1 of UM '70 and UM '71 comprise fewer excipients than H11 of Manning. With reference to the observations immediately below, I am ready to debate whether this pointer to the solution of the problem should actually be included in the problem formulation. However, I think it is prudent to do so. The consequence of deleting this part of the problem formulation would be that many more alternatives would be relevant, as the person skilled in the art when trying to solve the problem would have many more options, since he could instead of aiming for fewer excipients also e.g. add further excipients, use the same number of excipients or just modify the concentrations of the excipients used in H11. By way of example, if the person skilled in the art was 'just' tasked with developing a viable adalimumab formulation, the skilled person that uses H11 as the starting point would most likely identify formulation H12 (which has the same number of excipients as H11) as a solution to the problem. As explained by Anette Müllertz in paragraph 3.6 of her supplementary declaration, "*formulation H12 is a formulation that reflects the general suggestions provided in Manning's conclusion (page 107-108): Formulation 12 has a pH of 5.2; comprises a combined histidine-succinate buffer; and as stabilisers/tonicity modifiers comprises arginine and glycine instead of mannitol and NaCl*".

I note that the DKPTO in its statements of 29 March 2019 to the PTAB has formulated the technical problem in the following terms:

Re UM '70

Tydelig adskillelse
Indholdet af krav 1-6, 8 og 11-12 ifølge BR 2018 00070 som registreret afviger fra formulering 11, tabel H i Manning ved at sukkerstabilisatoren er valgt fra trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol.

Det objektive tekniske problem, som bliver løst ved indholdet af krav 1-6, 8 og 11-12, er anvisning af en alternativ sukkerstabilisator til brug i formuleringer af adalimumab.

Re UM '71
Tydelig adskillelse
Indholdet af krav 1 ifølge BR 2018 00071 som registreret afviger fra formulering 11, tabel H i Manning ved den specifikke overfladeaktive forbindelse PS 20.

Det objektive tekniske problem, som bliver løst ved indholdet af krav 1, er anvisning af en alternativ overfladeaktiv forbindelse i stabile vandige formuleringer af adalimumab.

When formulating the objective technical problem, the DKPTO incorporates in its problem formulation a pointer to the solution, i.e. to the replacement of mannitol/PS 80. In respect of UM '70, the problem formulation points to identifying an

alternative sugar stabiliser. In respect of UM '71, the problem formulation points to identifying an alternative surfactant. Such problem formulation incorporates hindsight as it points to the solution. As the guidelines of the EPO and DKPTO point out, the objective problem must be so formulated that it does not contain pointers to the technical solution:

It is noted that the objective technical problem must be so formulated as not to contain pointers to the technical solution, since including part of a technical solution offered by an invention in the statement of the problem must, when the state of the art is assessed in terms of that problem, necessarily result in an *ex post facto* view being taken of inventive activity (see **T 229/85**). Where the claim refers to an aim to be achieved in a non-technical field, however, this aim may legitimately appear in the formulation of the problem as part of the framework of the technical problem to be solved, in particular as a constraint that has to be met (see **T 641/00**, **T 172/03** and **G-VII, 5.4.1**).
…

Det bemærkes, at det objektive tekniske problem skal formuleres således, at det ikke angiver eller peger mod den tekniske løsning. Angives en del af den tekniske løsning ved angivelsen af problemet, indebærer det nødvendigvis anvendelsen af en vis form for bagklogskab.

(http://bmguidelines.dkpto.dk/aa/behandling-af-brugsmodelansoegninger/proevning-af-brugsmodelansoegning-foer-registrering/registrerbarhedsvurdering/tydelig-adskillelse/problem-and-solution-approach-(psa)/objektive-tekniske-problem.aspx)

In my opinion, the DKPTO's observation that claim 1 of UM '70 lacks creative step over H11 seems to be a result of the formulation of an objective problem that includes a part of the technical solution and thus necessarily results in an *ex post facto* view being taken in the assessment of what the person skilled in the art would do.

I note that even in a situation where the problem formulation in respect of UM '71 incorporates hindsight and points to identifying an alternative surfactant, the DKPTO finds that claim 1 of UM '71 (and therefore also claim 7 and 9-10 of UM '70) involves a creative step over H11 of Manning, because Manning explicitly teaches away from replacing PS 80 with PS 20.

3.2.2 In paragraphs 83-84 of Sven Frøkjær's supplementary declaration, Sven Frøkjær observes as follows in the context of Sven Frøkjær's analysis of claim 1 of UM '70 over H11 over Manning:

83. As I explained above, Manning contains teaching supported by data that either sorbitol or trehalose (both of which are listed in part (c) of claim 1 above) could be substituted for mannitol at a 1:1 concentration. Making such a substitution is more than a mere suggestion, with Manning positively stating that sorbitol and trehalose "*may be substituted*" for mannitol if desired.

84. In any event, in my opinion it would be obvious for the skilled person that such a substitution could be made based on the data and teaching in Manning and their knowledge and experience of formulation.

Do you agree with Sven Frøkjær?

Yes, apart from the fact that sorbitol and trehalose in adalimumab formulations do not substitute mannitol 1:1 on a concentration base (see Manning, page 7, line 6-9)), I actually do agree with Sven Frøkjær that having the knowledge of Manning, the skilled person could indeed exchange mannitol for sorbitol or trehalose. However, the relevant question to answer is not whether the skilled person could make this substitution, but rather whether he would.

The relevant question to answer is: Having H11 as a starting point and being presented with the technical problem of how to provide a viable adalimumab formulation that allows for fewer excipients, would the skilled person substitute mannitol for trehalose or sorbitol. As observed in paragraph 3.2 of my original declaration, there is no motivation for the skilled person to make such substitution. In fact, according to paragraph 3.2 of Anette Müllertz supplementary declaration, Manning teaches away.

3.2.3 In support of their invalidity allegations, the defendants have submitted four prior art documents, (i) WO 2014/068029 A1 (exhibit W) ("Rast"), (ii) WO 2014/039903 A2 (exhibit X) ("Manning"), (iii) WO 2012/121754 A1 (exhibit Y) ("Dai") and (iv) WO 2010/129469 (exhibit Z) ("Fraunhofer"). Within the proceedings at hand, the defendants have identified H11 of Manning as the closest prior art in the context of the inventive step assessment of both UM '70 and UM '71. Please explain which document(s) the EPO, in your opinion, would consider as closest prior art.

If the EPO during examination had only identified the above four prior art documents, I am convinced that the EPO would itself identify Manning as the closest prior art. Dai and Rast do not as such relate to aqueous protein formulations and would therefore be a less promising starting point. Further, adalimumab is not in focus of either document. Manning and Fraunhofer, on the other hand, both relate to aqueous adalimumab formulations and could equally be chosen as 'closest prior art' based on the fact that they relate to the same purpose as the utility models-in-suit. Upon a closer look on Fraunhofer, this document relates to maintaining physical and chemical stability of high concentration formulations of proteins, whereas Manning relates to adalimumab formulations that are suitable for long term storage. As such, the two documents would be equally qualified for being chosen as closet prior art. In such situation, the EPO would choose the particular document requiring the minimum of structural modifications and thus constituting the easiest route for the skilled person to arrive at the claimed solution. It then appears that Manning, more specifically H11, is the most suitable starting point.

3.3 In Sven Frøkjær's supplementary declaration, Sven Frøkjær review the utility models-in-suit in paragraphs 15-36 and concludes:

36. In conclusion, in my opinion the experiments presented in the Utility Models test formulations containing standard excipients, all of which were well known in the protein formulation field well before 2014. There is nothing unusual or surprising to me about any of the excipients tested. The methods used to screen and test stability were all also routine methods. However, as I have described, I do not believe that it is possible to place any weight on these data alone to allow any meaningful conclusions to be drawn. Further, even if one were to rely on the conclusions drawn by the authors of the Utility Models themselves, the formulations that are concluded to be best are not formulations that would be covered by the claims of UM '070 or UM '071 due to their requirement for inclusion of a (particular) surfactant and a citrate buffer. Moreover, even for the best performing of the formulations tested in the Utility Models, no improvement over Humira® was demonstrated.

In your opinion, does Sven Frøkjær's observations compromise the validity of the utility models-in-suit?

In my reading, Sven Frøkjær reviews the utility models-in-suit as if the models were academic articles where the claims represent the conclusions. I have not considered whether Sven Frøkjær's observation in such context are sound. However, in the context of a utility model/patent, it is not a requirement that the technical effects are documented by scientific data disclosed in the application as filed. What is required is that the creation is disclosed in a manner that enables the person skilled in the art to work the technology, and further that it is plausible that the technical effect is achieved. In the case at hand, at least Imraldi® documents that the technical effect – i.e. achieving a viable formulation – is achieved. In my understanding, the defendants do not dispute that the creation of UM '70 and UM '71 is enabled. As easy reference, please see the following from *Case Law of the Boards of Appeal of the European Patent Office* (2016), page 182:

> In **T 578/06** the board stated that the EPC requires no experimental proof for patentability and considered that the disclosure of experimental data or results in the application as filed and/or post-published evidence is not always required to establish that the claimed subject-matter solves the objective technical problem. This is in particular true in the absence of any formulated substantiated doubt. The board re-emphasised in this context however that this case law considers the establishment of plausibility only relevant when examining inventive step if the case at hand allows the substantiation of doubts about the suitability of the claimed invention to solve the technical problem addressed and when it is thus far from straightforward that the claimed invention solves the formulated problem. This is all the more clear from decisions where an inventive step was in fact denied because the **formulated problem** was **not** considered to have been solved. By way of example the board referred to **T 893/02** and **T 1329/04**.

As a final remark I note that since it is H11 and not Humira® that is closest prior art, it is irrelevant how the creations of UM '70 and UM '71 perform relative to Humira®. Actually, even if Humira® had been considered as closest prior art, it would not be a requirement that the creations of UM '70 and UM '71 perform better."

Daniel Erik Otzen har i erklæring af 24. april 2019, som revideret den 20. maj 2019, anført bl.a.:

"…
Professor Frøkjær's declaration
9. In paragraphs 15 - 36 of his declaration, Professor Frøkjær presents a review of the general description of the Utility Models and stability testing generally, the claims, and what they include, as well as the description of the two formulation screens that they describe and his conclusions. I concur with the views and conclusions set out by Professor Frøkjær in these paragraphs. Thus, I share his view that there is nothing unusual or surprising about any of the excipients tested and that the methods described in the Utility Models are, and would have been at the priority date, routine for the skilled person.

10. Prior to reading Professor Frøkjær's declaration, I had reviewed the Utility Models myself and came to the same views on the data that they contained, inde-

pendently. The points made by Professor Frøkjær underlying his view that it is difficult to draw any meaningful conclusions from the data particularly resonated with me.

11. Further, the fact that the claims of the Utility Models include requirements for excipients that had not been tested in the Utility Models seemed particularly strange to me. This is well illustrated by reference to the claimed surfactants. In the experiments included in the Utility Models, Screening Experiment 1 does not include any formulations containing any surfactant at all and Screening Experiment 2 only tests formulations containing polysorbate 80. Polysorbate 20 is not included in any of the formulations tested in the Utility Models, nor do the Utility Models teach any advantage associated with the use of polysorbate 20 as compared to polysorbate 80. However, surprisingly, claim 1 of UM '071 requires polysorbate 20 to be present in the claimed formulations and claim 1 of UM '070 requires that the formulations contain either polysorbate 20 or polysorbate 80 (which is narrowed down to just polysorbate 20 in claim 7). The claims are particularly surprising since, as also noted by Professor Frøkjær at paragraph 32 of his declaration, the conclusion drawn in the Utility Models in relation to Screening Experiment 2 is that formulations containing polysorbate 80 are inferior to those which do not contain any surfactant. Accordingly, the formulation which is concluded to be the best, which is referred to in the penultimate paragraph of the Utility Models (at page 82), does not include any surfactant at all, let alone polysorbate 20. For this reason, the inclusion of a surfactant (in particular polysorbate 20, which was not even tested) as a requirement of the claimed formulations seems entirely out of place and inconsistent with the information provided in the Utility Models.

12. I concur with Professor Frøkjær's summary of the teachings in Manning set out in paragraphs 37 – 67 of his declaration. I also concur with the conclusions made by Professor Frøkjær in his declaration regarding what Manning teaches, including that the skilled person would conclude that adalimumab is a relatively resilient antibody and amenable to being formulated using common buffers, sugars and surfactants, to obtain an alternative formulation to Humira®.

13. Professor Frøkjær has made a comparison between the teaching of Manning and that of the Utility Models in paragraphs 68-87 of his declaration, and I share Professor Frøkjær's views that Manning discloses a number of alternative formulations of adalimumab, some of which match those that are claimed in the claims of the Utility Models. Furthermore, where it is necessary to swap excipients it would be routine formulation work, based on the data and teaching in Manning and the skilled person's knowledge and experience of protein formulation, to switch from one excipient to another.

14. Based on my reading of the documents that I have been provided with, and on the basis of my own technical knowledge and background and my detailed review of Manning and the Utility Models, I fully concur with the conclusions made by Professor Frøkjær in paragraphs 88-89 of his declaration.

Choice of surfactant based on Manning

15. I understand the comments made in the DKPTO Letters to mean that it is the assessment of the Danish Patent and Trademark Office that the teaching in Manning would dissuade a person skilled in the art from using polysorbate 20 when formulating adalimumab. I disagree, for the reasons set out below. I do not believe that Manning teaches that polysorbate 80 is better than polysorbate 20 for use in a

formulation of adalimumab and even less so, that the skilled person would be dissuaded from using polysorbate 20 in a liquid formulation of adalimumab.

16. The DKPTO Letters reference a statement on page 7 of Manning relating to the use of surfactants. The statement on page 7 of Manning is very brief, but in his conclusions on page 108 Manning additionally states that "[s]*urprisingly, polysorbate 80 (PS 80) provides significant protection against thermal stress. While the mechanism of stabilization is not known, it appears that other surfactants tested (PS 20 and F-68), do not appear to be nearly as effective as PS 80. Hence the selection of PS80 versus PS20 is a preferred feature of the present invention*". It is not clear to me what the basis for these statements is. Thus, the skilled person presented with these statements in Manning would have considered the underlying data and would have concluded that there was no appreciable difference between any of the three surfactants tested.

17. The relevant experiments in Manning are those in Block G (from page 75), where F-68 and polysorbate 20 were evaluated in addition to polysorbate 80. From Table G-2 (page 78) it can be seen that the adalimumab monomer content of the citrate-phosphate samples was actually marginally better at t1 for the formulation containing 0.1 mM polysorbate 20 (formulation 2) than for the formulation containing 0.1 mM polysorbate 80 (formulation 1). In other words, there was less aggregation observed in those formulations containing polysorbate 20. The same is true for the formulations containing 0.05 mM polysorbate 20 and 0.05 mM polysorbate 80 in Histidine buffer (formulation 5 versus formulation 7), with polysorbate 20 again showing marginally higher monomer content at t1 (and therefore less aggregation). The results for formulations 1 and 2 are also identical at t1 in Table G3, where the percent purity is assessed by RP HPLC [note: Given that the t0 values are quite close to each other (but differ by amounts which are significant compared to the change after incubation at 40 or 25oC), one should look at the decrease in the amount of monomer from t0 to t1 (and to t2): PS80/PS20/F68 decrease by 1.72/1.32/1.27%, respectively, from t0 to t1 (i.e. one week at 40oC) and by 1.08/1.02/1.07%, respectively, from t0 to t2 (i.e. 2 weeks at 25oC).]. Thus, on the basis of these experiments polysorbate 20 seems to perform at least as well as polysorbate 80.

18. Furthermore, in my view the Block G results for formulations containing polysorbate 80 are no better than the results for those containing F-68.

19. The purity of formulations 1 to 12, described in the table at page 80 in Manning, was measured by CE-SDS, a method commonly used to establish the presence of the components that are to be expected for a monoclonal antibody i.e. light chain polypeptide, heavy chain polypeptide, non-glycosylated heavy chain and the absence of any "other" contaminating fragments e.g. degradation products of the antibody. The results obtained for formulations 1, 2 and 3, in which only the surfactant varies between 0,1% polysorbate 80, 0,1% polysorbate 20 and 0,1% F68 respectively, indicates that the formulation with polysorbate 20 was essentially free of any "other" fragments while the formulation containing polysorbate 80 included "other" fragments, although in low amounts (approximately 0,30%). Thus, the inclusion of polysorbate 20 would seem to confer slightly better stability for this particular formulation of adalimumab. For formulations 5 and 7, containing 0,05% polysorbate 80 and 0,05% polysorbate 20 respectively, there would appear to be no differences in the presence of "other" fragments. Thus, based on these data, there is no reason for concluding that polysorbate 80 is better than polysorbate 20.

20. In my opinion, it is clear from the Block G data in Manning that polysorbate 20 and polysorbate 80 are both equally suitable for use in formulating adalimumab. Thus, the skilled person would not have been dissuaded by the statement at page 7 of Manning, and would accordingly have had no hesitation in progressing formulations containing either of the surfactants tested in Manning with the expectation that the presence of either one would result in comparably stable formulations of adalimumab.

21. I have studied the description and the Examples of the Utility Models to consider what they teach the reader about the comparative usefulness of polysorbate 20 and polysorbate 80 in the formulations of adalimumab that were tested:

(a) In my view the Utility Models suggest that, if a surfactant should be present in the formulation at all (which is in itself at odds with the conclusions in the Utility Models as I have explained at paragraph 11 above), then both polysorbate 20 and polysorbate 80 would be suitable. Whilst I note that the main focus of the Utility Models is on polysorbate 80 and that, for some unexplained reason, the authors selected polysorbate 80 for use in the majority of the embodiments disclosed in the description, the relevant passages in the Utility Models discuss the impact of polysorbates and surfactants generally, rather than being specifically concerned with polysorbate 80 only. Accordingly, page 80, lines 11 to 19 (UM ´070), and page 80, lines 4 to 12 (UM ´071), of the Utility Models describe the problems associated with degradation products "*released by polysorbates*" [note: English-language text included here and in respect of other citations from the Utility Models are taken from the corresponding paragraphs of the description of European Patent EP 3 148 510 B1.] and the need to "*better elucidate the impact of surfactant*" and on page 81, lines 33 to 36 (UM ´070), and on page 81, line 26 to 29 (UM ´071), it is stated that "*there is no added value in adding a surfactant with the aim of preventing particles and aggregates*". It does not surprise me at all that the Utility Models do not appear to be discriminating between polysorbate 80 and polysorbate 20 in terms of the deleterious effects that are reported in Screening Experiment 2, since the effects of using polysorbate 80 and polysorbate 20 are typically very similar, which was well known by the priority date of the Utility Models.

(b) Thus, the Examples of the Utility Models do not suggest to me that polysorbate 20 would provide a better stabilising effect on adalimumab formulations than polysorbate 80 as none of the formulations tested comprised polysorbate 20. Since, in the view of the authors, the inclusion of polysorbate 80 did not add any benefit to these formulations, I would not expect that adding polysorbate 20 would give a different result – however – I would not be dissuaded from testing another polysorbate (for instance polysorbate 20) either.

22. I also believe that the skilled person would expect that polysorbate 20 and 80 should be readily substitutable, given that both were widely used in approved antibody formulations by May 2014 and were known to generally behave similarly in stabilising protein formulations. In this respect, I note that the Bender publication (which I discuss further below and which states that it relates to "*obvious alternative formulations*" of adalimumab) sets out proposed formulations of adalimumab on page 5, and teaches that either polysorbate 20 or 80 may be used. Moreover, the formulation comprising a histidine-citrate buffer that is described by Bender has the exact same set of excipients as formulation H-11 in Manning (citrate, histidine, mannitol and NaCl as well as surfactant), but provides that either polysorbate 20

or polysorbate 80 may be used as surfactant while H-11 uses polysorbate 80. I believe this is reflective of the skilled person's expectation, and is consistent with my view that they would not be dissuaded from using polysorbate 20 (in place of polysorbate 80 used in formulation H-11) in the context of the formulations disclosed in Manning.

PLS Modelling

23. Manning carries out a so-called Partial Least Squares ('PLS') analysis of the combined data on adalimumab physical stability (viz. the fraction of monomeric adalimumab left after t1 (one week at 40° C) and/or t2 (two weeks at 25° C), measured either by SEC or HPLC), using data in blocks A-H, in particular blocks B to G. Based on correlation coefficients in Table J (using t0-t1 values measured by SEC), he concludes that His, Gly, Arg and polysorbate 80 are the most potent stabilizers while NaCl, citrate and phosphate are destabilizers. According to Table K (SEC monomer contents t1 and t2), His, Gly, Arg and polysorbate 80 are potent stabilizers. In fact, in the text Manning claims polysorbate 20 to be stabilizing (page 103) but the data in the table suggest that this is a typographical error, so that it is rather polysorbate 80 which is stabilizing, while polysorbate 20 has no significant effect in this analysis; although I note that Manning states on page 102 (also in relation to PLS Model A) that "*PS20 provides significant stability when used above 0.04%*". On page 103 Manning also states that citrate, phosphate and NaCl are again significant destabilizers; that pH is significant (presumably destabilizing) and EDTA is destabilizing but Met stabilizing. Finally, from Table L (loss in HPLC monomer content at t1 compared to t0), Manning concludes that phosphate, citrate, acetate and EDTA are destabilizing while only His (and to an insignificant extent Gly and Arg) are concluded to be stabilizing.

24. A great weakness of these analyses is that no statistical significance is provided. Manning states that statistically significant parameters are highlighted in bold in Table J and also mentions in one instance (phosphate in Table L) whether effects are statistically significant or not but does not provide additional information to support these claims. He also seems to use the terms "potent stabilizer" and "significant stabilizer" interchangeably in Tables J and K, further confusing any statistical conclusions. Accordingly, I have reanalysed the data using the same software (Unscrambler X from Camo Software) to evaluate the statistical significance of the different parameters with particular focus on polysorbate 80 and polysorbate 20. The first conclusion I make based on my own analysis is that the data clearly cluster in two groups, namely (1) data from incubation at low pH (around pH 3.5, only 8 data points) and (2) data from incubation around pH 5.2, 72 points). Incubation at low pH leads to a very significant loss of monomer (ca. 25-75% according to SEC t1 and up to 35% at SEC t2) while incubation around pH 5.2 only reduces monomer content by ca. 1-2%. This makes it in my view inappropriate to combine the two data sets since low pH data can skew the contributions of different parameters and in any case are irrelevant for realistic formulation studies. I therefore exclude the 8 data points recorded at low pH conditions. For the remaining 72 data points, I have reconstructed the Manning analysis in the 3 blocks using Unscrambler X using as far as possible the same analysis parameters as Manning. [note: Specifically I have used a random cross validation model in which sample data are stepwise and systematically left out from the calibration data set to gauge the prediction power of the data. I also include quadratic terms to include buffer-buffer and buffer-pH interactions.] The analysis provides a number of insights. Of particular relevance here are:

i) score plots (which identifies potential subclusters of data; for the 72 data points used, there was no obvious clustering);
ii) predictability, *i.e.* correlation between measured (reference) data values (here monomer concentration at t1 and/or t2) and predicted values; the correlation is generally rather poor with correlation coefficients between 0.1 and 0.6, many well below 0.4;
iii) identification of significant variables. This is estimated from the weighted regression coefficients which has to be significantly different from zero at the 5% level for the parameter in question (e.g. buffer concentration) to be considered relevant (i.e. determined to be different from zero with statistically significant accuracy). The magnitude of the regression coefficient describes to what extent the parameter affects the stability.

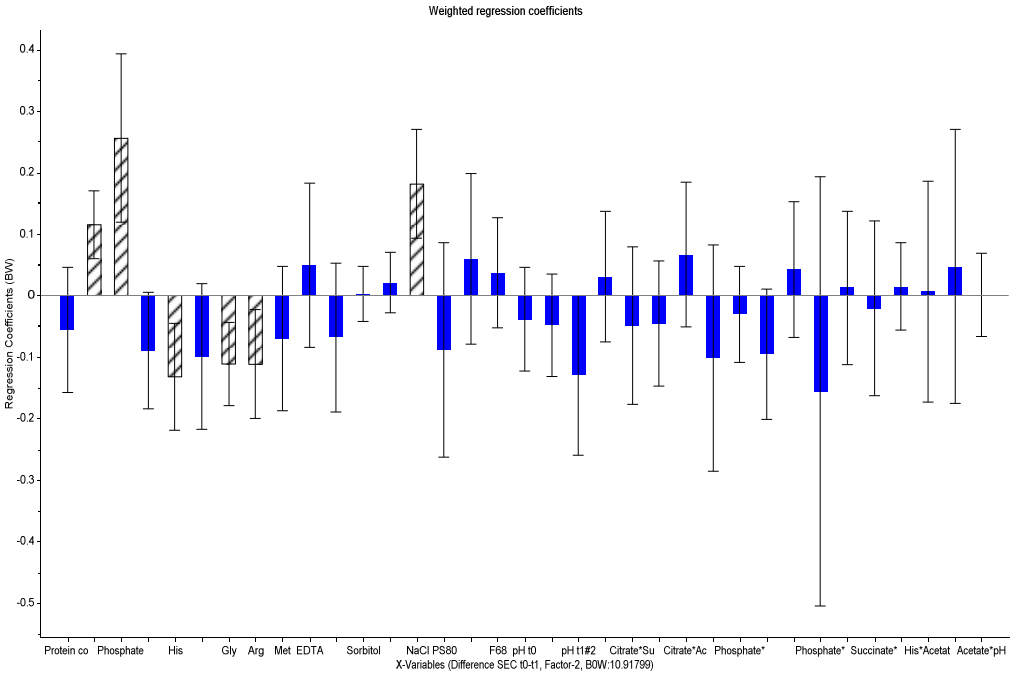
25. Below I have summarized which parameters were found to be statistically significant in my analysis following the three different approaches described by Manning:

Y-variable: SEC t0-t1 (Model A)		Y-variable: SEC t1, t2 (Model B)		Y-variable: HPLC t0-t1 (Model C)	
Parameter	Effect	Parameter	Effect	Parameter	Effect
NaCl Phosphate Citrate	Destabilizing	NaCl Phosphate Citrate Succinate-His	Destabilizing	Succinate-pH	Destabilizing
Histidine Glycine Arginine	Stabilizing	Histidine Glycine Arginine Succinate	Stabillizing	pH	Stabilizing

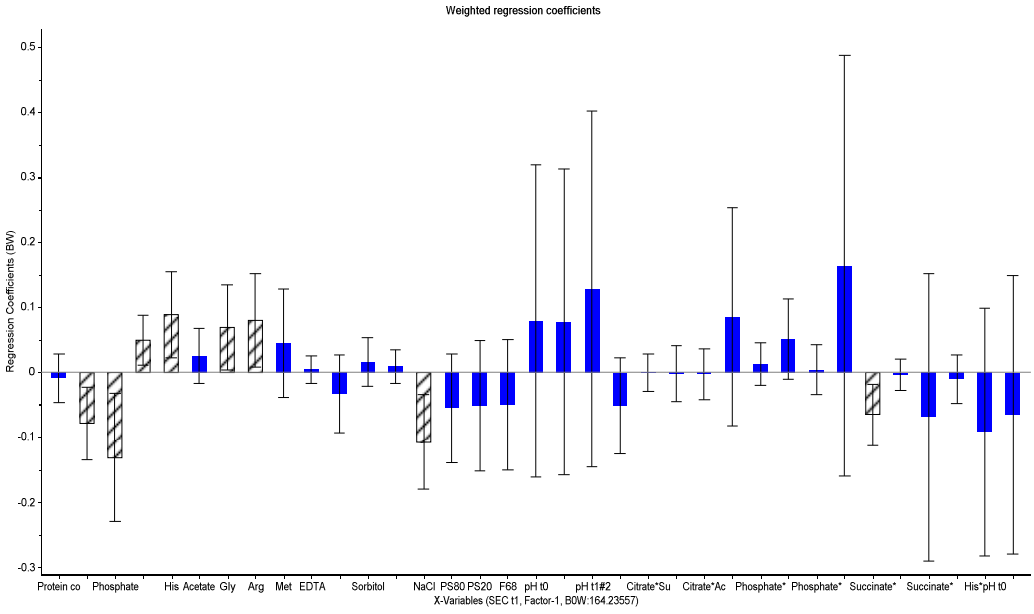
26. Plots indicating the magnitudes and errors of the regression coefficients for the different parameters are shown below. As mentioned above, the *magnitude* (overall size) of the regression coefficient describes how strongly that parameter influences

the stability (*i.e.* the t1 and/or t2 value). For Tables J and L, a negative value means that the parameter is stabilizing (because an increase in that parameter leads to a decrease in the loss of monomer); for Table K, a positive value means that the parameter is stabilizing (because an increase in that parameter leads to an increase in monomer amount and thus stability) and vice versa for a negative value. Parameters which are statistically significant (*i.e.* whose associated error bars are smaller than the value of the regression coefficients) are shown as hatched columns, while parameters which are *not* statistically significant (because their error bars are larger than their values and therefore cross the zero line) are shown in blue. In addition, all significant parameters are listed in the Table above.

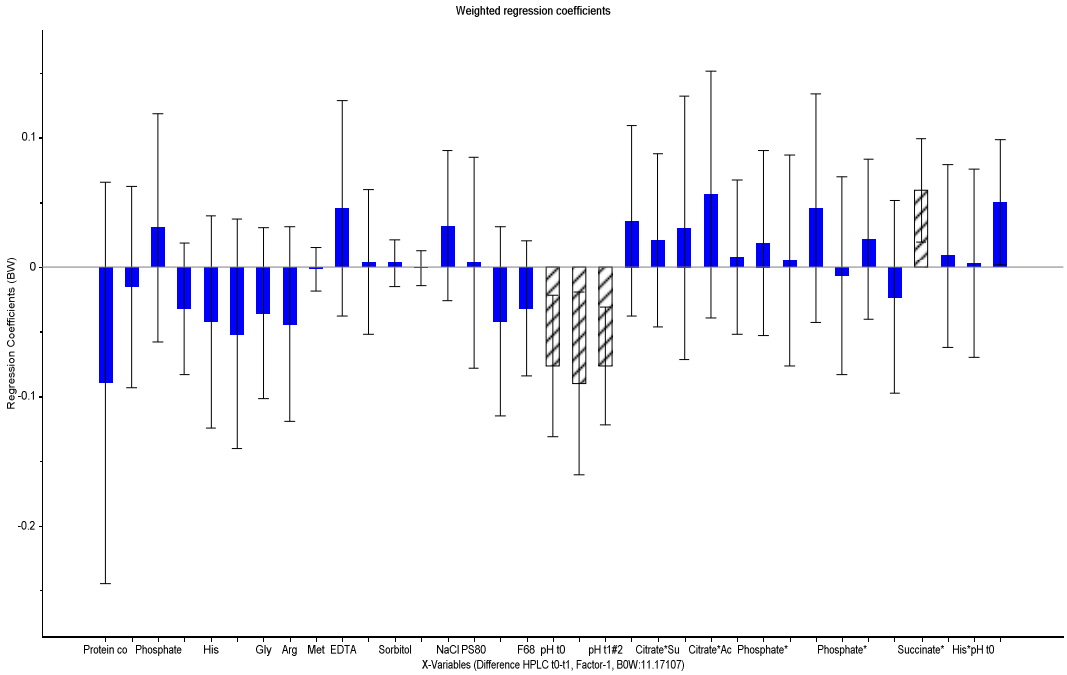
Model A:



Model B:



Model C:



27. I should emphasize that this data analysis is aimed at identifying which parameters are significant, unlike the analysis in Manning. It is striking that none of the analyses identify any surfactant as having a statistically significant effect on stability.

28. Thus, a properly conducted PLS analysis based on the data in Manning does in my view not provide any basis for concluding that polysorbate 80 should be more stabilizing than polysorbate 20.

The Bender Publication

29. I have been provided with and considered a copy of a paper entitled 'Alternative buffers for pharmaceutical anti-TNFalpha monoclonal antibody formulations', authored by A Bender (the "Bender publication") which is dated 6 February 2013.

30. The Bender publication states that it concerns "*further suitable liquid formulations for Adalimumab based on obvious alternative buffer systems*" (page 2, under the heading Summary).

31. The publication focuses on alternative buffers to the Humira® phosphate-citrate system, and on page 5 it summarises "*alternative Adalimumab compositions*". For each component in the alternative compositions a wider and narrower range of values are provided, the narrower range being said to be more preferable. I set out the compositions in the table below, and where different units are used in claim 1 of the Utility Models I have provided these in brackets.

Component	**Wider range**	**Preferred range**
pH	4.9 – 6.5	4.9 – 5.5
Adalimumab	20 – 130 mg/ml	45 – 55 mg/ml

Sodium chloride	1 – 10 mg/ml	6.0 – 6.4 mg/ml
Mannitol	2 – 25 mg/ml (11.0 – 137.2 mM)	10 – 14 mg/ml (54.9 – 76.9 mM)
Polysorbate 20 or 80	0.1 – 5 mg/ml	0.5 – 2 mg/ml
Buffer (selected from 1-9 on pages 6 and 7)	0.5 – 30 mM	0.5 – 30 mM

32. In addition to adalimumab, the alternative compositions all comprise mannitol and sodium chloride as used in Humira®. The alternative compositions provide a choice between polysorbate 20 or 80, and as I explained above I believe this reflects the skilled person's expectation that either surfactant would be suitable to use. The nine different buffer options are set out on pages 6-7, and list phosphate, citrate, histidine and acetate, and all dual-buffer combinations of them apart from phosphate-citrate. In relation to the buffers it notes that the "*suggested buffer alternatives are commonly used in liquid formulations*" and that "*[a]ll suggested alternatives provide sufficient buffer capacities, show good long term stability, and have a good safety record*." Tables 1 and 2 also show how the various buffers and combinations can be made and the buffering range for each [note: I note that Table 1 contains an obvious typographical error by using 'Monobasic sodium phosphate' twice, whereas, as is apparent from Buffer 1 and Buffer 2 on page 6, this should be 'Monobasic sodium phosphate' (first line) and 'Dibasic sodium phosphate' (second line). The skilled person would immediately recognise this as an obvious error. Monobasic sodium phosphate is the more acidic of the two salts, and therefore it can also be combined with sodium hydroxid(e) (column 1b) to create buffer solutions in the pH range 5.8-8.0; conversely, the more alkaline dibasic sodium phosphate could be combined with phosphoric acid (column 1c) to achieve the same pH buffer range.]. I note the histidine-citrate combination is effective over pH 3.5 – 7.0, so well beyond even the wider range of the alternative compositions.

<u>Claim 1 of UM 070</u>

33. Claim 1 of UM 070 provides ranges for the pH, sugar stabiliser and surfactant. The wider ranges in the Bender publication all overlap with those in claim 1 of UM 070, and with the preferred ranges the values are all fully within claim 1 (except that the pH extends to 4.9 not 5.0).

34. Therefore, starting from the citrate-histidine buffer combination in the formulation described by Bender, whether using either polysorbate 20 or polysorbate 80, the only difference from claim 1 of UM 70 is that mannitol is present as the sugar, not a sugar listed in claim 1 of the UM. However, substitution of the sugar excipient would have been routine formulation work, and I note and agree with the comments made by the DKPTO in their letter relating to UM 070 where it states that it was "*known within aqueous formulations of adalimumab that mannitol may be replaced with other sugar stabilisers such as sorbitol and trehalose as suggested in Manning…".*

<u>Claim 1 of UM 071</u>

35. Starting from the citrate-histidine buffer in the formulation described by Bender, and making use of polysorbate 20, would produce a formulation which would fall directly within claim 1 of UM 071.

Comments on Professor Müllertz's supplementary declaration
36. In light of the conclusions that Professor Müllertz draws as to the teachings that a skilled person would take from Manning, I stand by what I have previously stated, namely that when it comes to any conclusions drawn in Manning (for instance on page 108 with regard to the different surfactants tested), the skilled person would always have looked at the underlying data presented in Manning to seek to understand the basis for such a conclusion, and to judge how significant such a conclusion could be considered to be. This would especially have been the case if a finding is described by Manning himself as "surprising".

37. Professor Müllertz states that the teachings on pages 107 et seq. of Manning are "*…backed by the PLS model A-C analyses that Manning explains in details on pages 94-107*" (section 3.2) and that "*Manning's teachings on page 107 et seq. are based on the PLS analyses…*" (section 3.5.). As I believe is clear from my comments with regard to the strength of the PLS analyses and the results thereof reported in Manning in Section 5 above, I do not agree that the skilled person would have concluded that the PLS analyses in Manning provide any basis for the comments on page 107-108 that "*other surfactants tested (PS20 and F-68), do not appear to be nearly as effective as PS80.*". My analysis shows that none of the two surfactants have any statistically significant effect on adalimumab stability, neither in Table C nor the other two tables.

38. Thus, in my opinion neither the relevant data per se nor the PLS analyses in Manning provide any basis for concluding that polysorbate 80 is better than polysorbate 20.

Conclusions
39. In conclusion, I do not agree that the teaching in Manning would dissuade the person skilled in the art from formulating adalimumab with the use of polysorbate 20. As I have explained above, based on Manning the skilled person would expect to achieve a formulation performing just as well as a formulation containing polysorbate 80, which is well in line with polysorbate 20 being amongst the relatively few commonly used surfactants in formulations of monoclonal antibodies prior to 2014. This is further reinforced by the Bender publication.

40. The teachings disclosed in the Utility Models would not make me depart from this approach since they do not support a conclusion that either polysorbate 80 or 20 would provide an advantageous effect over the other."

Sven Frøkjær har i erklæring af 25. april 2019 anført bl.a.:

"…
The Utility Models
4. As I explained in my First and Second Declarations, I have read the Utility Models including the claims and I understand that the claims define the scope of protection of a utility model and that the claims are to be read and construed in light of the description of the utility model, which includes the data and figures. The Utility Models are concerned with the development of alternative formulations of

adalimumab to that of AbbVie's Humira®. I have considered in my previous declarations the approach that the skilled person embarking on such a project in 2014 would have taken.

5. In both of the Utility Models, claim 1 describes an aqueous formulation of adalimumab in which certain excipients are present (adalimumab, histidine, a citrate buffer, a sugar stabiliser, and polysorbate 20 or, in the case of UM '070, either polysorbate 20 or polysorbate 80). It is also a requirement for those claims that certain other specified excipients are not present – the formulation has to be free of amino acids other than histidine (or include one or more amino acids other than histidine in a collective concentration of at most 0.1 mM) and be free of a phosphate buffer (or include a phosphate buffer at a concentration of at most 0.1 mM). The claims describe the excipients as a "*histidine buffering agent or histidine buffering system*", a "*citrate buffer*", a "*sugar stabiliser*" and a "*surfactant*".

6. I have been shown the Summary of Product Characteristics for Imraldi® and note that histidine and sorbitol (amongst others) are included in the list of excipients at section 6.1. I have also reviewed the declaration of Professor Anette Müllertz dated 4 March 2019 [note: I discuss below Prof Müllertz' further comments on this issue in her Supplementary Declaration. Once again she does not directly comment on whether or not sorbitol is acting as a stabiliser of adalimumab in Imraldi®, although I note that in the final paragraph of her report she points to data in Manning and Fraunhofer as showing that sorbitol has a positive effect on adalimumab stability in those particular formulations.], in which she has been asked to consider the functions of the histidine and the sorbitol in the Imraldi® formulation. I understand her views to be as follows:

- histidine plus citrate is a good buffer combination at pH 5.2. In addition to acting as a buffer in Imraldi®, Prof Müllertz considers that histidine will also have a protein stabilising effect; and

- as regards the role of sorbitol, she references my text book and notes that "*sorbitol* generally works as a stabilising agent"[note: Prof Müllertz notes also, in both of her declarations, that sorbitol inherently acts as a tonicity agent to increase the osmolality of the formulation.]. I do not understand Prof Müllertz to be arguing that sorbitol acts as a stabiliser of all antibodies in all formulations or that it is necessarily doing so in Imraldi®, at least she does not say so.

7. As I have explained in my earlier declarations, sorbitol may affect the physical stability of a protein formulation, in the sense that it mitigates against protein denaturation. This is well known and can be found in text books such as my own. However, whether, and if so to what extent, it does so in any particular formulation depends upon multiple factors, most notably the particular protein of interest, but also the concentration of sorbitol, the other excipients present, the pH and/or the presence of contaminants and impurities in the formulation note: The following review articles from 1999 and 2007 illustrate this point. Wang (1999) (International Journal of Pharmaceutics 185 129-188) discusses the different impacts of sugar stabilisers on different proteins, see in particular section 4.2 on stabilisation of proteins in aqueous formulations by excipients. Wang notes that the stabilising effects of different excipients are "usually concentration- and protein-dependent, although high concentrations of excipients may not be necessarily more effective, and

in some cases can have negative effects" and also that "not all proteins can be stabilized by sugars or polyols" pp163 and 166, respectively (examples concerning sorbitol are given and an instance of a protein (IL-1R) being destabilised by mannitol is also described). Similarly, Wang et al 2007 (Journal of Pharmaceutical Sciences, Vol 96, 1: 1-26) explains that a variety of excipients in addition to sugars may be used as stabilisers and in some formulations may be "equally or even more effective in protecting antibodies"(p16) and that sugars are not always effective as stabilisers or could even promote aggregation (an example is given of sucrose having been shown to promote aggregation of an IgG1 antibody).]. Accordingly, whether or not sorbitol acts to stabilise adalimumab in SB5/Imraldi® by mitigating against denaturation needs to be tested, e.g. by looking at whether its inclusion prevents the formation of aggregates, which would otherwise have formed, when adalimumab is subjected to different kinds of stress.

8. I set out the definitions of a "stabiliser" used in the Utility Models in paragraphs 21 – 22 of my Second Declaration (essentially this is "…a component which facilitates maintenance of the structural integrity of the biopharmaceutical drug…"). I note that the Utility Models also consider that the degree of stabilisation is important. For example, as also mentioned in my Second Declaration, the "Parameters when subjected to thermal stress" are set out on page 36, lines 20 – page 40 line 16 (UM '070) and page 36 line 17 – page 40 line 13 (UM '071) of the Utility Models, and set limits for the changes in stability which are considered acceptable when the formulations are exposed to thermal stress [note: Similarly, numerical thresholds of stability are set for mechanical, light and freeze/thaw stress.]. For the amount of aggregates (a common measure of denaturation and instability), the Utility Models state that when the formulation is subjected to 40^0C for 28 days (i.e. 4 weeks): "Suitably the quantity (or concentration) of aggregates … present within the liquid pharmaceutical composition increases by no more than a factor of 4 (i.e. 4 times the amount relative to an arbitrary start time) …, suitably by no more than factor of 3, suitably by no more than factor of 2.5, suitably *by no more than factor of 2.2*."

9. In this declaration I have considered the data from experiments performed by SB with the SB5 formulation to determine the functional effect of the various excipients on the overall stability of this specific formulation. Specifically, I address below whether the sorbitol present in the SB5 formulation is functioning as a 'sugar stabiliser' according to the Utility Models.

Contribution of the components of SB5 to stability

10. I understand from the lawyers representing SB that a number of experiments were performed by SB in order to investigate the contributions of certain of the components of the SB5 formulation to the stabilisation of adalimumab. The protocols which were followed by SB in these experiments and the results obtained are set out in Annex 1 and Annex 2 to this declaration, respectively.

11. The experiments described in Annex 1 corresponds to the stress testing performed in the Utility Models (which I described at paragraph 16 of my Second Declaration), except that SB's experiments were all performed in triplicate by measurement of 3 independent samples of the same formulation (each sample prepared

and the testing performed separately). The purpose of the SB experiments was to systematically investigate the role of three of the different excipients (citrate, histidine and sorbitol) present in the SB5 formulation, and in particular to assess their contribution to the physical stability of the formulation. By removing each of these excipients in turn (while holding the concentration of all other excipients constant), it is possible to see the contribution of each of these excipients to the overall physical stability of the formulation, i.e. whether a given excipient acts to stabilize adalimumab in the SB5 formulation by mitigating against protein denaturation.

12. The experiments were carried out using:

(i) SB5 drug substance (i.e. the same drug substance as is used in the formulated Imraldi® product in the form ready to fill into syringes) as a control; and

(ii) alternative 'test' formulations in which SB's adalimumab product were prepared in accordance with the approved 'recipe' for Imraldi®, but in each case with the systematic removal of one excipient (citrate, histidine or sorbitol) [note: The other excipients are all present at the same concentration as in SB5/Imraldi®. As noted in the protocols at Annex 1 the pH of all formulations was adjusted to be around 5.2.].

13. In summary, the following formulations were prepared and tested:

Formulations	**3.** 50mg/mL Adalimumab	**5. Excipients**			
		10mM Na-Citrate	59mM Histidine	25mg/mL D-sorbitol	0.8mg/mL Polysorbate 20
SB5 (control)	15. ✓	16. ✓	17. ✓	18. ✓	19. ✓
Citrate-free	22. ✓	23. ×	24. ✓	25. ✓	26. ✓
Histidine-free	29. ✓	30. ✓	31. ×	32. ✓	33. ✓
Sorbitol-free	36. ✓	37. ✓	38. ✓	39. ×	40. ✓

14. The stability of these formulations was investigated by exposing them to physical stress under the following experimental conditions:

A. Samples exposed to extended thermal stress – storage at 40^0C for 1 week, 2 weeks and 4 weeks.
B. Samples exposed to freeze-thawing – five cycles of freezing to -70^0C and thawing.

C. Samples exposed to mechanical agitation – 200 revolutions per minute (rpm) for 48 hours at room temperature.

15. For each sample in Experiments A – C, protein aggregation (measured as %HMW (high molecular weight species)) and the osmolality were recorded at the start of the experiment and after the samples had been exposed to the relevant stress test. The analytical techniques used by SB in these experiments are very similar to those followed in the Utility Models.

16. This is a standard experimental design for preliminary assessment of a formulation, using methods of stability testing which are described in the Utility Models for investigating the role of each of the excipients in the formulation. My comments on the results are set out below.

Formulation stability – no stress

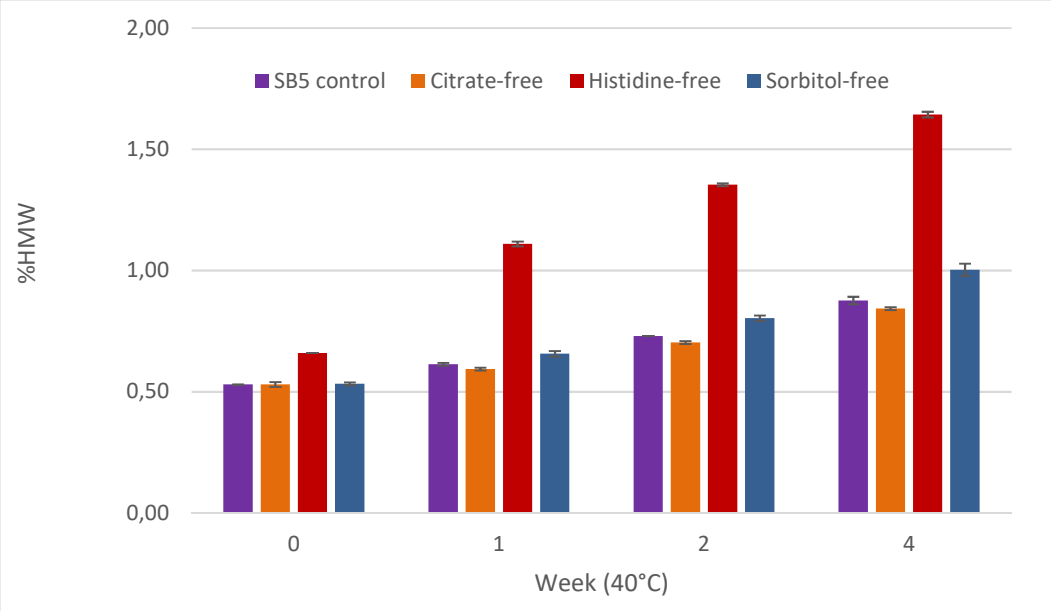
17. Tables 1 – 3 in Annex 2 show the initial osmolality and aggregation (%HMW) of each of the samples, as measured before the thermal, freeze-thaw and mechanical stresses had been applied (see columns 5 and 7). As seen in Tables 1 and 2, the initial %HMW of all three SB5 (control) samples in Experiments A (thermal stress) and B (freeze-thaw) was 0.53%. In the absence of citrate and sorbitol (separately), the initial %HMW values for all of the samples remained at 0.53 ± 0.01%. However, in the histidine-free samples the initial %HMW was consistently slightly higher (0.66% in all three samples). This is not a large increase over the 'baseline' of 0.53%. The results of the mechanical stress experiment are shown in Table 3. Again, in Experiment C, the histidine-free formulations have a consistently higher initial %HMW than the other formulations. The fact that a higher initial level of aggregation is seen in all of the samples lacking histidine suggests that there is a slight decrease in the stability of these formulations without histidine compared to the control SB5 formulation, even prior to subjecting these samples to the stress tests.

18. Osmolality is a measure of the osmotic pressure exerted by the formulation across a semipermeable membrane and depends upon the number of molecules present in solution and is unrelated to the issue of "stability" as used in the Utility Models. Accordingly, as would have been expected, the removal of each of the different excipients will reduce the osmolality to some extent. However, the formulations lacking sorbitol each showed a much greater reduction in osmolality (from a mean of 289 mOsm/Kg to 136 mOsm/Kg (across all three experiments), compared with a reduction to 262 mOsm/kg in the absence of citrate and to 179 mOsm/Kg in the absence of histidine). This demonstrates (as expected) the significant impact of sorbitol on tonicity [note: As Prof Müllertz notes on page 3 of her first declaration, sorbitol will "inherently always work as a tonicity agent".]. This result is entirely as expected, since sorbitol is commonly used in pharmaceutical formulations (including for protein drugs) as a tonicity modifier i.e. to increase the osmolality of the formulation in order to achieve compatibility with physiological fluids (e.g. to achieve an isotonic solution) and thereby avoid problems with tolerability of the formulation upon subcutaneous or intramuscular injection.

Experiment A – thermal stress

19. Experiment A records the effects of exposure of the samples to thermal stress (i.e. storing the samples at 40ºC). The results of this experiment are shown at Annex 2, Table 1 and depicted below in Figure 1.

20. An increase of 0.35 ± 0.02% HMW was seen in the SB5 (control) samples after 4 weeks exposure to elevated temperature [note: Throughout this declaration the change reported is the mean of the changes for the three samples tested. As can be seen from the data in Annex 2 and the error bars in the figures, the degree of variability between sample formulations made up separately and tested in triplicate is extremely low. The standard deviation of the relevant experimental data are also set out in the Tables at Annex 2.]. This was similar to the results for the samples without citrate (0.31 ± 0.01% increase) and those without sorbitol (0.47 ± 0.03% increase). However, the histidine-free samples showed a much greater increase in aggregation of 0.98 ± 0.01% after 4 weeks. When adjusted by deducting the increase of 0.35% HMW seen in the control formulations, the increase in formation of high molecular weight aggregates seen in the samples lacking histidine was 0.63% (corresponding to a 2.8 fold increase over the SB5 (control) formulation), compared with 0.12% in samples lacking sorbitol (corresponding to a 1.3 fold increase over the SB5 (control) formulation) and no increase at all in the citrate-free formulations. Figure 1 below illustrates how the increase in %HMW upon heat stress is much greater in the absence of histidine (compared with the other formulations tested). Whereas the increase in aggregates over time (the gradient of the line connecting the bars) is much the same for the SB5 (control) formulation and the formulations lacking citrate or sorbitol, the rate of increase in aggregates is much greater for the histidine-free formulations.



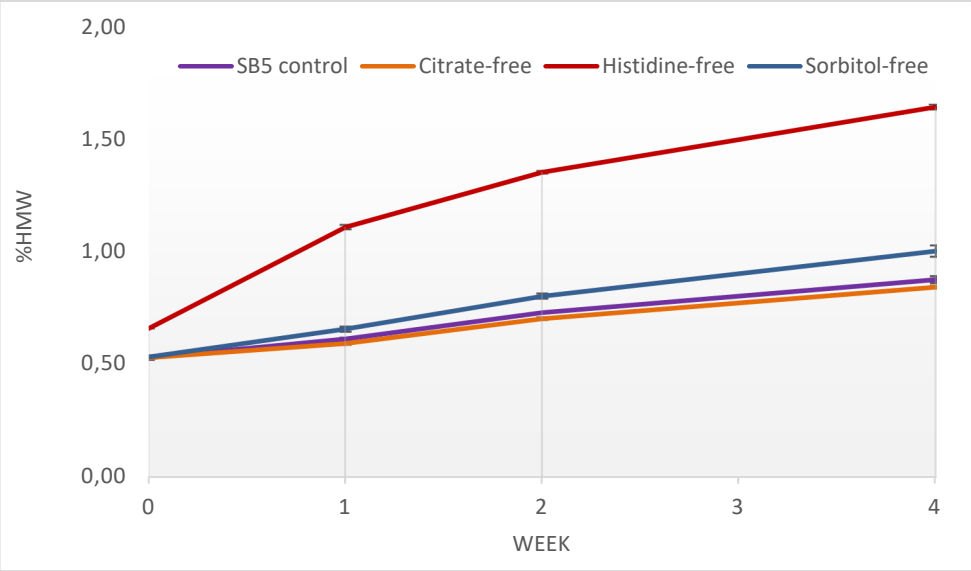


Fig. 1. Impact of elevated temperature on protein aggregation – the same data is shown both as a bar chart and as a line graph. SB5 formulations tested in absence of (separately) citrate, histidine and sorbitol. Error bars show standard deviation; although in some instances the standard deviations are so small that the error bars are barely/not visible. See Annex 2, Table 1 for values.

21. No material impact on osmolality was seen as a result of exposure to elevated temperatures (40^{0}C) for 4 weeks.

Experiment B – freeze-thaw

22. It is well known that repeated cycles of freezing and thawing a protein can stimulate aggregation by providing nucleation surfaces at the ice-water interface and sometimes by causing pH changes and/or phase separation. Experiment B examined the effect of repeatedly freezing and thawing the samples on protein aggregation, as measured by %HMW, and osmolality. The results are set out in Annex 2 at Table 2 and depicted below in Figure 2.

23. The formulations also seem fairly robust so far as protein aggregation is concerned after exposure to 5 cycles of freezing to -70^{0}C and then thawing. The protein aggregation in the SB5 (control) samples increased by 0.04 %HMW when exposed to freeze/thaw cycling. The increase in %HMW when sorbitol was removed was 0.05 ± 0.01%, and when citrate was removed the increase in %HMW was also around 0.05%. However, when histidine was removed the %HMW was slightly higher; an increase of 0.18% HMW above an already elevated baseline level of protein aggregation in this formulation (from 0.66% to 0.84% in all three samples) i.e. an increase of 0.14% after deduction of the increase in %HMW seen in the SB5 (control) samples.

24. Sorbitol along with other non-reducing saccharides such as sucrose and trehalose is known to have a particular effect on stabilising proteins upon freezing and for this reason sorbitol is sometimes used as a lyo/cryoprotectant e.g. in lyophilised protein formulations (although sucrose and trehalose are usually the first choice). Accordingly, if sorbitol is acting as a stabiliser in the SB5 formulation, one would have expected its removal to have had a particularly significant impact upon the amount of aggregation seen upon freeze/thaw testing. However, this experiment

shows that this is not the case. Figure 2 below shows no increased instability upon freeze/thaw stress (5 cycles) in the sorbitol-free formulations.

1.

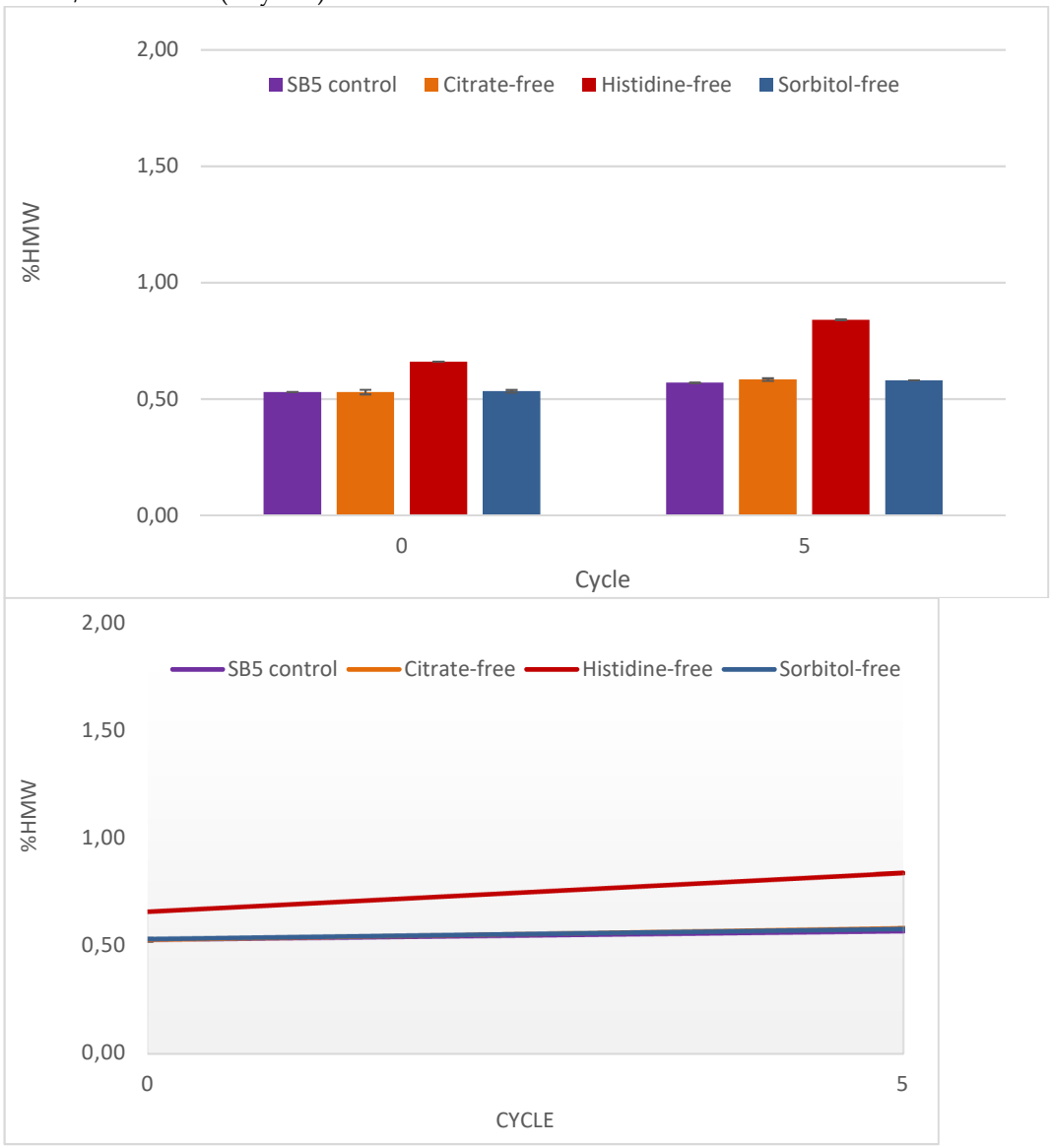


Fig. 2. Impact of freeze/thaw cycling on protein aggregation – the data is shown as a bar chart and as a line graph. SB5 formulations tested in absence of (separately) citrate, histidine and sorbitol. Error bars show standard deviation although in some instances the standard deviations are so small that the error bars are barely/not visible (and see also Annex 2, Table 2).

25. There does not appear to be any significant impact on osmolality of the formulation by exposure to 5 cycles of freezing to -70^{0}C and then thawing.

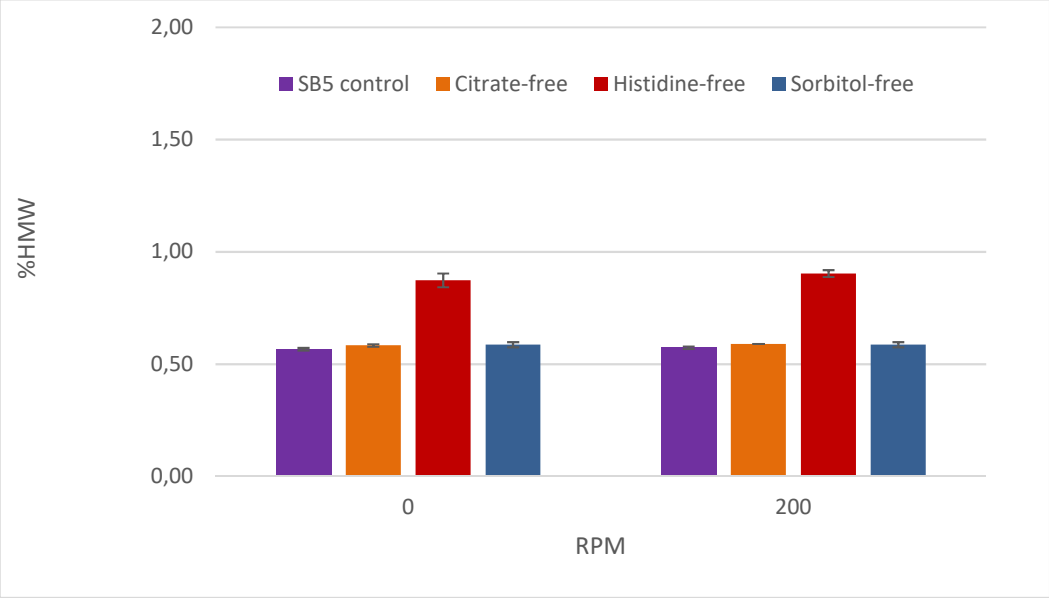
Experiment C – mechanical stress

26. Experiment C is a mechanical stress test. The samples were agitated at 200rpm for 48 hours and the amount of high molecular weight (%HMW) aggregates measured. The results are set out in Annex 2 Table 3 and depicted below in Figure 3.

27. As set out in the protocols new samples were prepared for Experiment C, both for the controls and for the test formulations. This is also evident from the different initial osmolality and %HMW values measured in Experiment C compared with

the formulations tested in Experiments A and B. However, as can be seen by comparing the osmolality and aggregation (%HMW) of the formulations prior to exposure to mechanical stress with the formulations tested in Experiments A and B, the osmolality and aggregates content of the samples and also the impact of 'removing' the individual excipients (citrate, histidine and sorbitol) were very similar. In the samples without histidine, the levels of protein aggregates were higher compared to the control samples of SB5 and those without either citrate or sorbitol. There was, however, no increase in %HMW in any of the samples upon being subject to mechanical stress.

28. Further, as with the formulations tested in Experiments A and B, the osmolality was impacted by removal of each of the excipients, with a particularly marked reduction in osmolality seen in the sorbitol-free formulations (again the osmolality was more than halved in the absence of sorbitol). I note, however, that in this experiment the increase in the starting level of high molecular weight aggregates measured in the histidine-free samples (prior to exposure to mechanical stress) was even more pronounced than in the formulations tested in Experiments A and B.



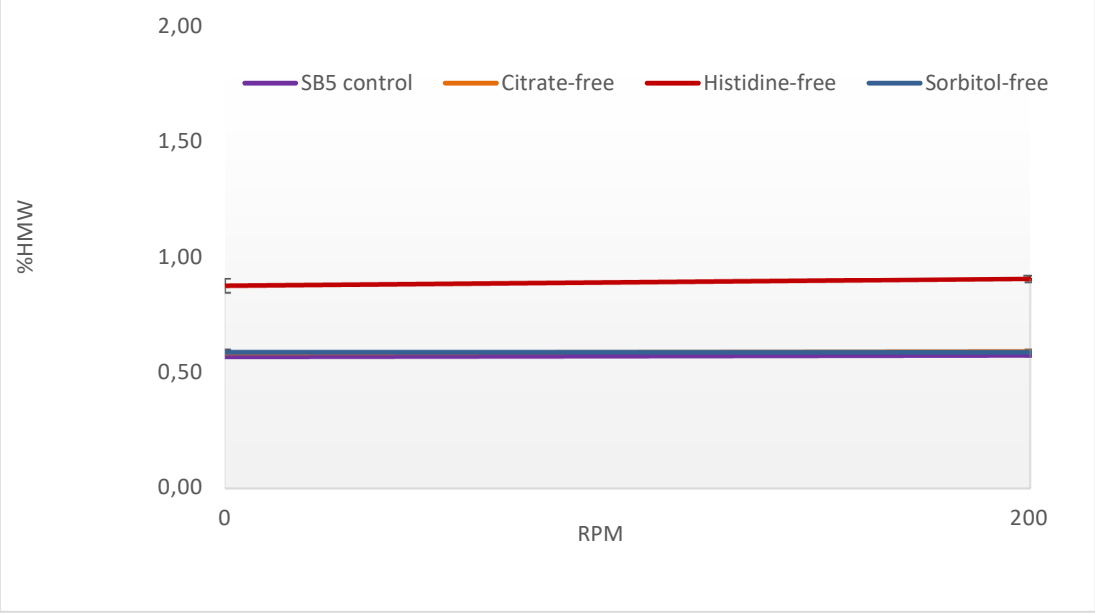


Fig. 3. Impact of mechanical stress (agitation at 200 rpm for 48h) on protein aggregation – the data is shown as a bar chart and as a line graph. SB5 formulations tested in absence of (separately) citrate, histidine and sorbitol. Error bars show standard deviation although in some instances the standard deviations are so small that the error bars are barely/not visible (and see also Annex 2, Table 3).

Conclusions on the SB experiments

29. In these experiments the role of histidine, sorbitol and citrate in the approved formulation of Imraldi® was tested in a systematic manner by 'removing' each of these excipients one at a time (whilst keeping all other excipient concentrations constant) and studying the impact on osmolality and protein aggregation (%HMW) relative to the results of the control SB5 samples. The experiments were performed in triplicate and showed very low levels of variation and good reproducibility between repeated experiments.

30. Based on the results of these experiments to investigate the impact of the presence/absence of each of these excipients on the SB5 formulation and on its robustness to different types of physical stress (heat, freeze/thaw and mechanical agitation), it is apparent that:

- Consistent with my conclusions based on Manning (at paragraphs 71-73 of my Second Declaration), adalimumab seems to be a resilient protein, as demonstrated by the fact that removing a single excipient from SB5 (either sorbitol, citrate or histidine) and exposing the formulation to different stresses has only a very limited impact upon the level of denaturation measured as the amounts of aggregates formed. The exception was the significant increase in %HMW observed in the histidine-free samples upon exposure to heat stress (4 weeks storage at 40^0C).
- Histidine stabilises adalimumab in the SB5 formulation, as demonstrated by the slightly higher initial levels of aggregates formed in the formulations lacking histidine and the consistently greater increase in aggregation measured in the histidine-free formulations upon exposure to thermal stress.

31. I comment below on the functions of the excipients in the context of the claims of the Utility Models.

Conclusions in light of the Utility Model definitions

32. I have been asked to comment on whether the sorbitol present in Imraldi® satisfies the definition of a 'sugar stabiliser' as used in the Utility Models. In my view it does not.

33. As I have noted above and in my Second Declaration, the Utility Models set thresholds for demonstrating an effect on stability [note: I am not aware of any of the thresholds applied by the Utility Models as being 'standard' cut-offs for stability e.g. in accordance with regulatory guidance. Although these thresholds seem like reasonable ones to apply, my preference would be to set absolute levels for %HMW aggregates, rather than a test based solely on the fold increase.]. For thermal stress testing (28 days at 40^0C) the Utility Models set a series of thresholds for the level of aggregates (as determined by SE-HPLC) – that the amount of adalimumab aggregates should increase by no more than a factor of 4, by no more than a factor of 3, by no more than a factor of 2.5 or by no more than a factor of 2.2 (see page 36 lines 20-28 (UM '070) and page 36 lines 17-25 (UM '071). In other

words, according to the Utility Models, for a formulation to be considered stable in the particular heat stress test protocol used therein (and also used by SB in its experiments) %HMW needs to increase by less than a factor of 4 upon exposure to 40^0C for 28 days or most preferably by less than a factor of 2.2 above the starting level.

34. For SB5 the initial level of %HMW is 0.53 ± 0.00% and this increases to 0.88 ± 0.02% after 4 weeks at 40^0C – an increase of a factor of 1.66 ± 0.02. Accordingly, SB5 satisfies even the most stringent test for thermal stability set by the Utility Models (less than or equal to an increase of a factor of 2.2).

35. Applying the same analysis to the formulations lacking histidine, citrate or sorbitol gives the following results:

Formulations	**%HMW t=0**	**%HMW t=4 wks**	**Fold increase**	**Test satisfied ≤ x 2.2**
SB5 (control)	0.53	0.88	1.66 ± 0.02	Y
Citrate-free	0.53	0.84	1.59 ± 0.02	Y
Histidine-free	0.66	1.64	2.49 ± 0.01	N
Sorbitol-free	0.53	1.00	1.89 ± 0.04	Y

36. Thus, removal of citrate or sorbitol does not impact upon the assessment of formulation stability to thermal stress set by the Utility Models. Even in the absence of sorbitol or citrate the formulation remains stable (as defined). In contrast, the removal of histidine raises the fold increase in %HMW to a factor of 2.49 ± 0.01 meaning that at least the most stringent test for stability is not satisfied for formulations lacking histidine.

37. According to the Utility Models, different thresholds are set for the level of aggregates that is acceptable upon exposure to each of the following stresses: mechanical, light and freeze/thaw (see page 36 line 20 to page 40 line 16 (UM '070) and page 36 line 17 to page 40 line 13 (UM '071)). As I have discussed above, exposure to mechanical stress or multiple freeze/thaw cycles had no material impact upon the level of denaturation measured as the amount of aggregates formed in the SB5 (control) formulations tested and this remained the case upon the removal of the excipients (histidine, sorbitol or citrate). In fact, in the freeze/thaw test the samples without histidine show an increase in aggregates of a factor of 1.27 ± 0.01 (from 0.66% to 0.84% (an increase of 0,18%)), which does not satisfy two of the tests set by the Utility Models (increased aggregation by no more than a factor of 1.1. or 1.2). For the formulations lacking sorbitol the %HMW increases by a factor of 1.09 ± 0.01 (from 0.53% to 0.58% (an increase of 0,05%)) and so narrowly satisfy these same stability tests. However, given how small the increases are in absolute terms

(0.18% versus 0.05% for histidine and sorbitol, respectively) I would not be comfortable drawing conclusions from these data. It is, however, supportive of the conclusion of the thermal stress testing – that in SB5/Imraldi®, histidine, but not sorbitol, is acting as a stabiliser (according to the Utility Models). Accordingly, SB5/Imraldi® satisfies even the most stringent thresholds for stability upon mechanical and freeze/thaw stress set by the Utility Models.

38. To sum up, in the heat stress experiments the negative effect on stability of removing the histidine is above the threshold set in the Utility Models as demonstrating an effect on stability. In contrast, for each of the three stress conditions tested, the SB5/Imraldi® formulations lacking sorbitol are still judged stable on even the most stringent criteria set by the Utility Models. Accordingly, I conclude from SB's experiments on its SB5/Imraldi® product that histidine is acting as a stabiliser, whereas sorbitol is not acting as a stabiliser (as such term is used in the Utility Models).

39. As can be seen from the osmolality data in SB's experiments, the inclusion of sorbitol has a significant effect on the tonicity of the formulation, and this would appear to be the reason for its inclusion in the SB5/Imraldi® formulation [note: Indeed I understand that this is consistent with how SB identified the role of the different excipients in SB5 in its 2014 regulatory submissions to EMA (i.e. histidine was referred to as the 'stabiliser' and sorbitol as the' tonicity agent').].

40. Related to the above, I note that on page 71, lines 25-28 (UM '070) and on page 71, lines 24-27 (UM '071) of the Utility Models it is stated that "…*polyols/sugars can positively impact the* thermal *stability of the protein, especially at pH≥ 6.2*…" [note: As I noted in my Second Declaration the Utility Models do not include results for the testing of any formulations having a pH below 6.0.]. The pH of the SB5/Imraldi® formulation is 5.2, i.e. much lower than the pH above which a positive impact of sorbitol on stability would be expected according to what is stated in the Utility Models.

Professor Müllertz' Supplementary Declaration

41. In section 4.1 on page 12 of Prof Müllertz' Supplementary Declaration she refers to the use of the term 'sugar stabiliser' in the claims of the Utility Models and states that "*The cited technical feature does not define what exact functionalities the adding of any of the mentioned sugar stabilisers will entail in an adalimumab formulation*" and that in her view the skilled person would understand "*that the term 'sugar stabilisers' is used to identify a group of compounds without defining exactly which technical function the adding of any member from the group in an adalimumab formulation will entail*". It is not clear to me whether Prof Müllertz' view is that a) the term 'sugar stabiliser' as used in the Utility Models does not require any functional activity or, if it does, that b) the Utility Models do not define exactly what that function is and/or what threshold level of activity needs to be achieved.

42. As I have already explained in paragraph 7 above and in my earlier declarations, whether or not (and to what extent) sorbitol acts as a stabiliser in SB5/Imraldi® needs to be determined by testing. This cannot be determined simply on the basis that sorbitol is known to act as a stabiliser of other proteins or even if, as here, sorbitol is known to act as a stabiliser of other adalimumab formulations containing different excipients. As above, I have concluded that, based on SB's experimental data, sorbitol is not acting as a 'sugar stabiliser' in SB5/Imraldi® (as such term is used in the Utility Models).

43. In section 4.2 of her Supplementary Declaration Prof Müllertz cites the definition of a 'stabiliser' according to page 14 of the Utility Models that this term "*refers to a component which facilitates maintenance of the structural integrity of the biopharmaceutical drug, particularly during freezing and/or lyophilisation and/or storage (especially when exposed to stress). This stabilising effect may arise for a variety of reasons, though typically such stabilisers may act as osmolytes which mitigate against protein denaturation*".

44. She focuses then on the statement that "…*such stabilisers may act as osmolytes which mitigate against protein denaturation*" (my emphasis). While I agree with Prof Müllertz that sorbitol will inherently act as a tonicity agent and also that certain 'tonicity agents' are also sometimes referred to as 'osmolytes' note: The term osmolyte (also sometimes referred to as organic osmolyte) is commonly used about compounds, which contribute to the (regulation of) osmotic pressure in living cells. Thus, in essence osmolytes are compounds affecting osmosis and play a central role in maintaining cell volume and fluid balance in living cells. Known osmolytes include a number of organic compounds such as polyols, amines, certain amino acids and urea. Urea, for instance, will not protect against protein denaturation, although it is a known osmolyte.], I disagree that "*Therefore it must follow that sorbitol is considered a 'stabiliser' in the context of the utility models*". This simply does not follow. Certain well-known osmolytes, e.g. urea, are known to *promote* protein denaturation, and are thus by definition not a stabiliser according to the definition in the Utility Models. In other words, Prof Müllertz seems to be ignoring the passages underlined above which state that the particular osmolytes referred to in this section of the Utility Models are a subset of osmolytes that are capable of acting as "stabilisers". According to the Utility Models, these stabilising osmolytes must satisfy the requirement of "*facilitat[ing] maintenance of the structural integrity of the biopharmaceutical drug*". Moreover to fall within the definition of "stabilisers" according to the Utility Models an osmolyte needs to "*mitigate against protein denaturation*" and thus provide a *stable formulation* as that term is defined in the Utility Models.

45. While sorbitol may be referred to as an 'osmolyte' and does, as I have explained above by reference to SB's data and the Utility Models, act as a 'tonicity agent' in SB5/Imraldi® it does not stabilise adalimumab in SB5/Imraldi®. Hence, it does not act as *an osmolyte that mitigates against protein denaturation* in SB5/Imraldi® as required by the Utility Models. Accordingly, the sorbitol present in SB5/Imraldi ® is not a 'sugar stabiliser' in the context of the Utility Models.

Annex 1 – Experimental Protocols

1. **Sample Preparation**

Three separate samples of each of the control and test formulations were prepared, according to the following method:

1.1 **Step 1 - 1L buffer / dialysate preparation**

The following buffers were prepared in triplicate:

Excipient	**SB5 control 50 mg/mL**	**Formulation 1 (citrate-free)**	**Formulation 2 (histidine-free)**	**Formulation 3 (sorbitol-free)**
Citric acid mono-hydrate (g/L)	68. 0.68	0	69. 0.68	70. 0.68

Sodium citrate dihydrate (g/L)	72. 2.00	0	73. 2.00	74. 2.00
L-Histidine (g/L)	75. 1.20	76. 1.20	0	77. 1.20
L-Histidine monohydrochloride monohydrate (g/L)	78. 10.80	79. 10.80	0	80. 10.80
D-Sorbitol (g/L)	81. 25.00	82. 25.00	25.00	0

All the buffers were formulated without surfactant and filtered with 0.22 μm bottle-top filters. The buffers were stored at room temperature (usually 20-22°C, although not recorded), until at least 1 hour prior to usage for dialysis when they were refrigerated (at 5 ± 3°C) for temperature equilibration.

1.2 Step 2 - Buffer / dialysate exchange

Buffer exchange was carried out at 5 ± 3ºC.
3 mL of SB5 drug substance (DS) (i.e. SB's formulated adalimumab product, Imraldi®, without the surfactant) was dialyzed using 3 mL Slide-A-Lyzers dialysis cassettes (10 kDa MWCO) in each of the different formulation buffers described above. Buffer exchange was carried out using 300mL buffer over a 17 hour period. The buffer was refreshed at 3, 3 and 10 hour intervals.
After dialysis, the protein concentration and pH were measured by UV spectrometer and pH meter, respectively, using the methodology as further described below.

1.3 Step 3 - Sample preparation

The buffer-exchanged DS was diluted down to 50 mg/mL ± 5% by adding the corresponding formulation buffer and 20X polysorbate 20 stock solution (1.6% PS20), to end up with final formulations with 0.08% polysorbate 20.
After the targeted protein concentration of the samples was determined to be within pre-defined internal criteria (50mg/ml ± 2.5 mg/ml, as determined by the test method described below), the formulations were filtered through a 0.22 μM sterile filter in a biosafety cabinet.
In order to prevent dilution of protein concentration as a result of the dialysis and the addition of polysorbate 20, the intermediate protein concentration was set at 60 mg/mL. 20X polysorbate 20 stock solution was then added to reach the target concentration.
The final samples for Experiment A (below) were then filled into 1.5 mL Eppendorf tubes. The samples for Experiments B and C (below) were filled into 0.2 mL tubes (Thermo Scientific).

2. Stress Tests

Measurements of osmolality and aggregates were taken before and after the samples had been exposed to the following stresses: heat (4 weeks at 40ºC), freeze/thaw (5 cycles) and mechanical agitation (200rpm for 48 hours), as described below.
All control and test formulations for each of the experiments were stored and tested in the same way and all tests were performed in parallel. All control and test formulations were analysed at the same time points.
At each predetermined sampling point, samples of each formulation were chambered out and stored at 5 ± 3°C until the time for analysis.

2.1 **Experiment A – thermal stress**

The control and test formulations for the thermal stress tests were made up and chambered-in straight away (i.e. on the same day).
The samples were placed in a stability chamber at 40 ± 2°C for 4 weeks.
Samples were taken for measuring osmolality and aggregates at the start point (t = 0) and after 1, 2 and 4 weeks of storage in the stability chamber. The samples were analysed straight away or, where there was any delay prior to analysis, those samples were kept refrigerated in the interim. In each case, the time between taking the samples and analysing the samples was the same for all samples in the Experiment.
The results are shown in Annex 2, Table 1.

2.2 Experiment B – freeze-thaw

- The control and test formulations for the freeze-thaw tests were made up and then stored in a refrigerator for 19 days until the tests were performed.
-

The samples were placed into a deep freezer at -70 ± 10°C and then thawed at room temperature until all of the ice had disappeared. The freeze and thaw cycle was repeated 5 times for each sample.
Samples were taken for measuring osmolality and aggregates before and after exposure to 5 freeze/thaw cycles. The samples were analysed straight away or, where there was any delay prior to analysis, those samples were kept refrigerated in the interim. In each case, the time between taking the samples and analysing the samples was the same for all samples in the Experiment.
The results are shown in Annex 2, Table 2.

2.3 **Experiment C – mechanical stress**

The control and test formulations for the mechanical stress tests were made up and then stored in a refrigerator for 19 days until the tests were performed.
The samples were mechanically agitated at 200 rpm for 48 hours at room temperature on a shaker.
Samples were taking for measuring osmolality and aggregates both before and after the agitation. The samples were analysed straight away or, where there was any delay prior to analysis, those samples were kept refrigerated in the interim. In each case, the time between taking the samples and analysing the samples was the same for all samples in the Experiment.
The results are shown in Annex 2, Table 3.

3. **Analytical Techniques**

The samples were analysed for protein concentration, osmolality, and aggregates using the following methods:

3.1 *Protein concentration determination* – The samples were diluted to 1 mg/mL with 0.9% NaCl buffer. 100 µL of diluted samples were injected into a plastic disposable cuvette. The absorbance of the samples was measured at 280nm using a UV spectrophotometer (Shimadzu). The value of 1.39 was used as extinction coefficient of adalimumab.

3.2 *pH determination* – pH was determined using potentiometric measurements conducted at room temperature with a Mettler Toledo pH meter.

3.3 *Osmolality determination* – Osmolality was measured based on the cryoscopic characteristics of the samples. The test was conducted with an osmometer 2020 (Advanced Instruments) subjecting 20 µL of the sample to freezing. The freezing temperature depends on the osmolality of

the solution (i.e. on the presence of agents dissolved such as salts, sugars, other ionic and non-ionic species etc).

3.4 *Aggregates determination (%HMW) by SE-HPLC* – The samples were diluted with pure water to a concentration of 10 mg/mL and 100 µg injected into a TSKgel G3000 SWxl Column (Tosoh). UV detection was carried out at 280nm at a flow rate of 0.5 mL/min. The duration of each analytical run was 36 minutes. Prior to analysis, the samples were maintained at 2-8^{0}C in the autosampler of the Waters Alliance HPLC system used for this test.

Annex 2 – Experimental Data

Table 1 – Experiment A: Thermal Stress Results (40^{0}C/4 Weeks)

Sample (1)	Buffer	Stabilizer	Tonicity Agent	Osmolality		%HMW									
	Varied (2)	Varied (3)	Varied (4)	Initial (5)	4 Weeks (6)	Initial (7)	Initial Average (8)	1 week (9)	1 week Average (10)	2 weeks (11)	2 weeks average (12)	4 Weeks (13)	4 weeks average (14)	4 weeks Gap (15)	4 weeks Gap Average (16)
SB5 (control)	10 mM Na-citrate	59 mM histidine	25 mg/mL sorbitol	283	290	0.53	0.53 ± 0.00	0.61	0.61 ± 0.01	0.73	0.73 ± 0.00	0.86	0.88 ± 0.02	0.33	0.35 ± 0.02
SB5 (control)	10 mM Na-citrate	59 mM histidine	25 mg/mL sorbitol	290	294	0.53		0.61		0.73		0.88		0.35	
SB5 (control)	10 mM Na-citrate	59 mM histidine	25 mg/mL sorbitol	286	292	0.53		0.62		0.73		0.89		0.36	
Citrate-free	N/A	59 mM histidine	25 mg/mL sorbitol	265	273	0.52	0.53 ± 0.01	0.59	0.59 ± 0.01	0.70	0.70 ± 0.01	0.84	0.84 ± 0.01	0.32	0.31 ± 0.01
Citrate-free	N/A	59 mM histidine	25 mg/mL sorbitol	262	264	0.54		0.59		0.71		0.85		0.31	
Citrate-free	N/A	59 mM histidine	25 mg/mL sorbitol	256	267	0.53		0.60		0.70		0.84		0.31	
Histidine-free	10 mM Na-citrate	N/A	25 mg/mL sorbitol	177	183	0.66	0.66 ± 0.00	1.12	1.11 ± 0.01	1.36	1.35 ± 0.01	1.65	1.64 ± 0.01	0.99	0.98 ± 0.01
Histidine-free	10 mM Na-citrate	N/A	25 mg/mL sorbitol	176	180	0.66		1.11		1.35		1.65		0.99	
Histidine-free	10 mM Na-citrate	N/A	25 mg/mL sorbitol	179	183	0.66		1.10		1.35		1.63		0.97	
Sorbitol-free	10 mM Na-citrate	59 mM histidine	N/A	136	138	0.53	0.53 ± 0.01	0.65	0.66 ± 0.01	0.79	0.80 ± 0.01	0.98	1.00 ± 0.03	0.45	0.47 ± 0.03
Sorbitol-free	10 mM Na-citrate	59 mM histidine	N/A	135	137	0.53		0.67		0.81		1.03		0.50	
Sorbitol-free	10 mM Na-citrate	59 mM histidine	N/A	135	138	0.54		0.65		0.81		1.00		0.46	

Note – all samples had a target protein concentration of 50 ± 2.5 mg/ml and the pH was adjusted to be around 5.2. Column numbers are shown in parentheses.

Table 2 – Experiment B: Freeze-Thaw Stress Results (-70^{0}C/5 Cycles)

Sample (1)	Buffer	Stabilizer	Tonicity Agent	Osmolality		%HMW					
	Varied (2)	Varied (3)	Varied (4)	Initial (5)	FT 5 (6)	Initial (7)	Initial Average (8)	FT 5 (9)	FT 5 Average (10)	Gap (11)	Average Gap (12)
SB5 (control)	10 mM Na-citrate	59 mM histidine	25 mg/mL sorbitol	283	298	0.53	0.53 ± 0.00	0.57	0.57 ± 0.00	0.04	0.04 ± 0.00
SB5 (control)	10 mM Na-citrate	59 mM histidine	25 mg/mL sorbitol	290	297	0.53		0.57		0.04	
SB5 (control)	10 mM Na-citrate	59 mM histidine	25 mg/mL sorbitol	286	289	0.53		0.57		0.04	
Citrate-free	N/A	59 mM histidine	25 mg/mL sorbitol	265	276	0.52	0.53 ± 0.01	0.59	0.58 ± 0.01	0.07	0.05 ± 0.02
Citrate-free	N/A	59 mM histidine	25 mg/mL sorbitol	262	265	0.54		0.58		0.04	
Citrate-free	N/A	59 mM histidine	25 mg/mL sorbitol	256	263	0.53		0.58		0.05	
Histidine-free	10 mM Na-citrate	N/A	25 mg/mL sorbitol	177	181	0.66	0.66 ± 0.00	0.84	0.84 ± 0.00	0.18	0.18 ± 0.00
Histidine-free	10 mM Na-citrate	N/A	25 mg/mL sorbitol	176	182	0.66		0.84		0.18	
Histidine-free	10 mM Na-citrate	N/A	25 mg/mL sorbitol	179	181	0.66		0.84		0.18	
Sorbitol-free	10 mM Na-citrate	59 mM histidine	N/A	136	136	0.53	0.53 ± 0.01	0.58	0.58 ± 0.00	0.05	0.05 ± 0.01
Sorbitol-free	10 mM Na-citrate	59 mM histidine	N/A	135	134	0.53		0.58		0.05	
Sorbitol-free	10 mM Na-citrate	59 mM histidine	N/A	135	132	0.54		0.58		0.04	

Note – all samples had a target protein concentration of 50 ± 2.5 mg/ml and the pH was adjusted to be around 5.2. Column numbers are shown in parentheses.

Table 3 – Experiment C: Agitation Stress Results (200rpm/48hrs)

Sample (1)	Buffer	Stabilizer	Tonicity Agent	Osmolality		%HMW					
	Varied (2)	Varied (3)	Varied (4)	Initial (5)	200 RPM (6)	Initial (7)	Initial Average (8)	200 RPM (9)	200 RPM Average (10)	Gap (11)	Average Gap (12)
SB5 (control)	10 mM Na-citrate	59 mM histidine	25 mg/mL sorbitol	292	297	0.57	0.57 ± 0.01	0.57	0.57 ± 0.01	0.00	0.01 ± 0.01
SB5 (control)	10 mM Na-citrate	59 mM histidine	25 mg/mL sorbitol	297	303	0.56		0.58		0.02	
SB5 (control)	10 mM Na-citrate	59 mM histidine	25 mg/mL sorbitol	290	301	0.57		0.57		0.00	
Citrate-free	N/A	59 mM histidine	25 mg/mL sorbitol	270	274	0.59	0.58 ± 0.01	0.59	0.59 ± 0.00	0.00	0.01 ± 0.01
Citrate-free	N/A	59 mM histidine	25 mg/mL sorbitol	265	267	0.58		0.59		0.01	
Citrate-free	N/A	59 mM histidine	25 mg/mL sorbitol	263	266	0.58		0.59		0.01	
Histidine-free	10 mM Na-citrate	N/A	25 mg/mL sorbitol	183	186	0.90	0.87 ± 0.03	0.92	0.90 ± 0.02	0.02	0.03 ± 0.03
Histidine-free	10 mM Na-citrate	N/A	25 mg/mL sorbitol	182	191	0.84		0.90		0.06	
Histidine-free	10 mM Na-citrate	N/A	25 mg/mL sorbitol	183	186	0.88		0.89		0.01	
Sorbitol-free	10 mM Na-citrate	59 mM histidine	N/A	137	141	0.58	0.59 ± 0.01	0.58	0.59 ± 0.01	0.00	0.00 ± 0.00
Sorbitol-free	10 mM Na-citrate	59 mM histidine	N/A	138	141	0.60		0.60		0.00	
Sorbitol-free	10 mM Na-citrate	59 mM histidine	N/A	138	140	0.58		0.58		0.00	

Note – all samples had a target protein concentration of 50 ± 2.5 mg/ml and the pH was adjusted to be around 5.2. Column numbers are shown in parentheses."

Anette Müllertz har i erklæring af 6. maj 2019 anført bl.a.:

"…

2. **ORIGINAL DECLARATIONS**

2.1 Upon having reviewed the above documents, please advise whether you would like to modify any of your observations set out in your original declarations.

I maintain the observations set out in my original declaration I of 4 March 2019 and II of 11 April 2019**.**

3. ON BENDER AND FURTHER ON MANNING VS UM '70 AND UM '71

3.1 If a 'person skilled in the art' was tasked with modifying formulation 11 from Table H (Manning page 88) with a view to provide ~~a viable~~ an alternative formulation ~~that allows for fewer excipients~~, what would (not simply could) the 'person skilled in the art', in your expectation, do in the light of his general technical knowledge and the particular technical teachings identified in your answer to question 3.1 of your original declaration I? In particular: (i) Would the 'person skilled in the art' replace mannitol with sorbitol or trehalose? (ii) Would the 'person skilled in the art' replace PS 80 with PS 20?

The above re-formulation of the question changes my answer slightly compared to what is set out in paragraph 3.3 of my declaration I and in paragraph 3.8 of my declaration II.

Re: ~~a viable~~

For the reasons set out in my declaration II, paragraph 3.8, this strike-out will not in itself change my answer, as I believe that a 'person skilled in the art' would realistically only focus on developing viable formulations in the sense explained by Sven Frøkjær in paragraph 17 of his declaration II.

Re: ~~that allows for fewer excipients~~
The strike-out '~~that allows for fewer excipients~~' slightly changes my answer set out in paragraph 3.3 of my declaration I and in paragraph 3.8 of my declaration II.

In my declaration I, paragraph 3.3, I have explained what I expect a 'person skilled in the art' - if tasked with modifying formulation 11 from Table H (Manning page 88) with a view to provide a viable formulation that allows for fewer excipients - would do in the light of his general technical knowledge and the particular technical teachings identified in my answer to question 3.1 of declaration I.

If a 'person skilled in the art' - with formulation H11 as the starting point - was asked to develop ~~a viable~~ an alternative formulation ~~allowing for fewer excipients~~, the 'person skilled in the art' would - using his general technical knowledge - identify at least the following overall strategies:

3) Adjust the concentration of the excipients in H11 [NEW]
4) Maintain the number of excipients by replacing one or more excipients – and possibly then adjust the concentration of the excipients [NEW]
5) Increase the number of excipients by adding (but not replacing) further excipients to H11 – and possibly then adjust the concentration of the excipients [NEW]
6) Increase the number of excipients by adding (as well as replacing) excipients to H11 – and possibly then adjust the concentration of the excipients [NEW]
7) Reduce the number of excipients by removing one or more excipients – and possibly then adjust the concentration of the remaining excipients [SAME]
8) Reduce the number of excipients by removing two or more excipients and adding fewer yet new excipients – and possibly then adjust the concentration of the excipients used [SAME]

("NEW" denotes new strategies as compared to those identified in declaration I, paragraph 3.3. "SAME" denotes the strategies I originally identified in declaration I, paragraph 3.3.)

As it appears, the deletion of "~~allowing for fewer excipients~~" triples the development strategies from 2 to 6. It is notoriously clear that the deletion of "~~allowing for fewer excipients~~" entails that 'the person skilled in the art' would have many more modification options than in a scenario where tasked with developing only formulations that allows for fewer excipients.

In such scenario and with reference to the observations in my declaration I, paragraph 3.3, and declaration II, paragraph 3.8, it would, in my expectation, be even more unlikely that the 'person skilled in the art' would replace mannitol with sorbitol or trehalose. And it would be even more unlikely that the 'person skilled in the art' would replace PS 80 with PS 20.

3.2 Daniel Otzen observes in his declaration II, paragraph 15, that "*I do not believe that Manning teaches that polysorbate 80 is better than polysorbate 20 for use in a formulation of adalimumab and even less so, that the skilled person*

***would be dissuaded from using polysorbate 20 in a liquid formulation of adalimumab.*" Do you agree?**

No, I do not agree. As explained in paragraph 3.3 of my declaration I and as further elaborated below, I do not believe that a 'person skilled in the art' who had reviewed Manning would replace PS 80 with PS 20.

I have carefully reviewed Daniel Otzen's declaration. Daniel Otzen draws a number of conclusions that are opposite to the conclusions drawn by Manning. In essence, Daniel Otzen seems to base his conclusion on three factors:

1) According to Daniel Otzen, Manning suggests that PS 20 provides significant stability of adalimumab formulations
2) According to Daniel Otzen, Manning interprets his results without due regard to statistical significance
3) According to Daniel Otzen, Manning's PLS analyses include data points that are inappropriate to combine

With reference to my below observations, I do not find that the above three factors merit Daniel Otzen's conclusion.

Re 1): According to Daniel Otzen, Manning suggests that PS 20 provides significant stability in adalimumab formulations.

Based on the below observations, I do not agree.

Daniel Otzen observes on page 6:

> 23. Manning carries out a so-called Partial Least Squares ('PLS') analysis of the combined data on adalimumab physical stability (viz. the fraction of monomeric adalimumab left after t1 (one week at 40° C) and/or t2 (two weeks at 25° C), measured either by SEC or HPLC), using data in blocks A-H, in particular blocks B to G. Based on correlation coefficients in Table J (using t1 values measured by SEC), he concludes that His, Gly, Arg and polysorbate 80 are the most potent stabilizers while NaCl, citrate and phosphate are destabilizers. According to Table K (SEC monomer contents t1 and t2), His, Gly, Arg and polysorbate 80 are potent stabilizers. In fact, in the text Manning claims polysorbate 20 to be stabilizing (page 103) but the data in the table suggest that this is a typographical error, so that it is rather polysorbate 80 which is stabilizing, while polysorbate 20 has no significant effect in this analysis; although I note that Manning states on page 102 (also in relation to PLS Model A) that "*PS20 provides significant stability when used above 0.04%*". On page 103 Manning also states that citrate, phosphate and NaCl are again significant destabilizers; that pH is significant (presumably destabilizing) and EDTA is destabilizing but Met stabilizing. Finally, from Table L (HPLC monomer content at t1), Manning concludes that phosphate, citrate, acetate and EDTA are destabilizing while only His (and to an insignificant extent Gly and Arg) are concluded to be stabilizing.

As it can be seen, Daniel Otzen identifies a typographical error in Manning, page 103. On page 103, Manning has typed "PS 20" where the text should have read PS 80. Daniel Otzen and I agree that the 'person skilled in the art' would understand that Manning on page 103 advises that "*On the other hand, His, Gly Arg, and **PS 80** are potent stabilizers*".

Having identified this typographical error, Daniel Otzen further observes "*I note that Manning states on page 102 (also in relation to PLS Model A) that "PS20 provides significant stability when used above 0.04%"*." When reading this observation, my

original understanding was that Manning, in Daniel Otzen's opinion, suggests that PS20 provides significant stability when used above 0.04%. However, also this citation is subject to an obvious typographical error. In Manning, the relevant paragraph reads:

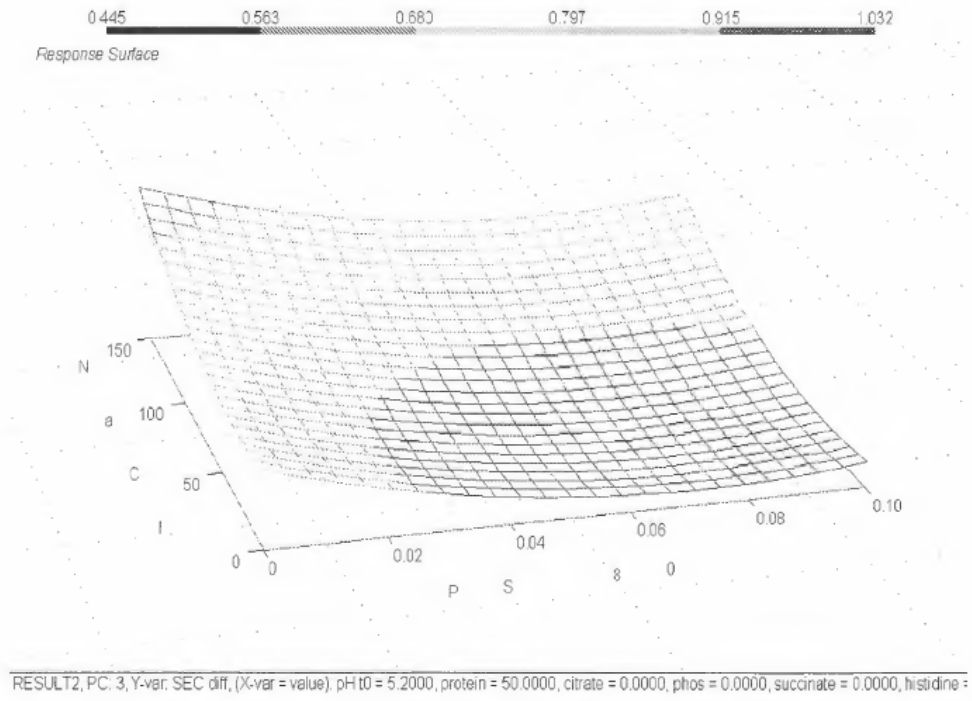
Discussion of PLS Model A--Figure 16

The final response surface shown for PLS Model A is for the effect of NaCl and PS 80 (Figure 16). It shows that the stability of adalimumab decreases upon addition of NaCl, especially above 100 mM. Meanwhile, PS 20 provides significant stability when used above 0.04%.

Figure 16 of Manning reads:

FIGURE 16

Effect of NaCl and polysorbate 80 (PS 80) according to PLS model A using the difference in monomer content at t1 as the endpoint. The pH is fixed at 5.2 and the protein concentration is fixed at 50 mg/ml.



It is clear that Figure 16 of Manning regards PS 80, and not, as noted in error on page 102, PS 20. It explicitly follows from Figure 16 that PS 80 provides significant stability when used above 0.04 %. (Figure 16 displays "the difference in monomer content", i.e. the difference in the content of adalimumab when the lab test starts as compared to when it ends. An increase in "difference in monomer content" implies that more adalimumab proteins have been denatured – or in plain language, destroyed. The lower the "difference in monomer content", the more stable is the formulation. I note that consistent with the above, also Figure 26 of Manning illustrates that PS 80 provides significant stability when used above 0.04%.

Re 2): According to Daniel Otzen, Manning interprets his results without due regard to statistical significance

In the opening of paragraph 24 of declaration II, Daniel Otzen observes that "*A great weakness of [Manning's] analyses is that no statistical significance is provided*". However, on page 96, line 1-3, Manning has described that the so-called jack-knife algorithm has been used to determine statistical significance for any factor used in constructing the PLS models described in Manning. Manning provides multiple observations on statistical significance when discussing the subsequent PLS blocks. I have no reason to believe that Manning has not considered the statistical significance of his data when formulating his observations. I add that Manning is a recognised scientist. On MIT's website, Manning's CV's is recorded as follows:

Dr. Mark Manning is Chief Scientific Officer, Legacy BioDesign, LLC. Dr. Manning has been involved in the development of biopharmaceutical products since 1988, when he joined the faculty at the University of Kansas. He then moved to the University of Colorado, where he helped found the Center for Pharmaceutical Biotechnology, widely considered to be the leading educational program in the country for training formulation scientists to handle biotechnology-based products. Dr. Manning has consulted for more than 40 companies on a wide variety of projects. In addition, he has directed numerous formulation development projects for clients, first as Chief Technical Officer for HTD BioSystems and then as Chief Scientific Officer for Legacy BioDesign. Dr. Manning has published over 100 scientific articles, holds five U.S. patents, and has edited three books on protein formulation. Dr. Manning received an A.B. degree in chemistry from Hope College and his M.S. and Ph.D. degrees from Northwestern University. He conducted post-doctoral work at Colorado State University.

…

Re 3): According to Daniel Otzen, Manning's PLS analyses include data points that are inappropriate to combine

Daniel Otzen observes as follow in paragraph 24 of his declaration II:

24. A great weakness of these analyses is that no statistical significance is provided. Manning states that statistically significant parameters are highlighted in bold in Table J and also mentions in one instance (phosphate in Table L) whether effects are statistically significant or not but does not provide additional

information to support these claims. He also seems to use the terms "potent stabilizer" and "significant stabilizer" interchangeably in Tables J and K, further confusing any statistical conclusions. Accordingly, I have reanalysed the data using the same software (Unscrambler X from Camo Software) to evaluate the statistical significance of the different parameters with particular focus on polysorbate 80 and polysorbate 20. The first conclusion I make based on my own analysis is that the data clearly cluster in two groups, namely (1) data from incubation at low pH (around pH 3.5, only 8 data points) and (2) data from incubation around pH 5.2, 72 points). Incubation at low pH leads to a very significant loss of monomer (ca. 25-75% according to SEC t1 and up to 35% at SEC t2) while incubation around pH 5.2 only reduces monomer content by ca. 1-2%. This makes it in my view inappropriate to combine the two data sets since low pH data can skew the contributions of different parameters and in any case are irrelevant for realistic formulation studies. I therefore exclude the 8 data points recorded at low pH conditions. For the remaining 72 data points, I have reconstructed the Manning analysis in the 3 blocks using Unscrambler X using as far as possible the same analysis parameters as Manning.[4] The analysis provides a number of insights. Of particular relevance here are:

(i) score plots (which identifies potential subclusters of data; for the 72 data points used, there was no obvious clustering);

(ii) predictability, *i.e.* correlation between measured (reference) data values (here monomer concentration at t1 and/or t2) and predicted values; the correlation is generally rather poor with correlation coefficients between 0.1 and 0.6, many well below 0.4;

(iii) identification of significant variables. This is estimated from the weighted regression coefficients which has to be significantly different from zero at the 5% level for the parameter in question (e.g. buffer concentration) to be considered relevant (i.e. determined to be different from zero with statistically significant accuracy). The magnitude of the regression coefficient describes to what extent the parameter affects the stability.

Manning's Block A-H comprise 94 different formulations.

In the above citation, Daniel Otzen criticises that Manning's PLS analyses include all Manning's data and do not exclude data points recorded at low pH conditions. Daniel Otzen explains that he has specifically excluded 8 particular data points with a low pH. I assume these are the data points in respect of the 8 formulations having a pH of 3.5 in Block E.

In my opinion, Daniel Otzen runs a significant risk of weakening the data set by de-selecting the 8 data points from Block E. The data points recorded at low pH conditions are of particular relevance when investigating how stabilising excipients work under the stressed conditions caused by low pH. By excluding these data points, important information may be lost.

I also note that it seems somewhat peculiar that Daniel Otzen on the one hand de-selects pH data at 3.5 from Manning, while on the other hand in his declaration II, paragraph 32, with reference to Bender observes that "*I note the histidine-citrate combination is effective over pH 3.5-7.0*".

Apart from de-selecting the 8 data points at pH 3.5, Daniel Otzen has de-selected further 14 data points. (Manning's Block A-H comprise 94 different formulations. Daniel Otzen has analysed only 72 data points. 94-72-8=14.)

As I cannot establish which further 14 data points Daniel Otzen has de-selected, I am not able to provide further comments on Daniel Otzen's analyses and the conclusions he draws on the correlation coefficients.

3.3 Would you expect that a 'person skilled in the art' when reading Manning would use the data provided by Manning to perform a PLS analysis similar to the analysis performed by Daniel Otzen?

As noted in my declaration I, paragraph 1, I have been asked to base my assessment on the defendants' suggestion that the 'person skilled in the art' is a "formuleringskemiker" [formulation chemist] or "proteinkemiker" [protein chemist] "med interesse for formulering af proteiner, herunder antistoffer til terapeutisk brug" [with an interest in the formulation of proteins, including antibodies, for therapeutic use].

A formulation chemist or a protein chemist will have a basic knowledge of statistical methods, but statistics is not their speciality. Statistical analysis of data sets similar to those comprised by Manning are typically handled by bio-statisticians, i.e. specialists within the field of statistical analysis of data sets such as those presented by Manning. While a formulation chemist and a protein chemist could probably perform a PLS analysis if asked to, the performance of PLS analyses falls outside what ordinary formulation chemists and protein chemists do in their daily work.

When I reviewed Manning, I did not notice anything that gave me reason to question the basis for Manning's PLS analyses or the conclusions that Manning draws. Certainly, I would not expect an ordinary formulation chemist or protein chemist to question the basis for Manning's PLS analyses or the conclusions that Manning draws. Rather, I would expect that an ordinary formulation chemist or protein chemist would find that Manning's teachings are backed by Manning's experiments and analyses. Further, I cannot see what would motivate a formulation chemist or protein chemist to embark on a PLS statistical analysis of Manning's data, let alone a sub-selection of Manning's data. My own review of Manning did not motivate me to do so. As explained above, Manning is a well-respected scientist and his conclusions seem to be backed by his experiments and analyses.

I appreciate that Daniel Otzen shows interest in considering whether an advanced statistical analysis of a sub-set of Manning's data may lead to new insights. However, as mentioned above it is not clear to me which strategy – besides the pH – that Daniel Otzen has used in his data mining exercise. Also, it appears to me that the new insights suggested by Otzen is a result of Otzen's own creative data selection and subsequent analysis hereof.

3.4 If a 'person skilled in the art' based on Manning would use the data provided by Manning to perform a PLS analysis similar to the analysis performed by Daniel Otzen, would you expect the person skilled in the art to arrive at Otzen's results and conclusions?

As explained above, unless explicitly told to do so would I very much doubt that the 'person skilled in the art' would perform a PLS analysis, let alone perform the data selection performed by Daniel Otzen.

It is, however, impossible for me to advise on what the result of a PLS analysis performed by 'a person skilled in the art' would be, because I do not know which particular data Daniel Otzen has used for his analysis.

In Daniel Otzen's declaration II, paragraph 36-38, Daniel Otzen provides the below critic of your declaration II.

Comments on Professor Müllertz's supplementary declaration

36. In light of the conclusions that Professor Müllertz draws as to the teachings that a skilled person would take from Manning, I stand by what I have previously stated, namely that when it comes to any conclusions drawn in Manning (for instance on page 108 with regard to the different surfactants tested), the skilled person would always have looked at the underlying data presented in Manning to seek to understand the basis for such a conclusion, and to judge how significant such a conclusion could be considered to be. This would especially have been the case if a finding is described by Manning himself as "surprising".

37. Professor Müllertz states that the teachings on pages 107 et seq. of Manning are "*…backed by the PLS model A-C analyses that Manning explains in details on pages 94-107*" (section 3.2) and that "*Manning's teachings on page 107 et seq. are based on the PLS analyses…*" (section 3.5.). As I believe is clear from my comments with regard to the strength of the PLS analyses and the results thereof reported in Manning in Section 5 above, I do not agree that the skilled person would have concluded that the PLS analyses in Manning provide any basis for the comments on page 107-108 that "*other surfactants tested (PS20 and F-68), do not appear to be nearly as effective as PS80.*" In fact based on the correlation coefficients predicted in one of the PLS models of Manning (PLS Model C), polysorbate 20 would appear to be a better stabiliser than both polysorbate 80 and F-68 (cf. table L on page 105), and this is also observed in my own PLS analysis of the Manning data.

38. Thus, in my opinion neither the relevant data per se nor the PLS analyses in Manning provide any basis for concluding that polysorbate 80 is better than polysorbate 20.

Please provide your comments to Daniel Otzen's criticism.

I understand that Daniel Otzen after having reviewed Manning finds that 'PLS Model C' provides basis for that "*polysorbate 20 would appear to be a better stabiliser than both polysorbate 80 and F-68 (cf. table L on page 105)*". The table that Daniel Otzen base this finding on reads as follows:

TABLE L

PLS "MODEL C" CORRELATION COEFFICIENTS

Factor	*r-value*
pH	-0.115
protein	-0.139
citrate	+0.014
phosphate	+0.084
succinate	-0.051
histidine	-0.075
acetate	+0.159
glycine	-0.096
arginine	-0.045
sorbitol	+0.029
trehalose	+0.020
mannitol	-0.060
NaCl	+0.068
F68	-0.047
PS 20	-0.067
PS 80	-0.028
EDTA	+0.099
Met	-0.015

PLS Model C demonstrates that RP HPLC is stability-indicating, even though the sensitivity may be less than for SEC. The model finds that both phosphate and citrate are destabilizing, with the effect of phosphate being statistically significant (Table LI). Likewise, acetate is a strong destabilizer as is EDTA. Both Gly and Arg are shown to be stabilizers, but the effects are not deemed to be statistically significant. Only His was found to be a significant stabilizer (along with protein concentration).

The above list presents calculated 'correlation coefficients'. In this particular list, a negative value indicates that the excipient in question stabilises adalimumab, while a positive value indicates that the excipient in question destabilises adalimumab.

In line 12-18 Manning provides observations on the statistical significance of the indications set out in the table. By way of example, Manning observes that the de-stabilising effect of phosphate (value +0.096) is statistically significant, and that the stabilising effect of histidine (value -0.075) is significant. On the other hand, the sta-bilising effect of Gly (glycine) (value -0.096) is deemed not to be significant. It is therefore clear that one cannot assume statistical significance or lack hereof based on the numerical value. It is also clear that Manning does not advise whether the measurements on PS 20/PS 80 are statistically significant. In sum, I would assume that Daniel Otzen against this background agrees that one cannot from Table L draw any conclusions on the stabilising effects of PS 20 vs PS 80.

Whereas the correlation coefficients presented in Table L does not provide solid information on the stabilising effect of PS 20 and P 80, solid information on PS 80 is provided within the context of PLS Model C. On page 101, Manning explicitly highlights:

While the table of correlation coefficients is helpful to gauge the effects of various factors, they do not capture the non-linear and interaction effects, so it is helpful to view response surfaces to examine the effects of various parameters in greater detail, as shown in the response surfaces that are reproduced in Figures 13 through 28.

Manning's 'PLS Model C' section indeed does provide detailed information on PS 80's potency as a stabiliser. With reference to Figure 26, Manning observes that *"that chemical stability [of adalimumab] is greatly improved by adding PS 80, especially at concentrations above 0.04 %"*:

Discussion of PLS Model C--Figure 26

The effect of mannitol and PS 80 is seen in the response surface in Figure 26[14]. It is clear that chemical stability is greatly improved by adding PS 80, especially at concentrations above 0.04%. Meanwhile, mannitol is also stabilizing, but even 240 mM mannitol has less effect than a small about of the surfactant.

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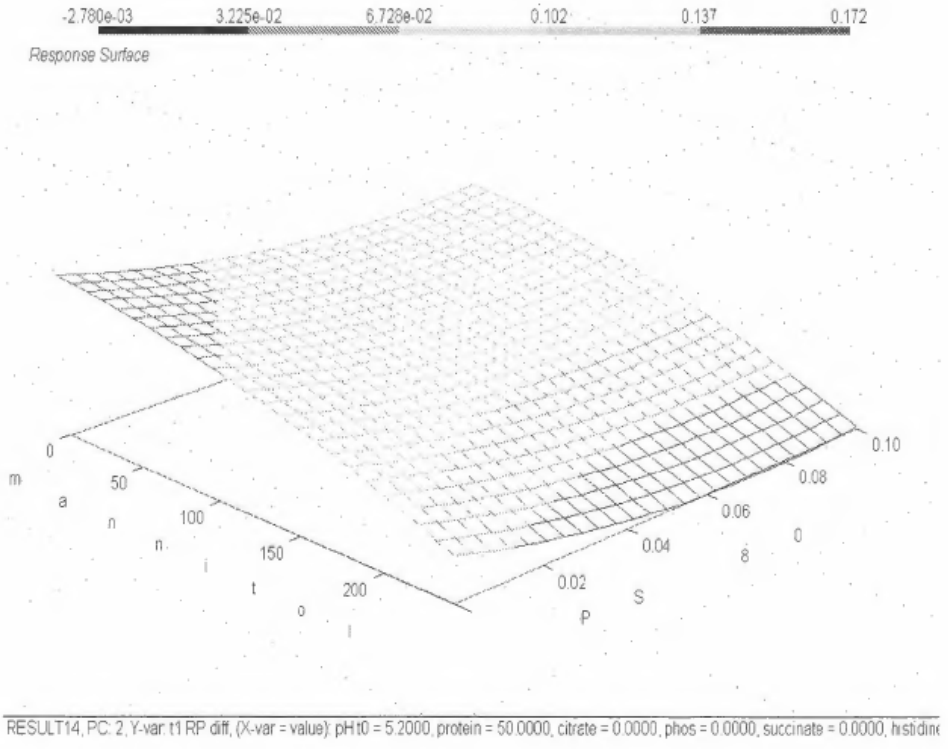
FIGURE 26

Effect of mannitol and PS 80 according to PLS model C using the difference in purity at t1 by RP HPLC as the endpoint. The pH is fixed at 5.2 and the protein concentration is set at 50 mg/ml.



In sub-conclusion: Manning's 'PLS Model C' section does not provide basis for deducing the relative stabilising effects of PS 20 vs PS 80. The section, including specifically Figure 26, only provides basis for deeming PS 80 a good stabiliser in concentrations above 0.04 %.

Also, Manning's section on 'PLS Model A' and 'PLS Model B' provide information that PS 80 is a good stabiliser, in fact a significant stabiliser.

Re 'PLS Model A'
In the context of 'PLS Model A', Manning presents the below Table J:

TABLE J

PLS "MODEL A" COEFFICIENTS

Note: Overall correlation coefficients for each linear factor includes in the first PLS model (PLS Model A) using the difference in monomer content by SEC at t1 as the endpoint. Factors deemed to be statistically significant are highlighted in bold text.

Factor	*r-value*
pH t0	0.041
protein	-0.025
citrate	**+0.123**
phos	**+0.267**
succinate	-0.089
histidine	-0.174
acetate	-0.053
glycine	**-0.190**
arginine	**-0.128**
sorbitol	-0.003
trehalose	+0.020
mannitol	**-0.104**
NaCl	**+0.250**
F68	+0.018
PS 20	+0.021
PS 80	**-0.152**
EDTA	+0.112
Met	-0.062

The model quality is acceptable, considering the correlation coefficients of the calibration and validation sets. The overall correlation coefficients for the various factors included in the model are summarized in Table J. Note that the quadratic and interaction terms are not listed here. As the endpoint is the difference in monomer content, one wishes to minimize this value. Thus, stabilizers exhibit negative correlation coefficients, while destabilizers have positive r-values. Of the stabilizers, His, Gly, Arg, and PS 80 are the most potent, although mannitol and succinate also have a stabilizing effect (Table J). Meanwhile, there are some significant destabilizers, such as NaCl, citrate, and phosphate. Keep in mind that these models are a composite of all of the stability data gathered across the various blocks of formulations, A through H, and individual formulations could vary from the model. While the table of correlation coefficients is helpful to gauge the effects of various factors, they do not capture the non-linear and interaction effects, so it is helpful to view response surfaces to examine the effects of various parameters in greater detail, as shown in the response surfaces that are reproduced in Figures 13 through 28.

[…]

Discussion of PLS Model A--Figure 16

The final response surface shown for PLS Model A is for the effect of NaCl and PS 80 (Figure 16). It shows that the stability of adalimumab decreases upon addition of NaCl, especially above 100 mM. Meanwhile, PS 20 provides significant stability when used above 0.04%.

[As noted in my above paragraph 0, the text pertaining to Figure 16 is conferred with a typo. The text should read "PS 80" instead of "PS 20".]

In Table J, negative values indicate a stabilising effect, while positive values indicate a destabilising effect. Bold text indicates statistical significance.

It can be seen both from Table J and Figure 16 (including the text pertaining hereto) that PS 80 is a good stabiliser. In fact, it is highlighted as a statistically significant stabiliser in Table J.

Although not statistically significant, it is noteworthy that PS 20 in Table J is represented with a positive value of +0.021 (i.e. a destabilising effect) vs the negative value of PS 80 of -0.152 (i.e. a stabilising effect). This data certainly does not contra-indicate Manning's overall conclusion that PS 80 is superior to PS 20 in terms of stabilising adalimumab.

Re 'PLS Model B'

In the context of 'PLS Model B', Manning presents the below Table K:

TABLE K (L)

PLS "MODEL B" CORRELATION COEFFICIENTS

Factor	*r-value*
pH	-0.086
protein	+0.030
citrate	-0.079
phos	-0.157
succinate	+0.060
histidine	+0.185
acetate	+0.063
glycine	+0.126
arginine	+0.150
sorbitol	+0.025
trehalose	+0.006

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mannitol	+0.014
NaCl	-0.215
F68	-0.044
PS 20	-0.028
PS 80	+0.227
EDTA	-0.097
Met	+0.096

The endpoints for PLS Model B are the total monomer contents at both t1 and t2. Therefore, one will wish to maximize these values. This means that stabilizers with have positive correlation coefficients and destabilizers will display negative r-values (Table K). As with the previous model, citrate, phosphate, and NaCl are significant destabilizers. On the other hand, His, Gly Arg, and PS 20 are potent stabilizers. In this model, trehalose, sorbitol and mannitol have very little effect. The primary differences are that pH is now a significant factor and that EDTA is a significant destabilizer, while Met appears to be a stabilizer as well.

[As noted in my above paragraph 0, the text pertaining to Figure 16 is conferred with a typo. The text should read "PS 80" instead of "PS 20".]

Discussion of PLS Model B—Figure 20

The PLS model B shows a modest effect of mannitol on stability, whereas PS 80 is an effective stabilizer above concentrations near 0.05% (Figure 20). Thus, one could conclude from this data that a stable formulation could be comprised of 240 mM mannitol and 0.1% PS 80 at pH 5.2.

In Table K positive values indicate a stabilising effect, while negative values indicate a destabilising effect.

Manning explicitly identifies PS 80 as a "potent stabiliser". Manning does not provide any observations in relation to PS 20. It is, however, noteworthy that while PS 80 has a positive value of +0.227, PS 20 has a negative value of -0.028.

In conclusion:
All presented PLS models (Model A-C) comprises data that explicitly identifies PS 80 as a stabiliser. Model A highlights that PS 80 is a statistically significant stabiliser. Model B that PS is a potent stabiliser. Model C that "*It is clear that chemical stability is greatly improved by adding PS 80, especially at concentrations above 0.04 %*" (page 106, line 23-24).

In contrast, none of the PLS models comprise any data or text from which it can be deduced that Manning identifies PS 20 as a stabiliser.

Based hereon, the fact that Manning's data systematically identifies PS 80 as a good stabiliser while being unable to clarify whether PS 20 provides any stabilising effect at all does certainly not lead the reader to distrust Manning's teaching that PS 80 is superior to PS 20. Rather the opposite. Unlike Daniel Otzen, who only bases his conclusions on correlation coefficients on a sub-set of data points, Manning uses his entire data set to produce to PLS correlation coefficient of Tables J-L and the PLS response surface curves of Figures 3-28.

3.6 In your assessment, which of the following two starting points (i) H11 of Manning vs (ii) the framework on page 5 of Bender, do you think would be the better springboard for the 'person skilled in the art' in order to arrive at the creation of UM '70/UM '71?

H11 of Manning provides an individualised formulation, which is presented in a document that not only provides data on its stability, but also multiple suggestions on development paths that seem relevant to pursue. Manning also provides conclusions on what effects can be expected from the individual excipients, cf. his general teachings on page 107-109.

Bender, on the other hand, does not provide any individualised formulation to start from. Bender only provides a framework, and there is no indication or data as to the effect of any particular formulation that may be derived from this framework. In my opinion, the 'person skilled in the art' will see Bender as an idea catalogue of hypothetical, non-tested adalimumab formulations, as actually also indicated on page 2 of the article where the article just under the headline reads "idea". Bender identifies a number of well known stabilisers and provides the mere idea to use these stabilisers alone, in combination and in various concentration ranges, alone with the objective to arrive at formulations that use another buffer/buffer system than Humira®.

In my opinion, when comparing H11 of Manning and the framework of Bender, Manning provides a much better starting point for the 'person skilled in the art' in order to arrive at the creation of UM '70/UM '71.

3.7 In section 15.2.5 of the defendants' consolidated brief it is submitted that UM '71 lacks creative step because claim 1 of UM '71 identities PS 20 as the surfactant. According to the defendants, the selection of PS 20 entails a foreseeable disadvantageous modification of the closest prior art (i.e. H11 of Manning), which

the skilled person could clearly predict and correctly assess. Please review section 15.2.5 and advise whether you agree with the defendants.

I do not agree with the defendants.

It is correct that one of Manning's teachings is that PS 80 is a more effective stabiliser than PS 20 in adalimumab formulations.

However, as indicated by Sven Frøkjær in declaration III, paragraph 42, the nature of stabilisation of an excipient in a formulation cannot be predicted with certainty. Imraldi® is a formulation according to the creation of UM '71 and functions well.

4. THE EXCIPIENTS OF IMRALDI®

4.1 Exhibit AB comprises the following table that advises on the excipients of Imraldi®, including their functionality:

Formule du médicament

Component[a]	Nominal Quantity/ 0.8 mL	Function	Quality Standard	Component[b] (List of Excipients in the SPC)
Adalimumab	40 mg	Active substance	In-house	N/A
Sodium citrate dihydrate	1.6 mg	Buffer	Ph. Eur./USP/JP	Sodium citrate
Citric acid monohydrate	0.544 mg	Buffer	Ph. Eur./USP/JP	Citric acid monohydrate
L-Histidine	0.96 mg	Stabiliser	Ph. Eur./USP/JP	Histidine
L-Histidine hydrochloride monohydrate	8.64 mg	Stabiliser	Ph. Eur./JP	Histidine hydrochloride monohydrate
Sorbitol	20.0 mg	Tonicity agent	Ph. Eur./USP/JP	Sorbitol
Polysorbate 20	0.64 mg	Surfactant	Ph. Eur./NF/JP	Polysorbate 20
Water for injection	*q.s.*	Solvent	Ph. Eur./USP	Water for injections

[a] As the formulation with the listed excipients occurs during SB5 drug substance (DS) manufacturing process, the name of the components follow the commercial trade name of the excipients added during SB5 DS manufacture.
[b] Name of the components listed in the summary of product characteristics (SPC), which follows the European

Please explain whether the above excipients have further functionalities in Imraldi® than those cited above.

General observations

As observed in my declaration I, paragraph 3.1, a particular excipient in a protein formulation such as Imraldi® may have multiple functionalities.

As also observed by Sven Frøkjær, declaration III, paragraph 18, all Imraldi®'s excipients function as tonicity/osmolality agents. As tonicity/osmolality will increase as a function of the number of molecules in solution in a particular formulation, all the excipients of Imraldi®, including adalimumab, positively impact the tonicity/osmolality level.

Re: citrate [identified as a "Buffer" on exhibit AB]

In Imraldi®, the citrate buffer is present in the form of the combination of citric acid (citric acid

monohydrate) and its corresponding salt (sodium citrate dihydrate). Apart from individually functioning as tonicity/osmolality agents, these molecules together function as a pH buffer at the pH level of Imraldi® (pH 5.2). By stabilising pH, the ingredients aid the stabilisation of adalimumab.

Re: histidine [identified as a "Stabiliser" on exhibit AB]
In Imraldi®, the histidine buffer is present in the form of the combination of histidine (L-Histidine) and its corresponding salt (L-Histidine hydrochloride monohydrate). Apart from individually functioning as tonicity/osmolality agents, these molecules together function as a pH buffer at the pH level of Imraldi® (pH 5.2).

As explained in my first declaration, paragraph 2.1, and as illustrated in Svend Frøkjær's first declaration, page 5, the pH 5.2 of Imraldi® is placed at a point where the two buffers have overlapping buffer capacity. Again, by stabilising pH, the ingredients aid the stabilisation of adalimumab.

Apart from separately functioning as tonicity/osmolality agents and as a pH buffer, histidine has - as also observed in i.a. my declaration II, paragraph 2.1, and Svend Frøkjær's declaration II, paragraph 44 - a further protein stabilising effect in Imraldi®. This is also illustrated by the lab tests discussed in Svend Frøkjær's declaration III, in particular in paragraph 20.

Re: sorbitol [identified as a "Tonicity agent" on exhibit AB]
In Imraldi®, sorbitol functions as a tonicity/osmolality agent.

I agree with Sven Frøkjær (declaration III, paragraph 44) that just because sorbitol will always function as an osmolyte, it needs not necessarily always function as a stabiliser. (I apologise if the observations made in my declaration II, paragraph 4.2 gives another impression. The point in my declaration II, paragraph 4, was that sorbitol in the context of UM '70/UM '71 is a member of the group denoted as 'sugar stabilisers' irrespective of its actual function in any given formulation.)

While sorbitol does not necessarily always function as a stabiliser, I believe that even without having performed any lab tests, one would expect that sorbitol with a very high degree of likelihood functions as a stabiliser in Imraldi®. I base this expectation on i.a. Manning, who is exclusively concerned with stability tests of formulations comprising the specific protein adalimumab. As explained in my declaration II, paragraph 4.2, and as appreciated by Sven Frøkjær, declaration III, paragraph 42, Figure 6 of Manning illustrates that sorbitol shows a positive effect on adalimumab stability. The same follows from Table 11 (page 49) and Example 7 (page 64) in Fraunhofer.

Under the experimental conditions applied in the lab tests discussed in Sven Frøkjær's declaration III, annex I, it is now after having performed lab tests unambiguously documented that sorbitol – as one with a very high degree of likelihood would expect - functions as a stabiliser of adalimumab in Imraldi®. Please see further below in paragraph 0.

Re: polysorbate 20 [identified as a "Surfactant" on exhibit AB]
In Imraldi®, polysorbate 20 functions as a tonicity/osmolality agent.

Polysorbate 20 will also function as a surfactant that i.a. mitigates the risk that the adalimumab adheres to the surface of the container in which it is stored before use. As such, the surfactant promotes the stabilisation of adalimumab.

4.2 In Sven Frøkjær's declaration III, Sven Frøkjær observes as follows:

32. I have been asked to comment on whether the sorbitol present in Imraldi® satisfies the definition of a 'sugar stabiliser' as used in the Utility Models. In my view it does not.

33. As I have noted above and in my Second Declaration, the Utility Models set thresholds for demonstrating an effect on stability[8]. For thermal stress testing (28 days at 40ºC) the Utility Models set a series of thresholds for the level of aggregates (as determined by SE-HPLC) – that the amount of adalimumab aggregates should increase by no more than a factor of 4, by no more than a factor of 3, by no more than a factor of 2.5 or by no more than a factor of 2.2 (see page 36 lines 20-28 (UM '070) and page 36 lines 17-25 (UM '071). In other words, according to the Utility Models, for a formulation to be considered stable in the particular heat stress test protocol used therein (and also used by SB in its experiments) %HMW needs to increase by less than a factor of 4 upon exposure to 40ºC for 28 days or most preferably by less than a factor of 2.2 above the starting level.

Do you agree with Sven Frøkjær?

No, I do not agree.

In paragraph 4.1 of my declaration II, I have tried to explain how I expect that a 'person skilled in the art' would understand the term 'sukkerstabilisator' [sugar stabiliser]. As explained, I believe a 'person skilled in the art' who reviews the definition of the term 'stabilisator' [stabiliser] on page 14 of the descriptions of the Utility Models would conclude that the term 'sugar stabiliser' identifies a group of compounds without defining exactly which technical function the addition of any member from such group in an adalimumab formulation would entail.

While the utility models-in-suit comprise a paragraph that defines the term 'stabilisator' [stabiliser], the utility models do not – as Sven Frøkjær seems to suggest – comprise a paragraph that specifically defines the term 'sukkerstabilisator' [sugar stabiliser]. However, the utility models do in their detailed descriptions (UM '70, page 23) comprise a paragraph that is specifically headed 'sukkerstabilisator' [sugar stabiliser]. This specific paragraph also uses the term 'sukkerstabilisator' [sugar stabiliser] as a marker for a group of compounds. The paragraph does not seek to provide any criteria to determining whether any particular compound, such as sorbitol, functions as a stabiliser in a specific formulation.

In sum, the utility models do not seek to provide any criteria to determining whether any particular compound, such as sorbitol, functions as a stabiliser in a specific formulation.

What the utility models do is to describe how different excipients can be combined with a view to obtain stable adalimumab formulations. The paragraphs that Sven Frøkjær refers to on page 36 regard methods to assess the stability of a given formulation (not a particular compound) that is subjected to thermal stress. The utility models describe multiple stability assessment methods on page 35-40. The paragraph that Sven Frøkjær refers to regards one of these assessment methods. The paragraph reads ('UM 70, page 36):

Parametre under udsættelse for varmestress.

Mængden (eller koncentrationen) af aggregater (fortrinsvis afledt fra adalimumab og fortrinsvis som bestemt ved SE-HPLC-protokollerne defineret heri) til stede i den væskeformige farmaceutiske sammensætning stiger fortrinsvis med højst en faktor 4 (dvs. 4 gange mængden i forhold til et arbitrært begyndelsestidspunkt), når sammensætningen varmebelastes til 40 °C (dvs. sammensætningen holdes ved en temperatur på 40 °C) over en periode på 28 dage, fortrinsvis med en faktor på højst 3, fortrinsvis højst 2,5, fortrinsvis højst 2,2.

Parameters when subjected to thermal stress

[00175] Suitably the quantity (or concentration) of aggregates (suitably derived from adalimumab, and suitably as determined by the SE-HPLC protocols as defined herein) present within the liquid pharmaceutical composition increases by no more than a factor of 4 (i.e. 4 times the amount relative to an arbitrary start time) when the composition is thermally stressed at 40°C (i.e. the composition is maintained at a temperature of 40°C) over a period of 28 days, suitably by no more than factor of 3, suitably by no more than factor of 2.5, suitably by no more than factor of 2.2.

[English text from EP '510]

The text provides kind of a score card. To pass the thermal test ('grade D'), the level of aggregates in the given formulation should preferably not develop more than 4 fold during 4 weeks at 40° C heat test. The thermal test is passed at a more preferred level ('grade C') if the level of aggregates in the given formulation does not develop more than 3 fold. The thermal test is passed at an even more preferred level ('grade B') if the level of aggregates in the given formulation does not develop more than 2.5 fold. The thermal test is passed at an even more preferred level ('grade A') if the level of aggregates in the given formulation does not develop more than 2.2 fold.

It is clear that the cited text by providing a test method and some preferred thresholds offers one optional way of assessing the stability of a given formulation. The text does not offer a method to evaluate the stabilising influence of any isolated excipient.

(Apart from discussing the use of thermal tests on formulation, the utility models also discuss multiple other models for testing different stability aspects of formulations. The utility models do not discuss or provide methods to evaluate the stabilising influence of any isolated excipient.)

4.3 Sven Frøkjær concludes his declaration III by observing that "*While sorbitol may be referred to as an 'osmolyte' and does, as I have explained above by reference to SB's data and the Utility Models, act as a 'tonicity agent' in SB5/Imraldi® it does not stabilise adalimumab in SB5/Imraldi®.*" Do you agree?

No, I do not agree.

As mentioned in my observations in the above paragraph 0, the lab tests carried out by Samsung Bioepsis unambiguously document that sorbitol functions as a stabiliser in Imraldi®. It follows from Annex 2, Table 1, of Sven Frøkjær's declaration

III that if sorbitol is removed from an Imraldi® formulation, the stability of adalimumab is – when subjected to the thermal test applied – reduced, as the level of aggregates in the sorbitol free formulation is increased by 34 % (0.47-0.35/0.35).

I appreciate that histidine also functions as a stabiliser in Imraldi®. It follows from Annex 2, Table 1, of Sven Frøkjær's declaration III that if histidine is removed from an Imraldi® formulation, the stability of adalimumab is – when subjected to the thermal test applied – reduced, as the level of aggregates in the sorbitol free formulation is increased by 180 % (0.98-0.35/0.35).

The fact that histidine seems to be a more potent stabiliser than sorbitol does not change the fact that both compounds have a stabilising function in Imraldi®."

Michael Bech Sommer har i erklæring af 6. maj 2019 anført bl.a.:

"…

2. ORIGINAL DECLARATIONS

2.1 Upon having reviewed the above documents, please advise whether you would like to modify any of your observations set out in your original declarations.

I maintain the observations set out in my original declarations I and II of 4 March 2019 and III of 11 April 2019.

3. ADDED SUBJECT MATTER

3.1 In the defendants' consolidated brief, the defendants observe on page 27 i.a.:

I sin supplerende erklæring (Bilag 34 (E4098)) peger Michael Bech Sommer på, at EPO skulle have fundet, at krav 9 ifølge EP '510 er i overensstemelse med EPK art. 123(2). Herved overser Sommer imidlertid, at EPO som udgangspunkt ikke vurderer, om der er basis for afhængige krav. Det bestrides på denne baggrund, at EPO specifikt har vurderet, om der er basis for krav 9 ifølge EP '510.

Do you agree with this criticism?

No, I do not agree.

The EPC stipulates the requirements for the grant of a patent. This means that the examiner must ascertain that all the requirements are met, before a patent can be granted. This includes in particular that the claims must fulfil the requirements for clarity, basis (in the application as filed) and of course patentability (i.a. novelty and inventive step). These conditions apply for the patent document in its totality. Whereas it necessarily follows that all dependant claims are novel and inventive when the relevant independent claim is novel and inventive, the same does not automatically apply for clarity and added matter. It is very common in our daily practice as patent attor-

neys that before grant, the examiner will have objections to one or more dependant claims before a patent can be granted. Similarly, although clarity is not a ground for opposition, opposition and appeal boards will examine all claims for both clarity and added matter in situations where a patent is upheld in amended form.

Based on these observations and my own experience as a European Patent Attorney, I feel convinced that the EPO in the matter at hand has also considered the basis for the dependant claims. It is certainly not correct that the "*EPO som udgangspunkt ikke vurderer, om der er basis for afhængige krav*" [English: "EPO as a general rule does not assess whether there is basis for dependant claims"].

3.2 In the defendants' consolidated brief it is observed that UM '70 and UM '71 cannot claim priority from the original priority date. On page 22, the defendants specifically observe:

De væsentlige ændringer, der blev introduceret under sagsbehandlingen, betyder også, at der ikke er nogen ret til at kræve prioritet fra Prioritetsdatoen. Den relevante dato for så vidt angår kvalificerende kendt teknik er i overensstemmelse hermed ansøgningsdatoen for EP '510, som er den 15. maj 2015 ("**Ansøgningsdatoen**").

Do you agree?
No, I do not agree.

As observed in my declaration I, paragraph 2.1, the content of the parent '510 application and the priority application '754 is the same. The defendants also seem to have acknowledged this in their defence, page 64, and to my knowledge the defendants have not since the filing of their defence taken any other position.

Therefore, the relevant date for qualified prior art is and can only be the priority date.

For the sake of clarity, I note that I am aware that the defendants dispute there being basis for the claimed subject matter of UM '70 and UM '71. However, this is a different question, which I have addressed in my declaration I, paragraph 2.

3.3 In the defendants' consolidated brief, paragraph 9.5, it is criticised that you have not addressed what the defendants denote as the 'reservoir issue'. Please provide your comments hereto.

I have tried to thoroughly address what the defendants denote as the 'reservoir issue' in paragraph 2.1 of my declaration III. As explained, I find – in agreement with the DKPTO - that the claims of UM '70 and UM '71 are not subject to unlawfully added subject matter.

4 PATENTABILITY

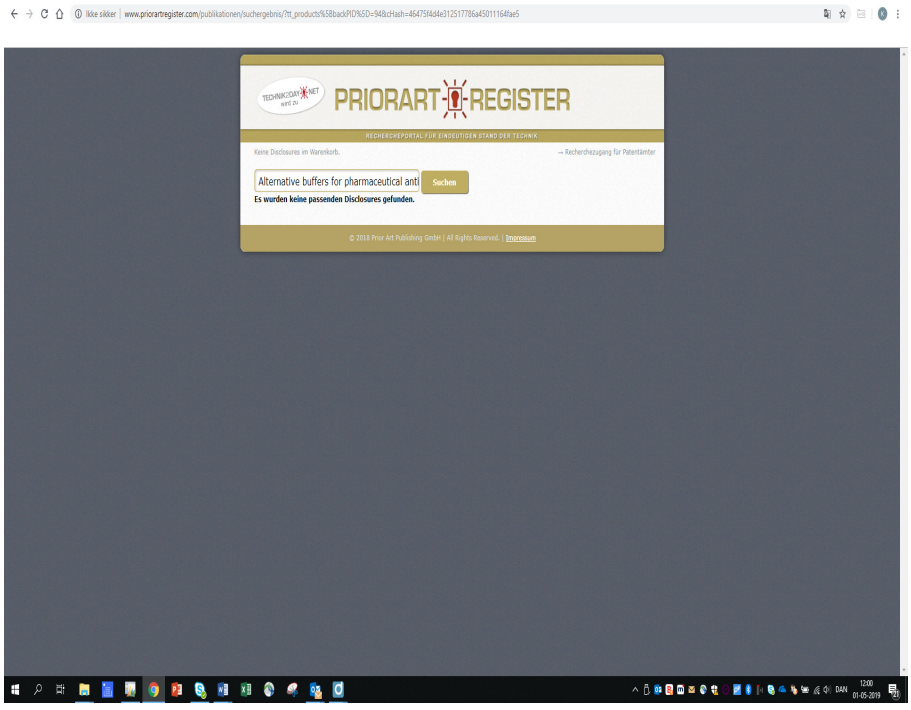
4.1 Novelty

4.1.1 In paragraph 14 of the defendants' consolidated brief, the defendants submit that UM '70 and UM '71 lack novelty over Bender. Do you agree?

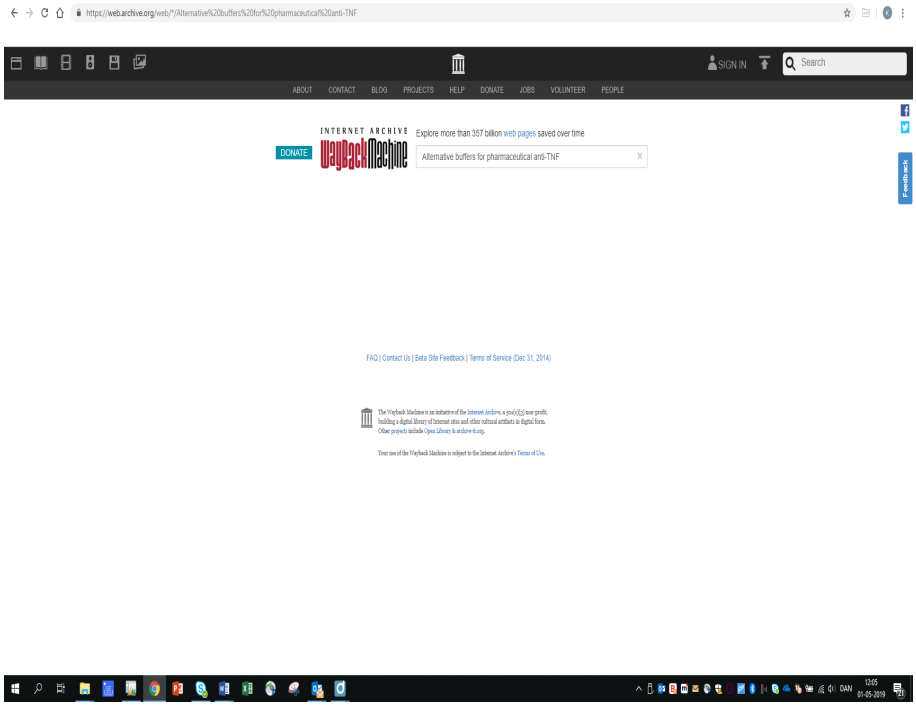
Publication of Bender

For a disclosure to be novelty destroying in respect of UM '70 and UM '71, said disclosure must first and foremost have been publicly available before the priority date of UM '70 and UM '71. I cannot verify whether - and in the affirmative when - Bender has been made publicly available.

I have taken note that according to the defendants, on 6 February 2013 Bender was made publicly available on the website administered by Prior Art Publishing GmbH. On the front page of Bender, the website www.tech-nic2day.net is identified. I have accessed this website and taken note that it is operated by Prior Art Publishing GmbH. I have tried to identify Bender by using the search tool on the website. However, the article cannot be found on the page ("Es wurden keine passenden Disclosures gefunden" [English: "No matching disclosures were found"]:



I have also tried to identify Bender by searching on WayBackMachine™ - but without any result:



I have further made a search on www.google.com, however again without being able to identify a copy of the document.

Against this background I cannot confirm that Bender was made publicly available, let alone on 6 February 2013.

For the sake of completeness, I note that according to the case-law of the EPO the burden of proof on publication is strict ('up to the hilt'). Specifically for internet publications, the EPO's practice, as described in *Case Law*, is:

> If, before the filing or priority date of the patent or patent application, a document stored on the World Wide Web and accessible via a specific URL (1) could be found with the help of a public web search engine by using one or more keywords all related to the essence of the content of that document and (2) remained accessible at that URL for a period of time long enough for a member of the public, i.e. someone under no obligation to keep the content of the document secret, to have direct and unambiguous access to the document, then the document was made available to the public within the meaning of Art. 54(2) EPC 1973.
>
> …

<u>If Bender is assumed publicised</u>

On the assumption that Bender was made available before the priority date of UM '70/UM '71, Bender does not destroy novelty of UM '70 and UM '71.

On page 5 (E2745), Bender provides a general framework for adalimumab formulations:

The alternative Adalimumab compositions are designed for formulation at a pH range between pH 4.9 and pH 6.5 [pH 4.9 – pH 5.5] and comprise basically:

20-130 mg/ml Adalimumab [45-55 mg/ml],

1-10 mg/ml sodium chloride [6.0-6.4 mg/ml],

2-25 mg/ml mannitol [10-14 mg/ml],

0.1-5 mg/ml polysorbate 20 or 80 [0.5–2 mg/ml] and

0.5-30 mM of the selected buffers 1) - 9).

On page 6-7, Bender provides 9 different buffer systems. No 6 is:

6) Citrate + Histidine

- 1-10 mM Citric acid
- 0.5-10 mM Trisodium citrate
- 1-30 mM L-Histidine-HCl
- 1-30 mM L-Histidine

In respect of UM '70

Claim 1 of UM '70 is, in my opinion, novel over Bender because Bender does not in one single embodiment disclose all the features of claim 1. This was also the case for H11 of Manning, see my declaration I, paragraph 3.1.

A formulation resulting from the above recipe of Bender does not comprise any of the sugar stabilisers of claim 1. It is further noted that NaCl is present in Bender's recipe. (With reference to my declaration III, page 7, last paragraph, the presence of NaCl in Bender does not impact the novelty assessment.)

The creation described in Claim 7 of UM '70 further differs from the general framework of Bender in the specific selection from two lists – i.e. the selection of (i) PS 20 and (ii) buffer #6. The same applies to claim 9 and claim 10. Claim 10 also differs from Bender in respect of the PS 20 content.

For the sake of completeness, I note that I agree with the DKPTO that feature (c) of claim 1 is a closed list of a number of particular sugar stabilisers that does not include mannitol, see the DKPTO's letter of 29 March 2019 (exhibit 31; E2313):

Det er ikke klart om mannitol er en del af den gruppe af sukkerstabilisatorer, der er eksemplificeret i krav 1 i BR 2018 00070. Vi har imidlertid læst krav 1, således at sukkerstabilisatoren skal vælges fra gruppen, der består af trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol. Mannitol er således ikke en del af gruppen af sukkerstabilisatorer nævnt i krav 1.

In respect of UM '71

Claim 1 of UM '71 differs from Bender in that in order to arrive at formulations according to claim 1, it is necessary to make a selection from two lists – i.e. selection of (i) PS 20 and (ii) buffer #6.

The general recipe of Bender incorporates two lists. The first list provides a choice between PS 20 and PS 80. The second list provides at choice between 9 different buffer systems. For this reason, Bender does not in one single embodiment disclose all the features of claim 1, cf. EPO's *Case Law*:

6.2. Novelty of chemical compounds and groups of compounds

According to the boards' case law, a specific combination of elements requiring the selection of elements from two known groups/lists cannot be regarded as disclosed in the art and so fulfils the novelty requirement (cf. **T 12/81**, OJ 1982, 296).

…

For the sake of completeness, I note that according to EPO practice, the groups/lists need not be long. Accordingly, a selection from a 2-by-5 list, as exemplified in T 0007/86, conferred novelty.

Claim 8 of UM '70 further differs from Bender in that it relative to the choice of sugar stabiliser specifies only sorbitol.

4.2 Creative step

4.2.1 In the defendants' consolidated brief, page 8, the following is observed:

Bender foregriber således direkte og entydigt hvert træk i Stridsbrugsmodellerne BR '070 og BR '071, og i hvert fald er det klart, at Stridsbrugsmodellerne ikke har frembringelseshøjde over Bender.

Fresenius har under denne sag fremlagt sagkyndige erklæringer fra professor Anette Müllertz (Bilag 21 (E3096) og 33 (E4085)) og europæisk patentagent Michael Bech Sommer (Bilag 22 (E3116) og 34 (E4098)).

Det er bemærkelsesværdigt, at Styrelsens indlæg i sagerne for Ankenævnet (Bilag 31 (E2313) og 32 (E2316)) udtrykkeligt går i rette med blandt andet det objektive tekniske problem formuleret af Michael Bech Sommer.

Uheldigvis er spørgsmålene til professor Annette Müllertz baseret på dette objektive tekniske problem (jf. afsnit 3.3 af professor Müllertz' erklæring (Bilag 21 (E3107)), hvor hun behandler det objektive tekniske problem, som består i at tilvejebringe "[…] *a viable formulation that allows for fewer excipients*" og tilsvarende afsnit 3.8 i hendes anden erklæring (Bilag 33 (E4094))), og det er på denne baggrund klart, at Fresenius' bevisførelse til støtte for Stridsbrugsmodellernes gyldighed allerede af denne grund ikke kan tillægges nogen vægt under denne sag.

On page 54, the defendants i.a. observe:

Desuden er Sommers definition af det objektive tekniske problem også fejlagtig, fordi den indeholder et fingerpeg i retning af løsningen af problemet (ordlyden *"that allows for fewer excipients"*). Dette vil blive diskuteret umiddelbart nedenfor i konteksten af Styrelsens tilgang til definering af det problem, der skal løses, hvilket lider under samme fejl.

…

Det er ikke i overenstemmelse med hverken kriterierne for anvendelse af PSA for brugsmodeller ved Styrelsen eller kriterierne for anvendelsen af PSA ved EPO at medtage nogen form for fingerpeg i retning af løsningen som et element i det objektive tekniske problem, der skal løses (i dette tilfælde et fingerpeg i retning af et alternativt overfladeaktivt stof). Sommer fremfører samme kritik i forhold til Styrelsens tilgang i sin supplerende erklæring på side 11 (og anfører i et forsøg på at være upartisk på side 9 i relation til hans egen formulering af problemet, som omfatter "*that allows for fewer excipients*" og dermed er fejlagtig af samme grund, at han er "*ready to debate whether this pointer to the solution of the problem should actually be included in the problem formulation*").

Please provide your comments to the defendants' criticism of your formulation of the objective technical problem caused by H11 of Manning.

I have addressed the defendants' criticism in my declaration III, page 9-12, to which I refer. As explained, I agree with the defendants that the formulation of the objective technical problem should not incorporate any pointer to the solution. The reason for this principle is to avoid any hindsight when assessing creative step.

I agree with the defendants that the DKPTO clearly incorporates a pointer to the solution in its formulation of the objective technical problem pertaining to UM '70 and UM '71. By doing so, the likelihood that the 'person skilled in the art' would actually arrive at the creation of UM '70/UM '71 obviously increases. And for this reason I agree with the defendants that the DKPTO's formulation of the objective technical problem errs.

In the case at hand, the consequence of eliminating pointers to the solution in the formulation of the objective technical problem is notoriously that it becomes less likely that the 'person skilled in the art' would actually arrive at the creation of UM '70/UM '71.

As explained in my declaration III, page 9, I am ready to debate whether the formulation 'that allows for fewer excipients' in my suggested objective technical problem is, in fact, a pointer to the solution and therefore should be eliminated.

However, as explained by Anette Müllertz in her declaration III, paragraph 3.1, the consequence of modifying the objective technical problem as suggested by the defendants is that it would simply be even less likely that the 'person skilled in the art' would actually arrive at the creation of UM '70/UM '71. In a situation where the 'person skilled in the art' would not just look for formulations that 'allow for fewer excipients' but also formulations with the same number or a higher number of excipients than H11, many more options would exist.

I therefore disagree with the defendants' allegation that the observations made by Anette Müllertz in her declaration I, paragraph 3.3, cannot be conferred with "*nogen vægt under denne sag*" [English: "any weight during these

proceedings"]. If the 'person skilled in the art' would not arrive at the creation of UM '70/UM '71 if confronted with an objective technical problem that suggests that the formulation should 'allow for fewer excipients', obviously the 'person skilled in the art' would neither arrive at the creation if this suggestion is eliminated from the problem formulation. This would make it more difficult – and thus even less obvious for the 'person skilled in the art', see Anette Müllertz' declaration II, paragraph 3.8, and declaration III, paragraph 3.1.

4.2.2 Do you find that UM '70 and/or UM '71 lack creative step over Bender?

No, I do not.

As explained in my declaration I, paragraph 3.2, the assessment of creative step follows the problem-solution approach. Assuming that Bender has been made publicly available before the priority date of UM '70/UM '71, these are my observations on creative step:

The Bender document opens with the following summary:

Summary

Aggregation is one of the major challenges when it comes to formulation development of therapeutic antibody drug products. Aggregation highly depends on antibody concentration and the pH of the formulation. The selection of a suitable buffer system is therefore a crucial step towards a stable formulation, especially with regard to highly concentrated monoclonal antibody formulations suitable for subcutaneous administration like in the case of Adalimumab (HUMIRA®; 50mg/ml), which is formulated with citrate and phosphate. The stability and safety of the product thus depends on both the type and the concentration of a buffering agent. The current article proposes further suitable liquid formulations for Adalimumab based on obvious alternative buffer systems.

It can be seen that the Bender document is focused on the aggregation problem in highly concentrated monoclonal antibody formulations. And further, that the Bender document focus on proposing "*suitable liquid formulations for Adalimumab based on obvious alternative buffer systems*" to the buffer system comprised by Humira®, i.e. the combination of citrate and phosphate.

On page 5 (E2745), Bender provides a general framework for adalimumab formulations. The framework provides 3 fixed and 2 variable positions for components. In addition, for all the components, both a broad as well as a preferred range for each of the components is given.

The 3 fixed positions for components are: adalimumab, sodium chloride (i.e. NaCl) and mannitol. Bender does not mention the possibility of modifying the choice of components on these positions.

The 2 variable positions for components are: surfactant and buffer/buffer system.

In respect of the 1st variable position, Bender provides the choice between PS 20 and PS 80. Bender neither provide any observations or data on the function of any of the surfactants, nor any suggestion on how to choose between the surfactants depending e.g. on the buffer/buffer system chosen and/or concentrations of other excipients.

In respect of the 2nd variable position, Bender provides the following observations:

> to the importance of a suitable buffer system, the proposed new formulations for Adalimumab mainly suggest alternative buffer systems comprising phosphate or citrate as single buffer agents, as well as acetate or histidine alone or in combination with phosphate or citrate. The suggested buffer alternatives are commonly used in liquid formulations, with sodium phosphate being a well-accepted and most frequent buffer in pharmaceutical formulations, buffering a pH range of 5.8 to 8.0 (26). All suggested alternatives provide sufficient buffer capacities, show good long term stability, and have a good safety record. Acetate buffer exhibits a low aggregation propensity (27) and stabilizes the pH of a formulation within the range of pH 3.6 to 5.6. Citric acid together with its conjugated base sodium citrate is preferably used to stabilize the pH of a formulation between pH 3.0 to 6.2 and is often used in concentrations of 20 mM (28). L-Histidine has been found to be an excellent buffer component for monoclonal antibodies (SYNAGIS®, HERCEPTIN®, XOLAIR®, SIMPONI®) and is maximally stabilizing around pH 6.0. The pKa of Histidine is 6.0 which makes it an ideal buffer in the range between pH 5.0 to pH 7.0 and suitable to control weakly acidic conditions (2). Moreover, L-histidine buffer was also shown to scavenge metal ions thus minimizing protein oxidation (29).
>
> The proposed alternative Adalimumab formulations are listed in the following. The preferred concentration ranges are disclosed within squared brackets.
>
> The alternative Adalimumab compositions are designed for formulation at a pH range between pH 4.9 and pH 6.5 [pH 4.9 – pH 5.5] and comprise basically:
>
> 20-130 mg/ml Adalimumab [45-55 mg/ml],
>
> 1-10 mg/ml sodium chloride [6.0-6.4 mg/ml],
>
> 2-25 mg/ml mannitol [10-14 mg/ml],
>
> 0.1-5 mg/ml polysorbate 20 or 80 [0.5–2 mg/ml] and
>
> **0.5-30 mM of the selected buffers 1) - 9).**

[yellow marking added]

As it can be seen in the above citation, Bender identifies - as an alternative to the citrate/phosphate buffer system of Humira® - the possibility of using "*buffer systems comprising phosphate or citrate as single buffer agents, as well as acetate or histidine alone or in combination with phosphate or citrate*".

On the following page 6-7 (E2742-2743) Bender has explicitly denoted the 8 different buffers/buffers systems that result from the above-cited text with yellow marking, plus as a 9th buffer system acetate/histidine.

When it comes to the choice between these 9 alternatives, Bender provides information on the well-known pH buffer range of the individual buffers. No observations are provided on pH ranges of any combinations. Beyond this, the only qualitative information that Bender provides on the buffers is:

- "*sodium phosphate being a well-accepted and most frequent buffer in pharmaceutical formulations, buffering a pH range of 5.8 to 8.0 (26).*"
- "*Acetate buffer exhibits a low aggregation propensity (27) and stabilizes the pH of a formulation within the range of pH 3.6 to 5.6.*"
- "*L-Histidine has been found to be an excellent buffer component for monoclonal antibodies (SYNAGIS®, HERCEPTIN®, XQLAIR®, SIMPONI®) and is maximally stabilizing around pH 6.0.*"
- "*L-histidine buffer was also shown to scavenge metal ions thus minimizing protein oxidation (29).*"

As explained, Bender merely provides a framework for adalimumab formulations. Bender does not provide one or more individualised embodiments.

Based on the above, I will now move on to the creative step assessment using the problem-solution approach.

<u>Step 1 – identification of closest prior art</u>
The first step is to identify the closest prior art. I understand that the defendants have identified formulation H11 of Manning as closest prior art. In my understanding, the defendants do not discuss whether Bender is 'more close' than Manning so that Bender should be considered more suitable as closest prior art instead of Manning.

In my opinion, Manning H11 remains the better starting point, and therefore Manning H11 is the closest prior art. Relative to both UM '70 and UM '71, H11 of Manning provides a concrete and tested embodiment that differs only with respect to mannitol (for UM '70) and PS 80 (for UM '71). As pointed out in Anette Müllertz' declaration III, paragraph 3.6, Bender is an idea catalogue of hypothetical, non-tested adalimumab formulations. Bender

does not provide any individualised embodiment. If the 'person skilled in the art' was provided with Bender as closest prior art, the 'person skilled in the art' would need to start from the framework and not – as would be the case for H11 of Manning – an individualised starting point. Therefore, in my opinion, H11 of Manning provides a much better springboard for the 'person skilled in the art' to develop the formulations of UM '70/UM '71.

In consequence of H11 of Manning being the closest prior art, the assessment of creative step should be performed in view of H11 of Manning and not in view of Bender. With reference to my previous declarations, I find that the condition for creative step over H11 of Manning is met for both UM '70 and UM '71. In addition, if looking to Bender, the notion of keeping mannitol as the sugar stabiliser is reinforced.

However, for the sake of completeness I will below provide an assessment based on the assumption that Bender was the closest prior art.

Re: UM '70

Step 2 – defining an objective technical problem, claim 1/7, UM '70
In respect of claim 1 as well as claim 7 of UM '70, i.a. the absence of mannitol is a differing feature. Thus, an objective technical problem may be formulated as how to establish a viable adalimumab formulation. (Since Bender does not disclose any individualised embodiment(s), the objective technical problem cannot be to provide an alternative to embodiment of Bender, since no embodiments are presented in Bender. The problem is thus to establish an individualised viable adalimumab formulation. This is somewhat in line with Bender's expressed purpose, though Bender's focus is confined to alternative buffer systems as compared to the citrate/phosphate buffer system of Humira® (see Bender's summary as cited above).) On page 3 (E2743), Bender observes that "*an acceptable pharmaceutical formulation has to ensure a shelf life of the antibody nowadays of at least about 24-36 months*".

Step 3 – determining whether the skilled person (i) presented with the above objective technical problem, and (ii) with the outset in the closest prior art chosen, would have arrived at the creation of claim 1/7, UM '70
Bender is concerned only with variations of the buffer systems and does not discuss variations of any of the other components, let alone exchanging the sugar stabiliser mannitol with another sugar stabiliser. Thus the 'person skilled in the art' is primarily induced by Bender to develop new formulations based on making new choices of buffer systems rather than making any other changes. When the 'person skilled in the art' works on developing new formulations, it follows from EPO *Case Law*, that the person is bound by the framework offered by Bender:

3.4.3 Chosen type of starting point

In **T 570/91** the board emphasised that although a person skilled in the art was completely free in choosing a starting point, he would of course be bound afterwards by that choice. If, for instance, the skilled person preferred and decided to start from a specific compressor piston, he could further develop that piston but at the end of that development the normal result would still be a compressor piston and not an internal combustion engine piston. In **T 439/92** it was explained that a conscious choice of starting point, made in the knowledge of the respective benefits and drawbacks of the various types concerned, not only determined the subject-matter serving as a starting point but also defined the framework for further development, i.e. a further development within this particular type. A change of type during the further development of the consciously chosen type, to another type, which was previously known but had not been chosen, could then only be seen as the result of an ex-post-facto analysis (see also **T 1040/93**, **T 35/95**, **T 739/95**, **T 255/03**). It is unlikely, and normally not obvious, for the invention type originally chosen to be changed during development (**T 817/94**, recently cited in **T 749/11** and **T 535/10**). A generically different document cannot normally be considered as a realistic starting point for the assessment of inventive step (**T 870/96**, **T 1105/92**, **T 464/98**).

(https://www.epo.org/law-practice/legal-texts/html/caselaw/2016/e/clr_i_d_3_4_3.htm)

The 'person skilled in the art' would – as explained in Anette Müllertz' declaration II, paragraph 3.1 - not chose to change mannitol with any of the sugar stabilisers defined in claim 1 of UM '70. There is no motivation in Bender for making such modification. Therefore claim 1 as well as 7 involves a creative step over Bender.

On a side note: If a 'person skilled in the art' was provided with the objective technical problem and Bender, the 'person skilled in the art' would try to develop a viable formulation, and when choosing a buffer/buffer system, the 'person skilled in the art' would take note of Bender's observation that:

- "*sodium phosphate being a well-accepted and most frequent buffer in pharmaceutical formulations, buffering a pH range of 5.8 to 8.0 (26).*"
- "*Acetate buffer exhibits a low aggregation propensity (27) and stabilizes the pH of a formulation within the range of pH 3.6 to 5.6.*"
- "*L-Histidine has been found to be an excellent buffer component for monoclonal antibodies (SYNAGIS®, HERCEPTIN®, XQLAIR®, SIMPONI®) and is maximally stabilizing around pH 6.0.*"
- "*L-histidine buffer was also shown to scavenge metal ions thus minimizing protein oxidation (29).*"

Re: UM '71, claim 1

Step 2 – defining an objective technical problem, claim 1, UM '71

When confronted with the objective to establish a formulation of UM '71, claim 1, Bender's framework requires a choice of a particular surfactant and a particular buffer/buffer system. The differing features between claim 1 of UM '71 and Bender are that these choices have been made in claim 1, but not in Bender. As for UM '70, an objective technical problem may be formulated as how to provide a viable adalimumab formulation.

Step 3 – determining whether the skilled person (i) presented with the above objective technical problem, and (ii) with the outset in the closest prior art chosen, would have arrived at the creation of claim 1 UM '71

If a 'person skilled in the art' was provided with the objective technical problem and Bender, the 'person skilled in the art' would try to develop a viable formulation, and when choosing a buffer/buffer system, the 'person skilled in the art' would take note of Bender's observation that:

- "*sodium phosphate being a well-accepted and most frequent buffer in pharmaceutical formulations, buffering a pH range of 5.8 to 8.0 (26).*"
- "*Acetate buffer exhibits a low aggregation propensity (27) and stabilizes the pH of a formulation within the range of pH 3.6 to 5.6.*"
- "*L-Histidine has been found to be an excellent buffer component for monoclonal antibodies (SYNAGIS®, HERCEPTIN®, XQLAIR®, SIMPONI®) and is maximally stabilizing around pH 6.0.*"
- "*L-histidine buffer was also shown to scavenge metal ions thus minimizing protein oxidation (29).*"

These observations would motivate the 'person skilled in the art' to formulate formulations that comprises one of these buffers. Bender does not provide any observations that motivate the 'person skilled in the art' to combine the above 3 buffers, let alone to combine these buffers with any of the other buffers mentioned by Bender.

In addition to making a choice in respect of a buffer, the 'person skilled in the art' would need to choose a surfactant from between PS 20 and PS 80. Bender does not provide any observations that motivate the 'person skilled in the art' to choose a particular surfactant.

There is in particular nothing in Bender that specifically points to the combination of PS 20 and histidine+citrate as called for in claim 1 of UM '71.

Based on the above, the 'person skilled in the art' could define a formulation where he chose to combine the 3 fixed excipients (adalimumab, mannitol and NaCl) with PS 20 as surfactant and a buffer system combining histidine

and citrate. But there is simply nothing in Bender that points to this specific formulation, and therefore the 'person skilled in the art' would not arrive at such a combination. Therefore, claim 1 involves a creative step over Bender.

Re: UM '71, claim 8

Claim 8 of UM '71 narrows down the scope of claim 1 in that it specifies the sugar stabiliser to be sorbitol.

The objective technical problem is the same as above. For all the reasons set out in the contexts of UM '70 (claim 1 and 7) and UM '71 (claim 1), claim 8 of UM '71 involves a creative step over Bender.

Re: UM '70 and UM '71

In the course of making the above choices and modifications, the 'person skilled in the art' would need to establish whether particular formulations were viable. Whereas Bender observes on page 3 that "*an acceptable pharmaceutical formulation has to ensure a shelf life of the antibody nowadays of at least about 24-36 months*", Bender does not provide any guidance on how to assess this, and the 'person skilled in the art' would need to use his own general knowledge to develop and apply adequate protocols.

All this keeping in mind that the art of formulating monoclonal antibodies is unpredictable in the sense that the function of all the excipients and the active ingredient are interlinked as also explained by Anette Müllertz in declaration I, paragraph 3.1, and now also with specific reference to sorbitol by Sven Frøkjær in declaration III, paragraphs 7 and 42. In Sven Frøkjær's opinion "*whether or not (and to what extent) sorbitol acts as a stabiliser in SB5/Imraldi® needs to be determined by testing. This cannot be determined simply on the basis that sorbitol is known to act as a stabiliser of other proteins or even if, as here, sorbitol is known to act as a stabiliser of other adalimumab formulations containing different excipients.*"

4.2.3 In paragraph 9-11 of Daniel Otzen's declaration II, Daniel Otzen observes that in his opinion, the description of UM '70/UM '71 does not provide a foundation for defining that a formulation according to the claims should specifically comprise PS 20. As a concluding remark Daniel Otzen observes in paragraph 11, last sentence, that "*the inclusion of a surfactant (in particular polysorbate 20, which was not even tested) as a requirement of the claimed formulations seems entirely out of place and inconsistent with the information provided in the Utility Models.*" What are your comments to Daniel Otzen's criticism?

In Daniel Otzen's declaration II, paragraph 11, Daniel Otzen, in my understanding, views the utility models-in-suit as if the models were academic articles where the claims represent the conclusions. Sven Frøkjær did the same in his declaration II, paragraph 32 et seq. including the concluding paragraph 36.

I refer to the detailed observations in my declaration III, paragraph 3.3. As observed herein, I have not considered whether the academic criticism is sound. However, in the context of a utility model/patent, it is not a requirement that the technical effects are documented by scientific data disclosed in the application as filed. As observed in my declaration I, paragraph 3.2, documentation for the technical effect may be post-produced and -filed. In the case at hand, data for i.a. Imraldi® was actually filed with the EPO and found to adequately document the technical effect.

In addition to what is observed in my declaration III, paragraph 3.3, I add, that the protective scope of UM '70 and UM '71 has been narrowed as compared to EP '510. By way of example, whereas the description of UM '71 suggests that both PS 20 and PS 80 may be used in adalimumab formulations, UM '71 only covers formulations that comprises PS 20 and does not cover formulations that comprises PS 80. It is unproblematic that the protective scope of the claimed technology is narrower than the technology described in the application as filed.

4.2.4 Based on the observations made by Anette Müllertz in her declaration III, paragraph 3.3, please advise whether a 'person skilled in the art', in your opinion, would conduct a PLS analysis similar to the one conducted by Daniel Otzen in his declaration II.

The DKPTO's guidelines for utility models describes the 'person skilled in the art' as follows:

"Fagmanden" skal antages at være en almindelig praktiker, som har generel almenviden inden for teknikområdet på det relevante tidspunkt. Fagmanden skal forudsættes at have adgang til alt "kendt teknik", i særdeleshed de dokumenter, der er citeret i nyhedsundersøgelsensrapporten, og fagmanden har mulighed for at udføre rutinearbejde og almindelige eksperimenter.

Det tekniske område for fagmanden er fastlagt af det problem der skal løses på basis af den nærmest liggende, kendte teknik. Hvis det tekniske område for problemet henholdsvis løsningen er forskelligt, er fagmanden eksperten indenfor problemet - og ikke løsningen.

Fagmanden i relation til brugsmodeller er en person, der har et mere snævert kendskab til teknikområdet end en fagmand i relation til patenter. En brugsmodelfagsmand har således kendskab til frembringelsens teknikområde, han har normalt ikke kendskab til beslægtede teknikområder og han har ikke kendskab til fjerntliggende teknikområder.

…

In Anette Müllertz' declaration III, the 'person skilled in the art' is given to be a formulation chemist or a protein chemist. I understand from Anette Müllertz' observations that formulation chemists and protein chemists have

a basic knowledge of statistical methods, but that statistics is not their speciality. I also understand that statistical analyses of data sets similar to those comprised by Manning are typically handled by bio-statisticians, i.e. specialists within the field of analysing data sets such as those presented by Manning. I also understand that the performance of PLS analysis falls outside the scope of the ordinary work of formulation chemists and formulations.

Against this background it seems clear to me that the performance of PLS analyses similar to those undertaken by Daniel Otzen falls outside the technical area of 'utility model person skilled in the art' (in Danish: 'brugsmodelsfagmand'), it being a formulation chemist as well as a protein chemist. Even a 'person skilled in the art' was told to perform a PLS analysis, then it would require a creative selection of data to perform an analysis similar to the one performed by Daniel Otzen. In my opinion, this would clearly go beyond the "rutinearbejde og almindelige eksperimenter" [English: "routine work and ordinary experiments"] that 'persons skilled in the art' undertake."

Forbenyttelsesret

Den 27. februar 2012 bragte Business Wire en pressemeddelse, hvoraf fremgår bl.a.:

"**Samsung Biologics and Biogen Idec Announce Formation of Biosimilars Joint Venture Samsung Bioepis**
… Samsung Biologics and Biogen Idec announced today that the companies have established their Joint venture, Samsung Bioepis Co, Ltd, to develop, manufacture and market biosimilars in keeping with their agreement announced in December.
…
… In May 2010, Samsung announced the biopharmaceutical sector as one of five new strategic businesses that would lead the group's future growth, committing to invest 2.1 trillion won ($2 billion) in biopharmaceuticals by 2020. …"

Den 29. februar 2012 indgik Samsung Bioepis Co. Ltd som "purchaser" og Biogen Idec MA Inc. som "supplier" en"Manufacturing Agreement", hvoraf fremgår bl.a.:

"…
l. DEFINITIONS
Defined terms used in this Agreement, as indicated by the use of initial capitalization, shall have the meanings set forth in Schedule l.

2. SUPPLY OF PRODUCTS
2.1. License. Purchaser hereby grants to Supplier a non-exclusive, non-transferable, royalty-free, fully-paid-up license under (i) Purchaser's interest in the Biogen Product-Specific Technology, (ii) Purchaser's interest in the Joint Product-Specific Technology, and (iii) any other Intellectual Property Controlled by Purchaser that are

necessary or useful to manufacture, have manufactured and import each Product in the Territory, solely for the purpose of fulfilling Supplier's obligation under this Agreement during the Term. …

…

2.2.1. Clinical Supply of Drug Substance and Drug Product. Purchaser shall purchase from Supplier and Supplier shall sell to Purchaser the volumes of Bulk Drug Substance and Drug Product needed for clinical trials set forth in Sections 2.2;l(a) and (b) below.

(a) **Clinical Drug Substance.** Purchaser shall purchase from Supplier and Supplier shall sell to Purchaser.100% of Purchaser's Clinical Needs for (i) all Bulk Drug Substances for the Initial Products based on … [tekst hemmeligholdt] Humira and (ii) all phase 1 Bulk Drug Substance for thé Initial Product based on [tekst hemmeligholdt] in each case such percentage shall be the Minimum Clinical Volume Commitment for each such Sulk Drug Substance for use in clinical trials. …

(b) **Clinical Drug Product.** Purchaser shall use Commercially Reasonable Efforts to establish a relationship with one or more Third party contract manufacturers to supply Drug Product for the Initial Products based on … [tekst hemmeligholdt] as soon as possible after the Effective Date. With respect to each such Initial Product, in the event that Purchaser shall not have entered into any agreement with a Third Party contract manufacturer prior to the time that it requires Drug Product for such Initial Product, until Purchaser shall have entered into any such agreement, Purchaser shall purchase from Supplier and Supplier shall sell to Purchaser Drug Product for such Initial Product for clinical trials in the Territory in quantities to be proposed by Purchaser in accordance with the terms of this Agreement and with any terms of any agreement between Supplier and any Third Party contract manufacturer entered into with the prior written consent of Purchaser in accordance with Section 2.2.5, which are applicable to the supply of such Drug Product to Purchaser. For clarity, there is no Minimum Clinical Volume Commitment for Drug Products.

…

3. MANUFACTURE OF PRODUCTS

3.1. Manufacture. Subject to the provisions of this Agreement, Supplier shall Manufacture the Products in accordance with (a) the applicable Specifications, (b) the applicable Regulatory Approvals, as may be amended from time to time, (e) cGMP requirements and (d) all other applicable laws, rules and regulations.

[tekst hemmeligholdt]

3.4. Production Sites. Supplier shall Manufacture Bulk Drug Substances at its own Facilities. …

[tekst hemmeligholdt]

…

4. GOVERNANCE

[tekst hemmeligholdt]

…

4.2. Joint Steering Committee.

4.2.1. Composition; Purpose. A Joint Steering Committee consisting of three (3) representatives from each Party with the requisite experience and seniority to enable them to make decisions on behalf of the Parties shall be established for the purpose of facilitating information sharing pertaining to the activities of the Parties under this Agreement. The Joint Steering Committee shall have the responsibility to (i) oversee planning for an approved Manufacturing program; (ii) oversee Supplier's performance under this Agreemerit; (iii) establish a supply risk mitigation

plan, which shall address such matters as minimum inventory targets and minimum safety stock levels, qualified back-up Manufacturing. and such other matters as they deem appropriate to protect against the risk of interruption of supply, whether due to the occurrence of a force majeure event or otherwise; (iv) respond to and take action with respect to the occurrence of a CPK Index of less than 1 under Section 3.7; (v) take such other actions as are required of the Joint Steering Committee as set forth in this Agreement, if any, and (vi) otherwise set the Manufacturing objectives and monitor their achievement, including review of quality data trends and performance. The Joint Steering Committee shall endeavor in good faith to establish consensus. Each Party will designate its representatives to the Joint Steering Committee within thirty (30) days of the Effective Date.
…
4.2.3. Meetings. … The Joint Steering Committee shall meet not less than once each Calendar Quarter during the process development, on such dates and at such times as agreed to by Supplier and Purchaser. …
4.2.4. Minutes. …
4.2.5. Dispute Resolution. …
4.2.6. Designation of Coordinator. …
…
SCHEDULE 1
[tekst hemmeligholdt]
1.41 "**Facilities**" means Supplier's facilities in Cambridge, Massachusetts, in Research Triangle Park, North Carolina, and in Denmark or any other facility designated by Supplier with the prior written approval of Purchaser (each, a "**Facility**").
[tekst hemmeligholdt]…
1.100 "**Territory**" means the entire world.
…"

Den 18. september 2012 indgik Samsung Bioepis Co., Ltd. en "Quality Agreement" med Biogen Idec MA, Inc. og Biogen Idec, Denmark, Manufacturing ApS (samlet betegnet "Biogen Idec"), hvoraf fremgår bl.a.:

"**1 OBJECTIVE OF THE QUALITY AGREEMENT**
1.1 Samsung Bioepis and Biogen Idec desire to enter into a Quality Agreement with respect to the production of Bulk Drug Substances as set forth herein and consistent with the Manufacturing Agreement dated 29 February 2012 among Samsung Bioepis and Biogen Idec MA Inc. (hereinafter the "MSA). This Quality Agreement may be amended by both parties as set forth in Section 28 at any time, e.g., if PVR's or commercial production is undertaken.
1.2 This Quality Agreement outlines the specifics and responsibilities of Samsung Bioepis and Biogen Idec with respect to quality control and quality assurance relating to the Manufacture of Products listed in Appendix I.
This Quality Agreement is to ensure that the Manufacturing, testing, storage, labeling and shipping of Bulk Drug Substance and Drug Product are executed properly and in compliance with cGMPs and all relevant regulatory, Samsung Bioepis and Biogen Idec requirements as more fully set forth in the MSA.
…
2 DEFINITIONS
For all purposes of this Quality Agreement, and all amendments hereto, the capitalized terms defined in this Section shall have the meanings herein specified. Capitalized terms used but not defined herein shall have the meanings ascribed to them in the MSA.

[tekst hemmeligholdt]
…
Manufacture or Manufacturing: Shall mean activities directed to making, producing, manufacturing, processing, filling, finishing, packaging, labeling, quality assurance testing and release, shipping or storage of a product, including Products and other Biosimilar Pharmaceutical Products.
[tekst hemmeligholdt]
…
3 ROLES AND RESPONSIBILITIES
3. l Samsung Bioepis shall hold the Clinical Trial Application for the Products covered under this Quality Agreement as set forth in Appendix 1.
3.2 Biogen Idec has the responsibility to ensure that the Products are manufactured, packaged for storage and shipping, quality control tested and released in compliance with applicable cGMP and all other applicable laws and regulations. Other responsibilities of Samsung Bioepis and Biogen Idec with respect to the quality of Products are listed in Appendix 5.
…
5 MANUFACTURING ACTIVITIES
5.1 Manufacturing. Biogen Idec shall Manufacture Products at the Facilities in accordance with cGMPs, the applicable Regulatory Approvals, as may be amended from time to time, the agreed Specifications and the Master Batch Records.
…"

Aftalen er bl.a. underskrevet af Charlotte Kornbo, Director, Hillerod Quality, Biogen Idec Allé 1, 3400 Hillerød, Denmark. Charlotte Kornbo er også angivet som en ud af tre under "Responsible Personel" i "Appendix 3" som repræsentant for Biogen Idec, "Hillerød Site – Quality Assurance".

Den 12. marts 2013 blev følgende lagt på Samsungs hjemmeside:

Samsung Bioepis and MSD Enter Biosimilar Development and Commercialization Agreement
February 21 2013 at 4:36 AM Permalink Comments (0)

Logo Samsung Bioepis Co., Ltd. and MSD, known as Merck in the United States and Canada, announced on February 20 they have entered into an agreement to develop and commercialize multiple pre-specified and undisclosed biosimilar candidates.

"Samsung Bioepis has been building the capabilities needed to develop high-quality biosimilars," said Christopher Hansung Ko,Ph.D., CEO of Samsung Bioepis. "With this development and commercialization agreement, Samsung takes a significant step towards becoming a major player in the biopharmaceutical industry."

Under the agreement, Samsung Bioepis will be responsible for preclinical and clinical development, process development and manufacturing, clinical trials and registration. MSD will be responsible for commercialization. Samsung Bioepis will receive an upfront payment from MSD, product supply income and will be eligible for additional payments associated with pre-specified clinical and regulatory milestones. Further financial terms were not disclosed.

"The combination of Merck's global commercial presence with Samsung Bioepis' biologic development and manufacturing capabilities positions the two companies well to increase access to biosimilars to improve human health," said Rich Murray, Ph.D., senior vice president Biologics and vaccines research at Merck. "We look forward to this collaboration and its potential to complement our internal, expanding biologics portfolio."

Der er fremlagt en mail af 14. marts 2014:

Sender : [redacted] [redacted] /Program Mgt.[redacted]
Date : 2013-06-14 23:16 (GMT+09:00)
Title : [BIIB606, SB5] Selection of SB5 formulation

Dear All

Today SB DP team analyzed stability samples stored at 40oC for 2 weeks using SE-HPLC. Please find an attached file.

From the results, there was no significant difference in HMW increment between two candidate formulations (Candidate 1: 15 g/L Histidine, 1.0 g/L polysorbate 20 & Candidate 2: 12 g/L Histidine, 0.8 g/L polysorbate 20). To decrease any possible stability risk from impurities of excipients, candidate 2 formulation (12 g/L Histidine, 0.8 g/L polysorbate 20) is selected finally.

The composition of SB5 formulation is described below

Component	Concentration
Tri-sodium citrate dihydrate	2.0 g/L
Citric acid monohydrate	0.68 g/L
L-Histidine	1.2 g/L
L-Histidine HCl	10.8 g/L
D-sorbitol	25 g/L
Polysorbate 20	0.8 g/L

Best regards,
[redacted]

Samsung Bioepis Co., Ltd., Biogen Idec MA, Inc. og Biogen Idec, Denmark, Manufacturing ApS indgik den 5. september 2013 "Addendum to Quality Agreement", hvor SB5 var medtaget på listen over omfattede produkter.

Med ikrafttræden den 13. december 2013 indgik Samsung Bioepis "Development and Commercialization Agreement" med Biogen Idec International Holding Ltd., hvoraf fremgår bl.a.:

"**ARTICLE 1**
DEFINITIONS
[tekst hemmeligholdt]
…

1.18. "**Biogen Agreements**" shall mean (i) the License Agreement dated February 29, 2012 between Biogen Idec Therapeutics Inc. and Samsung (the "**Biogen License Agreement**"), (ii) the Technical Development Services Agreement dated February 29, 2012 between Samsung and Biogen Idec Therapeutics Inc. (the "**Technical Development Services Agreement**"), (iii) the Manufacturing Agreement dated February 29, 2012 between Samsung and Biogen Idec MA Inc. (and any quality agreement, quality control testing services agreement and/or similar agreement entered into or to be entered into in relation thereto, collectively, the "**Biogen Manufacturing Agreement**") and (iv) the Joint Venture Agreement dated December 6, 2011 between Samsung BioLogics Co. Ltd. and Biogen Idec Therapeutics Inc., in each case as such agreement may be duly amended from time to time.

[tekst hemmeligholdt]
…
1.46. "**Compound**" shall mean any and all of the following, as well as such other Biosimilars as the Parties mutually agree in writing to add to this Agreement:

1.46.1. Adalimumab/Humira Biosimilar;
1.46.2. [tekst hemmeligholdt] and
1.46.3. [tekst hemmeligholdt]
[tekst hemmeligholdt]
…
1.113 . "**Product**" shall mean any pharmaceutical preparation in final form that is comprised of, incorporates or contains any Compound (i) for sale by prescription, over-the-counter or any other method; or (ii) for administration to human patients in a clinical "trial.
[tekst hemmeligholdt]
…
1.151. "**Territory**" shall mean the following:
With respect to (i) Adalimumab/Humira Biosimilar and (ii) [tekst hemmeligholdt] all of the countries, territories and possessions set forth in Schedule 1.151; and…
[tekst hemmeligholdt]
…
ARTICLE 2
DEVELOPMENT OF COMPOUNDS AND PRODUCTS
2.1. **General.** Samsung shall, at its own expense, use Commercially Reasonable Efforts to carry out the Development of Compounds and Products. …
[tekst hemmeligholdt]
…
2.3. **Exclusive Efforts.**
2.3.1. Throughout the Term, except as set forth in (i) this Agreement and (ii) the Manufacturing Agreement dated February 29, 2012 between Samsung and Samsung BioLogics Co., Ltd. (and any quality agreement, quality yontrol testing services agreement and/or similar agreement entered into or to be entered into in relation thereto; collectively, the "**Samsung Manufacturing Agreement**"**),** and except for other contract manufacturing activities of Samsung BioLogics Co., Ltd. involving one or more Compounds and/or Products, in each case as such may be amended by the parties to such arrangements in good faith from time to time, Samsung shall not, and shall cause each of its Affiliates not to, (a) Develop or Manufacture any Compound or Product for the Territory for or *with* any party other than Biogen and its Affiliates (except to the extent that such Development or Manufacturing is permitted under the terms of the Biogen Manufacturing Agreement or the Technical Development Services Agreement) or (b) Commercialize any Compound or Product in the Territory for itself or for or with any party other than Biogen and its Affiliates.

2.3.2. Throughout the Term, except as set forth in-this Agreement and the Biogen Agreements, in each case as such may be amended by the parties to such arrangements in good faith from time to time, Biogen shall ·not, and shall cause each of its Affiliates not to, Develop or Manufacture any Compound or Product for the Territory for itself or for or with any party other than Samsung, or Commercialize any Compound or Product in the Territory for or with any pa1ty other than Samsung.
[tekst hemmeligholdt]
…
ARTICLE 3
COMMERCIALIZATION OF COMPOUNDS AND PRODUCTS

3. 1. **General.** Biogen shall, at its own expense, use Commercially Reasonable Efforts to carry out the Commercialization of Compounds and Products in the Territory in accordance with an initial Commercialization plan to be prepared by Biogen in English and provided to the JSC within nine (9) months after the Effective Date, as updated, supplemented and amended by Biogen from time to time and notified to the JSC (the "**Commercialization Plan**"**).** …
4.1.3. Samsung shalI have the exclusive right to Develop and, subject to the Biogen Agreements and Section 7 .1, Manufacture any and all Compounds and Products.

4.1.4. Biogen shall have the exclusive right to Commercialize any and all Compounds and Products in the Territory. The Parties acknowledge that Biogen and its Affiliates may authorize sublicensees, and may engage distributors, in each case in accordance with Biogen's and its Affiliates' general practice, to Commercialize the Products in the Territory. Unless otherwise agreed by the Patties in writing, Biogen shall not, either itself or through or together with any of its Related Parties, engage in or carry out any Commercialization activities outside of the Territory with respect to any Compound or Product Developed and/or Manufactured by, for or on behalf of Samsung.
[tekst hemmeligholdt]
…
4.5. **Development and Manufacture.** Subject to the terms of the Biogen Agreements and the Samsung Manufacturing Agreement, Samsung shall have sole responsibility for the Development of Compounds and Products, the Manufacturing of Compounds and Products, and all regulatory activities relating to the Development or Manufacturing of Compounds and Products, throughout the Territory, and Samsung shall, at its own expense, use Commercially Reasonable Efforts to Develop and Manufacture each Product for Commercialization in the Territory. As reasonably requested by Samsung, Biogen shall provide clinical and/or regulatory input to Samsung with respect to Compound(s) or Product(s) in the Territory. Throughout the Territory, Samsung shall be the holder of the Marketing Authorizations for the Products. …
4.6. **Commercialization.** Biogen shall have sole responsibility for the Commercialization of Compounds and Products, and all regulatory activities (such as review of promotional materials, distributor, import and export licenses, market access applications, etc.) relating to the Commercialization of Compounds and Products, throughout the Territory, and Biogen shall, at its own expense, use Commercially Reasonable Efforts to Commercialize each Product throughout the Territory. In connection with the Commercialization of Compounds and Products hereunder, Biogen hereby undertakes to perform and comply with the following:
[tekst hemmeligholdt]
…
ARTICLE 11
TERM AND TERMINATION
[tekst hemmeligholdt]
…
APPENDIX I TO SCHEDULE 1.145
INITIAL TARGET SUPPLY PRICE
(a) Adalimumab/Humira Biosimilar 40 mg prefilled syringe: [tekst hemmeligholdt]
(b) Adalimumab/Humira Biosimilar 40 mg autoinjector: [tekst hemmeligholdt]
(c) Adalimutnab/Humira Biosimilar 20 mg prefilled syringe (if FDA requires pediatric dosefor approval): [tekst hemmeligholdt]
(d) Adalimumab/Humira Biosimilar 20 mg autoinjector (if FDA requires pediatric dose for approval): [tekst hemmeligholdt]

(e) [tekst hemmeligholdt]
(f) [tekst hemmeligholdt]
(g) [tekst hemmeligholdt]
(h) [tekst hemmeligholdt]
…"

Det fremgår af en fortrolig Power Point præsentation fra den 21. januar 2014 fra Biogen Idec vedrørende markedsforhold, kommercialiseringsstatus- og organisation mv. i forhold til lancering og salg af SB5/Imraldi, at Danmark var et af de omhandlede lande.

Samsung Bioepis Co., Ltd. er i "EU Clinical Trials Register" registreret som sponsorerende organisation. Om "main objective of the trial" fremgår det, at "the primary objective of this study is to demonstrate the equivalence of SB5 to Humira® at week 24, in terms of American College of Rheumatology 20% response criteria (ACR20) response rate in subjects with moderate to severe rheumatoid arthritis (RA) despite methotrexate (MTX) therapy". Antallet af "trial subjects" på verdensplan var angivet til 544. Den 19. oktober 2015 var anført som "global end of trial date".

Af en pressemeddelse af 8. september 2015 vedrørende Samsung Bioepis og Merck fremgår bl.a.:

"Merck and Samsung Bioepis Announce Approval of BRENZYS™ (Etanercept), a Biosimilar of Enbrel, in Korea

…

About the Merck and Samsung Bioepis collaboration

Merck and Samsung Bioepis announced in February 2013 a collaboration to develop and commercialize in certain partnered territories multiple biosimilar candidates. In February 2014, the two companies expanded the collaboration to include MK-1293, an insulin glargine biosimilar candidate currently in Phase 3 clinical development for the treatment of patients with type 1 and type 2 diabetes. Under terms of the agreement, Samsung Bioepis is responsible for preclinical and clinical development, process development and manufacturing, clinical trials and regulatory registration, except for MK-1293, which Merck will continue to develop and manufacture. Merck will be responsible in its partnered territories for commercialization of all approved products resulting from the collaboration.

The portfolio includes biosimilar candidates in immunology, oncology and diabetes. There are five candidates in Phase 3 development [Merck partnered territories]:

SB4 Enbrel (etanercept) [worldwide ex-U.S./EU/Japan]
SB2 Remicade (infliximab) [worldwide ex-EU/Russia/Turkey]
SB5 Humira (adalimumab) [worldwide ex-EU/Russia/Turkey]
SB3 Herceptin (trastuzumab) [worldwide]
MK-1293 Lantus (insulin glargine) [worldwide]

Additional regulatory filings for each of these five biosimilar candidates are expected to occur in the 2015-2016 timeframe.

…"

Det fremgår af en pressemeddelse af 23. november 2015, at:

"**Samsung Bioepis Receives Positive CHMP Opinion for the First Etanercept Biosimilar in the EU**

…

Samsung Bioepis has commercial agreements with Biogen and Merck to commercialize and distribute biosimiiar products in immunology and oncology. The products and geographic responsibilities include:

Biogen

…

-SB5, investigational biosimilar candidate referencing Humira® (adalimumab)-European Union, Switzerland, Russia, Turkey

Merck
…
- SB5, investigational biosimilar candidate referencing HumiraR (adalimumab) - Worldwide, including United States, but excluding European Union, Switzerland, Russia, Turkey …"

Af "Assessment report" af 22. juni 2017 fra "European Medicines Agency" vedrørende Imraldi fremgår bl.a:

"**Manufacture, characterisation and process controls**
Description of manufacturing process and process controls
The manufacturing facility at Biogen Inc. (North Carolina, USA) is the intended site for commercial production.
…
2.4.2. Pharmacokinetics
Two clinical studies were performed in which the PK of adalimumab from SB5 was compared to that of EU-sourced Humira.
• Pivotal PK study (SB5-Gll-NHV) was a single-dose, phase 1, 3-way PK similarity study in healthy males and females comparing SB5 with EU-sourced Humira and US-sourced Humira.

• Randomized, double-blind, phase 3 study (SB5-G31-RA) in RA patients (having MTX medication), in which trough concentrations of adalimumab were compared between SB5 and EU-sourced Humira.

Pivotal PK study in healthy subjects (SBS-G11-NHV)
The study was conducted in Germany between May 02 (first subject signed informed consent) - Sept 02, 2014 (last subject last visit)."

Den 24. august 2017 gav Europa Kommissionen markedsføringstilladelse (EU/1/17/1216) til Imraldi. Indehaveren af markedsføringstilladelsen var oplyst at være Samsung Bioepis UK Ltd. Det fremgår af "Annex II", at Biogen Inc. i North Carolina, USA, og Biogen (Denmark) Manufacturing ApS i Hillerød skulle producere de aktive biologiske stoffer. Det danske selskab var anført som eneste selskab med ansvar for "batch release". Under "Annex III" "B PACKAGE LEAFLET" var Biogen (Denmark) Manufacturing ApS angivet som den eneste "manufacturer", mens Biogen (Denmark) A/S var angivet som den lokale repræsentant i Danmark for Samsung Bioepis UK Limited som "Marketing Authorisation Holder".

Markedsføring af Imraldi i Europa, herunder i Danmark, blev påbegyndt i 2018.

Tae Heui Lee har i erklæring af 15. februar 2019 bl.a. anført:

"**I**, **TAE HEUI LEE**, of 107, Cheomdan-daero, Yeonsu-gu, Incheon, Republic of Korea **WILL SAY AS FOLLOWS**:

Introduction

1. I am a Director at Samsung Bioepis Co., Ltd. ("**SB**") and, amongst other responsibilities, I am the project manager for SB's development of a biosimilar of Humira® (adalimumab), SB5 (now launched across Europe as Imraldi®). Before taking up this role, I studied Biology at university to Master's level and worked for over 10 years in the pharmaceutical industry in Korea. I moved to Samsung Electronics in 2010 and worked for about two years as a scientist (primarily focussed on the development of purification processes for biopharmaceuticals). I joined the project management team at SB in 2012 and I have been the project manager for SB5 since May 2012.

2. My personal involvement in respect of SB5 has been the management of the overall timeline and progress status of the project. I have overseen all of the major aspects of the development and formulation, clinical studies and launch of SB5. In this role I liaise with all of the relevant internal stakeholders at SB (including the group leaders within the development, commercial, regulatory and clinical divisions), as well as my counterparts within the Biogen group of companies ("**Biogen**") (primarily based in the R&D teams, as well as more recently on the commercialisation side in respect of manufacture and launch). I report to senior management at SB regarding the status of the project and escalate any issues to them as necessary. As an additional area of responsibility, I led the technology transfer program of the SB5 upstream and downstream manufacturing process to Biogen for the manufacture and purification of the clinical drug substance.

3. I have been asked to provide this declaration on behalf of Samsung Bioepis UK Limited, Biogen (Denmark) Manufacturing ApS and Biogen (Denmark) A/S. Biogen (Denmark) Manufacturing ApS and Biogen (Denmark) A/S are members of the Biogen group of companies. More specifically, I have been asked by counsel for Samsung Bioepis UK Limited, Biogen (Denmark) Manufacturing ApS and Biogen (Denmark) A/S to summarise in this statement the facts relating to the SB5 project, including the development of the SB5 formulation, the manufacturing plans for SB5 and the preparations for clinical trials for SB5 from the start of the SB5 project up until 23 May 2014.

4. I have reviewed a number of documents in preparation of this declaration. I was already familiar with many of these documents and have now refreshed my recollection of them.

5. I make this statement from facts within my own knowledge, except where I indicate the source of any information, in which case I confirm that I have received the information and I believe it to be true. Where I refer to the intentions of SB and Biogen, this reflects my understanding of the frequent discussions and communications I had with the relevant individuals in SB and Biogen throughout the SB5 project and the joint aims that were agreed.

6. My first language is Korean. However, I speak English as a second language and when preparing this statement all my discussions with SB's lawyers were in English. In order to ensure that this statement is as clear as possible, SB's lawyers have assisted me in its drafting. I have reviewed the language very carefully and I am confident that I fully understand and agree with its accuracy.

Samsung Bioepis and Biogen

7. SB is a Korean company which was formed in February 2012 as a joint venture between Samsung BioLogics Co., Ltd. and Biogen Idec Therapeutics Inc [note: See Biogen's press release announcing the joint venture: http://media.biogen.com/news-releases/news-release-details/samsung-biologics-and-biogen-idec-announce-formation-biosimilars ... (a member of the Biogen group of companies). The joint venture company was established for the purpose of the development, manufacture, commercialisation, distribution and sale of biosimilar pharmaceutical products. As of today, SB has 4 biosimilar drugs on sale in Europe and elsewhere in the world.

8. Biogen Idec MA Inc. (a member of the Biogen group of companies) was appointed by SB as the manufacturer of the biosimilar products for clinical use and commercial sales under a Manufacturing Agreement with SB in February 2012 [note: Manufacturing Agreement of 29 February 2012…]. As explained in that agreement, Biogen would carry out manufacture of biosimilar drug substances (including SB5) at one of its three plants, located in (1) Research Triangle Park (often referred to as "**RTP**"), North Carolina; (2) Cambridge, Massachusetts; and (3) Hillerød in Denmark.

9. As a general observation, the SB5 project was, in this period (from commencement through to May 2014) and remains today, an extremely close and productive collaboration between SB and Biogen. Although SB and Biogen each had primary responsibility for different aspects of the SB5 project (with areas of joint responsibility as well), as described below, there was input from SB on the 'Biogen aspects' and *vice versa*. As a result of the close collaboration throughout the project, both companies had visibility and involvement across all of the main areas of the program and key decisions were taken jointly.

10. For example, from at least April 2012, SB and Biogen held monthly Joint Steering Committee ("**JSC**") meetings to discuss the development, supply, clinical and regulatory strategy, workplans and budgets for each of the ongoing biosimilars under development. The meetings were attended by a small number of senior representatives of SB and Biogen. I did not always attend the JSC meetings, but I prepared slides for these meetings and reported to the SB senior representatives in advance of each meeting on the key developments in the SB5 project, which information was then fed into to the JSC meeting discussions. If necessary, I sometimes attended the JSC meetings myself in order to explain any issues on the SB5 project to the SB and Biogen leadership teams.

11. Decisions relating to key aspects of the development program, such as allocating responsibilities and agreeing timelines, as well as addressing and resolving any significant issues were taken at the monthly JSC meetings. Other meetings that were held regularly between SB and Biogen representatives included the Joint Venture ("**JV**") weekly meetings and Tech Transfer main and sub-team meetings (held weekly or biweekly). These more focused and more frequent meetings enabled dynamic discussions and decision making about each of the biosimilars projects. At the JV weekly meetings, representatives from SB and Biogen exchanged more detailed information about the development of the biosimilars, including SB5. I attended the JV weekly meetings, for which I prepared slides on the SB5 project, based on my discussions with the internal sub-teams at SB. These meetings were more focussed on the details of the SB5 project, such as discussing data from studies during the formulation development in order for SB to obtain input from Bio-

gen based upon their experience in this area or making arrangements for technology transfer to Biogen to enable manufacturing. Information from these meetings was fed into the monthly JSC meetings as I have described above. In addition, meetings of the JV Board were held every six months.

12. It was, from the beginning of the project, the intention of SB and Biogen to launch SB5 in essentially all European markets. In December 2013, SB entered into a Development and Commercialisation Agreement ("**DCA**") [note: Development and Commercialization Agreement of 13 December 2013…] with Biogen Idec International Holding Ltd [note: Biogen Idec International Holding Ltd is a member of the Biogen group of companies.], under which Biogen exercised its right to become the commercialisation partner for certain of SB's biosimilar candidates in Europe. The DCA granted Biogen the exclusive right to commercialise biosimilars, including SB5, in the Territory (as set out in Schedule 1.151 which individually listed all the jurisdictions for commercialisation in Europe, including Denmark).
In January 2014, SB established a wholly owned UK subsidiary, Samsung Bioepis UK Ltd ("**SBUK**"), to support SB's European activity, including obtaining and maintaining marketing authorisations for SB's medicinal products from European regulatory authorities. As at 2014, SBUK was SB's only European subsidiary. Much more recently, in 2018, SB has established a Dutch subsidiary and the marketing authorisations previously held by SBUK (including for SB5) have been transferred to that entity.

The Roles of SB and Biogen in the SB5 Project
14. The SB5 project was initiated in around 2009/2010, when Samsung Electronics first commenced cell line selection for this product, and continued at SB upon its incorporation in February 2012. SB's goal is to be the first to launch each of its biosimilars as soon as the primary patent protection has expired. SB and Biogen were therefore aiming to launch SB5 in Europe upon SPC expiry in April 2018 [note: At that time, the paediatric extension to the Humira SPC had not yet been granted, so we were aiming to be ready for launch upon the SPC expiry in April 2018 in the EU. When the paediatric extension was granted, the target launch date became October 2018 in Europe.]. In order to achieve this goal, SB and Biogen agreed that we would expedite our development and manufacturing programs, in order to be able to carry out the phase I and III clinical studies as early as possible and in parallel, to ensure that the necessary timelines could be met. Humira was then, as now, the biggest selling drug in the world and SB5 has always been seen as a very significant commercial opportunity for SB and Biogen. It was therefore especially important for the SB5 project that we expedited each stage of the process, in order to be ready to launch in April 2018.

15. Consequently, very considerable resources were applied to this project by both SB and Biogen and their parent companies (as I explain further below) in order to progress SB5 rapidly through pre-clinical and clinical development and to obtain regulatory approval as quickly as possible. As a result of SB5's expedited development timetable, the marketing authorisation ("**MA**") application for SB5 in Europe was accepted by the European Medicines Authority ("**EMA**") for review in July 2016 and SB leapfrogged other competitors in obtaining its MA for Imraldi. In my experience, the first couple of years of this project achieved far more than would usually be the case in the development of a new biologic (or even compared to most other biosimilars). By May 2014, SB and Biogen had agreed a target launch date for SB5, very significant progress in the development of SB5 had been made

and we were well on track for hitting the timelines set for commercial launch across Europe in April 2018, upon obtaining EMA approval.

16. As part of their close collaboration, roles and responsibilities were allocated between SB and Biogen for the development of each of the biosimilars programs. For the SB5 program, it was agreed that SB would take the lead on the development of SB5 drug substance ("**DS**") and drug product ("**DP**") [note: DS is the formulated adalimumab product. DP is the term used to describe the finished product (i.e. once the drug substance has been filled into the injection device).], as well as clinical development and the regulatory approval process, and that Biogen would be responsible for aspects including pilot scale studies [note: In fact, Biogen and SB jointly conducted the pilot scale studies.], as well as the manufacture itself and commercialisation in Europe in due course.

17. Whilst SB had primary responsibility for the formulation of SB5, Biogen provided technical support, with SB able to consult Biogen throughout the formulation and other development stages. We discussed the status of the development during our weekly JV meetings with Biogen and their team provided technical support throughout the development period, based on their own experiences of formulation development.

18. In parallel, SB and Biogen were also collaborating on the manufacturing process to be used by Biogen in making SB5 DS. As mentioned above, I was responsible for leading the technology transfer from SB to Biogen on the manufacturing process. This involved a very close collaboration between our teams, including numerous meetings (as well as several visits to RTP) to discuss the facility fit, the transfer of the manufacturing process developed and used by SB and to agree Good Manufacturing Practices ("**GMP**") to be used at Biogen's site [note: Good Manufacturing Practices (GMP) is a regulatory term, used to refer to the standards expected by regulatory authorities in the manufacture of pharmaceuticals.]. I attended many of these meetings and was part of the SB team that made several visits to the US in order to ensure that the manufacturing process was successfully transferred and implemented, so that manufacture could start at Biogen's RTP site by the target date in August 2013.

Selecting the Final Formulation of SB5

19. The final SB5 formulation was selected on 14 June 2013. Its composition was confirmed in my email to Biogen on behalf of the SB project management team [note: Email regarding final selection of SB5 formulation of 14 June 2013 and Attachment …], which set out the concentrations of each of the components in the final formulation, as follows:

Tri-sodium citrate dihydrate 2.0 g/L
Citric acid monohydrate 0.68 g/L
L-Histidine 1.2 g/L
L-Histidine HCl 10.8 g/L
D-sorbitol 25 g/L
Polysorbate 20 0.8 g/L

The rationale for the selection of this formulation was explained further in the slides attached to my email.

20. The selected formulation was used for the manufacture of the SB5 pilot batch DS and DP. It was also used for the clinical DS which was manufactured following the cell thaw in August 2013 and the clinical DPs which were filled starting in November 2013. This material was manufactured for the purpose of carrying out the Phase I and Phase III clinical trials for SB5 that were needed to obtain marketing authorisation approval in Europe [note: Typically Phase II trials are not necessary for a biosimilar product.].

21. As I explain in more detail below, SB planned to run the Phase I and III trials in parallel, with the Phase III trial scheduled to commence within just one month of the first administration of SB5 to a subject in the Phase I trial. This timetable had been planned since at least May 2013 (over a year before the clinical trials began), when SB and Biogen agreed a timetable with a target date for the Phase I Clinical Trial Application ("**CTA**") submission in February 2014 and the commencement of the Phase I and III trials in Q2 2014.

Manufacture of SB5

22. As I have explained, Biogen was responsible for manufacture of SB5 DS (for clinical trials, regulatory approval and subsequently for commercial manufacture). With the aim of launching Imraldi in Europe in April 2018, and because of the need to manufacture product for the purposes of the clinical trials, the question of manufacturing was discussed at an early stage. The decision was originally taken to plan for manufacture of the SB5 product at Biogen's RTP site. However, the Manufacturing Agreement also allowed SB to add a second source for the product. Although I do not recall Hillerød being discussed in relation to SB5 at that time, Hillerød was subsequently added as an additional manufacturing site for SB5.

23. Material for the clinical trials to test the SB5 product (three batches of GMP product to be manufactured following transfer of the manufacturing process technology from SB to Biogen) was requested by SB from Biogen on 27 February 2013. Following the selection of the final formulation of SB5 in June 2013, and the successful completion of the DS process development and DS technology transfer to Biogen, it was agreed that we would set the thaw date for the cells for manufacture of the first SB5 batch for 20 August 2013. Following the thaw, the manufacture took place at Biogen's RTP site as planned, between August and November 2013.

24. SB engaged contract manufacturing organisations ("**CMOs**") in the US to undertake DP manufacture (including filling the product into syringes), and a CMO based in the UK for the packaging of the material for use in the clinical trials. The role of the UK CMO was to label the pre-filled syringes and package the product into cartons ready for use in the clinical trials. In my role as project manager, I was aware of all of the arrangements with these CMOs and ensured that the manufactured DP was signed off and transferred between the CMOs in time for the next step in the project to be completed. All of these CMOs were obligated to act according to SB's instructions.

25. The SB5 DP was shipped from the US CMO responsible for DP manufacture to the UK CMO responsible for packaging in March 2014; it left the US CMO's site on 17 March 2014 and was received at the UK CMO's site on 19 March 2014. Packaging of the product used in the Phase I and Phase III trials took place in the UK between 19 March 2014 and 6 May 2014.

SB5 Clinical Trials

26. SB had primary responsibility for the clinical trials for SB5. The clinical, medical and regulatory affairs teams within SB worked together (in communication with the regulatory bodies) to design the trials, develop the protocols and select a clinical research organisation, Parexel, to run the trials under the direction of SB. As part of my role overseeing this process, I attended meeting with SB's agent, Parexel, where we discussed the clinical trial study design to ensure that the trial designs were followed to demonstrate similarity in pharmacokinetic ("**PK**") profiles, efficacy, safety and immunogenicity between SB5 and Humira [note: I attended the "kick-off" meeting with Parexel and was subsequently updated by members of SB's medical team on the status of the clinical studies, for me to report to senior management.].

27. Based on the results in the *in vitro* and cell-based assay studies, which had showed very high similarity between SB5 and Humira, SB and Biogen were very confident that SB5 would provide good results in clinical trials. In order to expedite the regulatory process and hit the tight timetables agreed between SB and Biogen, Phase I and Phase III trials were conducted in parallel. Based on further *in vivo* results we were very optimistic that the clinical trials would go as planned and expected that the results would demonstrate similarity with the originator's product.

28. As part of the preparations for the clinical trials, SB prepared an Investigator's Brochure for the clinical trial program for SB5 (first issued on 7 January 2014) [note: Investigator's Brochure for Phase I and III Clinical trials of 7 January 2014 […]] which set out a high-level summary of the extensive quality and pre-clinical studies that had been carried out in 2012-13 and then summarised the protocol for the Phase I and Phase III clinical trials. In the light of the very extensive quality and non-clinical similarity studies that had been carried out, we were able to satisfy the regulators that running the clinical trials in this way was appropriate. We remained confident that we would meet the aggressive timelines for filing our MA application for SB5 with the EMA and for product launch throughout Europe after the patent protection for the adalimumab compound had expired in April 2018.

Phase I clinical trial

29. A Work Order for the Phase I clinical trial was agreed between SB and Parexel in September 2013. The Phase I trial was a randomised, single-blind, three-arm, parallel group, single-dose study to compare the pharmacokinetics, safety, tolerability, and immunogenicity of three formulations of adalimumab (SB5, EU sourced Humira and US sourced Humira) in healthy subjects. It was carried out in Germany only.

30. Parexel recruited 189 healthy subjects to participate in the Phase I trial in Germany (63 subjects per arm). The duration of the study was a maximum of 14 weeks, including a 4-week screening period.

31. As noted above, the formulation of SB5 for the clinical trials was the same as the formulation which had been decided on in June 2013. This is apparent from the Investigator's Brochure, which sets out the formulation of SB5 in section 3.3 as follows:

Table 3-1. Formulation of SB5 DP

Ingredient	Concentration	Function	Specification
Adalimumab	50 mg/mL	Active ingredient	In-house
Tri-sodium citrate dihydrate	2.0 mg/mL	Buffering agent	Ph. Eur./USP
Citric acid monohydrate	0.68 mg/mL	Buffering agent	Ph. Eur./USP
L-Histidine	1.2 mg/mL	Stabiliser	Ph. Eur./USP
L-Histidine monohydrocholoride monohydrate	10.8 mg/mL	Stabiliser	Ph. Eur./BP
D-sorbitol	25 mg/mL	Tonicity agent	Ph. Eur./NF
Polysorbate 20	0.8 mg/mL	Surfactant	Ph. Eur./NF
Water for injection	*q.s.*	Solvent	Ph. Eur./USP

32. The CTA for the Phase I trial was submitted by Parexel, on SB's behalf, on 7 February 2014. Approval was received from the German regulator on 25 April 2014.

33. The material for the Phase I trial was packaged at our UK CMO and shipped to a pharmacy in Berlin on 6 May 2014, where it was received on 7 May 2014. On 8 May 2014, the material was then shipped to Parexel.

34. The first subject in the Phase I clinical trial received a subcutaneous ("**s.c.**") injection of 40mg SB5 on 9 May 2014. This can be seen on page 1 of the Data Subject Listing document, in the highlighted column. [note: Data subject listing for Phase I clinical trial […]] From this document, it can also be seen that 19 individuals had been injected with SB5 by 23 May 2014.

Phase III clinical trial

35. In parallel with the arrangements for the Phase I trial, SB and Parexel entered into a Work Order for the Phase III clinical trial in November 2013. The Phase III trial was a randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, tolerability, pharmacokinetics and immunogenicity of SB5 compared to Humira in subjects with moderate to severe rheumatoid arthritis ("**RA**") despite receiving methotrexate ("**MTX**") therapy.

36. For the Phase III trial Parexel recruited over 500 subjects with moderate to severe RA despite MTX therapy. The study compared SB5 with EU sourced Humira only. The duration of the Phase III trial was 60 weeks, with subjects receiving 40mg adalimumab at week 0 and every other week thereafter up to week 50. The primary endpoint was to demonstrate the equivalence of SB5 to Humira at week 24, using the American College of Rheumatology 20% response criteria (ACR20) response rate. In addition to evaluating the efficacy compared to Humira, the Phase III study provided further comparison data on safety and tolerability, pharmacokinetics and immunogenicity.

37. As a result of the large number of subjects to be recruited, a number of sites were planned for the Phase III trial. SB filed CTAs on 10 February 2014 in Poland, Czech Republic, Lithuania and Russia and on 15 April 2014 in the UK. CTAs in Ukraine, Bulgaria, Bosnia, Mexico and Korea were also planned to be filed.
The first patients were enrolled in the Phase III trial in May 2014, with the first injection of SB5 given (40mg s.c.) on 5 June 2014.

38. The results of the Phase I and III trials described above were the basis of the clinical data for supporting the regulatory submissions to the EMA for the marketing authorisation application for SB5 in Europe. As a result, SB5 received MA grant

on 24 August 2017 for Europe (including for Denmark), and these results are referred to in the SmPC for Imraldi.

40. The exact same formulation as that set out in paragraph 19 above has been used for SB5 since its first manufacture in August 2013. No alterations have been made to the components or their concentrations in the formulation that was used in the clinical trials which were submitted in support of the MA for SB5 (nor would this be possible without variation of the relevant regulatory approvals). The same formulation is currently used in the commercial manufacture of SB5 (Imraldi) at Biogen's Danish site at Hillerød, and for the product which is now available on the European market [note: See the List of Excipients at Section 6.1 of the Imraldi Summary of Product Characteristics…].

Investment in the SB5 Project
41. I have been asked by SB's counsel to estimate the total cost to SB of the SB5 project by 23 May 2014. As a very rough estimate, based on my knowledge of the overall costs of the SB5 project to date, I believe that tens of millions of US dollars would have already been spent by SB by May 2014.

42. The costs incurred by SB by that time would have included all of SB's internal and external R&D costs involved in developing the product and its formulation, development and validation of the manufacturing processes, the costs of engaging third parties for DS and DP manufacture and packaging of the finished product, the purchase of the reference product, Humira, for use in the clinical trials and the costs of running the clinical trials.

STATEMENT OF TRUTH
43. I believe that the facts stated in this witness statement are true."

Øvrige oplysninger
Fresenius udsendte den 18. oktober 2018 en pressemeddelelse, hvoraf fremgår bl.a.:

"**Fresenius Kabi reaches a global agreement with AbbVie regarding Fresenius Kabi's adalimumab, MSB11022, a biosimilar candidate of -AbbVie's Humira®**
…
On October 17, 2018 licenses under the agreement came into effect in certain countries in Europe in which AbbVie owns intellectual property. The application for marketing authorization for MSBl 1022 was submitted by Fresenius Kabi to the European Medicines Agency (EMA) at the end of last year. The dossier is currently under review. A first launch in Europe is expected in the first half of 2019."

Den 1. februar 2019 udsendte Fresenius en pressemeddelelse, idet de havde fået en positiv udtalelse vedrørende markedsføringstilladelse til deres biosimilære kandidat til Humira.

Biogen (Denmark) Manufacturing ApS, der er placeret i Hillerød, er 100 % ejet af Biogen (Denmark) New Manufacturing Aps. Selskabet hed fra 2003 frem til 2015 Biogen Idec (Denmark) Manufacturing ApS.

Biogen (Denmark) A/S er 100 % ejet af Biogen Netherlands B.V. Selskabet hed fra 2003 frem til 2015 Biogen Idec (Denmark) A/S.

Der er fremlagt regnskabserklæringer vedrørende Biogen Idec Inc. fra årene 2011 til 2018, hvoraf fremgår bl.a.:

> "**Consolidation**
> Our consolidated financial statements reflect our financial statements, those of our wholly-owned subsidiaries and those of certain variable interest entities where we are the primary beneficiary. For consolidated entities where we own or are exposed to less than 100% of the economics, we record net income (loss) attributable to noncontrolling interests in our consolidated statements of income equal to the percentage of the economic or ownership interest retained in such entities by the respective noncontrolling parties. Intercompany balances and transactions are eliminated in consolidation.
>
> In determining whether we are the primary beneficiary of an entity and therefore required to consolidate, we apply a qualitative approach that determines whether we have both (1) the power to direct the economically significant activities of the entity and (2) the obligation to absorb losses of, or the right to receive benefits from, the entity that could potentially be significant to that entity. These considerations impact the way we account for our existing collaborative relationships and other arrangements. We continuously assess whether we are the primary beneficiary of a variable interest entity as changes to existing relationships or future transactions may result in us consolidating or deconsolidating one or more of our collaborators or partners."

Fra 2011 til 2014 var bl.a. følgende selskaber nævnt som "subsidiaries": Biogen Idec MA Inc., Massachussetts, Biogen Idec Therapeutics Inc., Delaware, Biogen Idec (Denmark) A/S, Denmark, og Biogen Idec (Denmark) Manufacturing ApS, Denmark. Fra 2015 blev disse erstattet af: Biogen MA Inc., Massachusetts, Biogen Therapeutics Inc., Delaware, Biogen (Denmark) A/S, Denmark, og Biogen (Denmark) Manufacturing ApS, Denmark.

Den 10. januar 2014 blev Samsung Bioepis UK Limited registreret i England og Wales.

Forklaringer
Der er afgivet forklaring af Anette Müllertz, Michael Bech Sommer, Sven Frøkjær, Daniel Erik Otzen og Tae Heui Lee.

Anette Müllertz har vedstået de af hende afgivne erklæringer og har supplerende hertil forklaret bl.a., at hun er professor på Københavns Universitet, hvor hun forsker i lægemiddelformulering. Hun samarbejder endvidere med Bioneer-FARMA om formulering af lægemidler.

Hun har generelt vedrørende formulering af et lægemiddel som det omhandlede forklaret, at når lægemidlet skal kunne administreres af patienterne, da er det letteste at formulere en væske, som patienterne selv kan injicere. Den samlede volumen af lægemidlet, der ikke må være for tyktflydende, skal højst være 1-1,5 ml. pH skal være tæt på og lavere end kroppens pH på 7,4. Formuleringen skal endvidere være isotonisk, således at molekyletætheden er på 280-320 mOsm.

Antistoffet adalimumab er et stort molekyle, der skal beholde sin struktur for at være virksomt. Det er derfor afgørende, at molekylerne ikke aggregerer eller denaturerer. Der stilles højere krav til stabiliteten af et lægemiddel, der skal håndteres af private, end hvis det alene håndteres af professionelle. Sædvanligvis vil man ønske, at det er stabilt i 18-24 måneder.

Det isoelektriske punkt, hvor adalimumab ikke er opløselig, er pH 8. Det er derfor nødvendigt at udvikle en formulering med en lavere pH, så adalimumab opløses. Gennem forsøg kan man undersøge, ved hvilken pH adalimumab er mest stabilt. Ved et biosimilært lægemiddel vil man endvidere forsøge at formulere et lægemiddelstof, der er billigst muligt at fremstille.

Den fagperson, der får opgaven med at formulere et lægemiddelstof, vil arbejde med forskellige kendte aminosyrer, sukkerstabilisatorer (polyoler og disaccarider), syre-/basepar (buffere), overfladeaktive stoffer samt andre stoffer som eksempelvis salte.

Fagpersonen vil skulle iværksætte forsøg med henblik på at finde den bedste formulering. Langt de fleste stoffer vil påvirke flere ting i en formulering – eksempelvis vil aminosyrerne også kunne bruges som syren i et syrebasepar, og dermed fungere som buffer. De enkelte stoffer vil også kunne påvirke de andre stoffers funktion. Det er muligt eksempelvis at beregne pH'en, men det er lettere at måle sig frem til den. Det er derimod ikke muligt at beregne stabiliteten.

Hvis der er tale om formulering af et biosimilært lægemiddelstof, vil fagpersonen ud over at hente inspiration i litteraturen også se på formuleringen af allerede tilgængelige lægemidler – eksempelvis vil fagpersonen, der tager udgangspunkt i Humira, starte med samme pH, men dog vil et andet indhold i det biosimilære lægemiddelstof kunne betyde, at stoffet fungerer bedre ved en anden pH.

Hun kender ikke det tidsskrift, Benders artikel er publiceret i, og hun er heller ikke bekendt med den form for videnskabeligt dokument, det udgør. Benders artikel angiver intervalområder for enkelte indholdsstoffer, men peger ikke på konkrete formuleringer. Han fokuserer på egnede buffere til adalimumab, og

han drager den oplagte konklusion, at en buffer, der også fungerer som stabilisator, er ønskelig. Han fremhæver acetat og histidin som buffere, der også kan stabilisere en formulering. Fagpersonen vil med baggrund i Benders artikel tage udgangspunkt i formuleringer, der indeholder acetat alene eller acetat og histidin.

Manning er en respekteret og velrenommeret kemiker. Han skriver, at der er brug for yderligere formuleringer af adalimumab, der tillader "long term storage", hvilket han definerer som 3 måneder. Han har forskellige delkonklusioner under de enkelte forsøg, men de samlede anbefalinger findes i slutningen af patentansøgningen. Hun forstår således det af Manning anførte i det indledende afsnit "summary of invention"sådan, at de heri anførte fund vedrører bestemte udførelsesformer. Hans ansøgning består af forskellige blokke, hvor der er lavet et vist antal formuleringer over et bestemt tema. Afslutningsvis udleder han forskellige konklusioner på baggrund af en PLS-analyse, der er en analysemetode, der er anvendelig til at drage konklusioner fra et stort og komplekst datasæt. Sædvanligvis vil samtlige data indgå i analysen, da man ellers kan gå glip af oplysninger, som man måske ikke umiddelbart forudser er interessante.

Manning bruger en Jack Knife model til at vurdere, om resultaterne er statistisk signifikante. Det er eksempelvis ifølge tabel J statistisk signifikant, at mannitol er stabiliserende. Derimod er resultaterne vedrørende sorbitol og trehalose ikke statistisk signifikante. Det fremgår af figur 6, at såvel arginin som sorbitol har en stabiliserende effekt, men at arginin er bedst. Manning konkluderer, at mannitol fungerer bedst over 200 mM, og at sorbitol og trehalose fungerer næsten ligeså godt som mannitol. På baggrund af denne konklusion, vil hun ikke erstatte mannitol i en mængde under 200 mM med sorbitol og trehalose.

I blok G konkluderer Manning, at PS 20 har positive stabiliserende egenskaber, men i sin samlede konklusion, der er draget på baggrund af PLS-analysen af alle data, da er det PS 80, Manning anbefaler. Det er alene den samlede anbefaling, der er anvendelig.

Manning fremhæver i blok H, at formulering nr. 12 er at foretrække. Den har således potentiale til at være stabil ud over de 3 måneder, som var hans definition af long term, og H12 medtages derfor også som formulering J i tabel M, som er Mannings foretrukne adalimumab formuleringer. Hun er dog enig i, at Manning ikke har afskrevet H11.

Det fremgår af definitionen af "stabilisator" i brugsmodellerne, at den skal have en stabiliserende virkning. Når der står "sukkerstabilisator", henvises der efter hendes opfattelse til en bestemt gruppe af stoffer, der ikke nødvendigvis virker

stabiliserende. Det fremgår således ikke af brugsmodelkravene, at den tilstedeværende sukkerstabilisator skal stabilisere. Definitionerne i brugsmodellerne er lidt uklare.

PS 20 og PS 80 ligner hinanden meget, men har forskellig effekt, og man kan derfor ikke nødvendigvis udlede funktionen af PS 20 ud fra resultater med PS 80. En fagmand vil som udgangspunkt afprøve såvel PS 20 som PS 80. Der er ingen eksempler i brugsmodellerne med PS 20.

Stresstestresultaterne vedrørende Imraldi viser, at både histidin og sorbitol virker som stabilisator, idet histidin dog er den mest effektive. Forsøgene er udført ved at tage Imraldi og fjerne eksempelvis histidin. Det havde været bedre, hvis man var startet med at lave formuleringerne uden teststoffet. Antallet af aggregater ved t0 for formuleringen uden histidin må skyldes noget, der skete under dialysen. Det kan eksempelvis skyldes, at pH ikke var stabil under dialysen. Den begyndende aggregering ved t0 kan have accelereret den efterfølgende aggregering.

Michael Bech Sommer har vedstået de af ham afgivne erklæringer og har supplerende hertil forklaret bl.a., at han ønsker at berigtige punkt 5.b i skemaet i sin erklæring af 4. marts 2019, således at sætningen lyder "Surfactant individualised to 'polysorbate 20', which is derived from [168]."

Han er uddannet kemiingeniør, har været beskæftiget inden for lægemiddelindustrien og har de sidste 10 år været europæisk patentagent. Han har ikke været involveret i ansøgningsprocessen vedr. brugsmodellerne, men det er det firma, hvor han er ansat, der har stået for ansøgningen. Han beskæftiger sig alene med patentansøgninger.

Det er almindeligt at patentere formuleringer, da de ofte udgør en løsning på et teknisk vanskeligt problem. En patentansøgning kan ikke sammenlignes med en videnskabelig artikel – som Sven Frøkjær og Daniel Erik Otzen gør – idet patentkravene ikke skal kunne udledes af eksemplerne. Patentkravene skal have basis i ansøgningen, og patentmyndighederne kontrollerer, om dette er tilfældet. Det er således ikke tilladt at opstille patentkrav, der ikke kan udledes af ansøgningen.

Det er sædvanligt, at der bliver indleveret ansøgninger på et tidspunkt, hvor ansøgeren ikke har et endeligt produkt, hvorfor der ofte ikke er udførelsesformer vedrørende alle enkeltkrav. Der er ikke krav om, at der skal gives eksempler, og en foretrukken udførelsesform er ikke nødvendigvis essensen af opfindelsen.

I sin gennemgang af brugsmodellerne har han undersøgt, om hvert enkelt tekniske træk har basis i den indleverede patentansøgning til patent '510. Det fremgår af skemaet i hans erklæring af 4. marts 2019, at der er basis for samtlige træk i brugsmodellernes krav 1. De opstillede krav skal ikke have basis i en enkelt udførelsesform, men kan findes enten forskellige steder i den detaljerede beskrivelse af frembringelsen eller i en enkelt udførelsesform. Det fremgår af praksis fra Boards of Appeal, at kravene skal være "directly and unambiguously derivable" fra den originale ansøgning.

Basis og nyhed vurderes på forskelligt grundlag. Ved vurderingen af, om der er tale om et nyhedsskadeligt modhold, skal kravene være beskrevet i en udførelsesform eller eventuelt i en kombination af en udførelsesform og en generel lære. Det ville være et nyhedsmodhold, hvis Manning havde skrevet, at det ville være en god ide at udbytte mannitol med sorbitol.

Ved vurderingen af frembringelseshøjde er læsningen anderledes end ved vurderingen af nyhed, idet Manning her skal læses i sin helhed. Her anvendes den såkaldte "Problem and Solution Approach". Først skal den nærmeste kendte teknik bestemmes, herefter det objektive tekniske problem og endelig om fagmanden med udgangspunkt i den nærmeste kendte teknik og det objektive tekniske problem ville være kommet frem til den ansøgte opfindelse.

Der er enighed om, at Manning H11 er "closest prior art". Det objektive tekniske problem er, at fagmanden skal opstille et alternativ til H11, idet han skal lave en formulering, der virker, men indeholder færre ingredienser. Det er hans opfattelse, at brugsmodellerne har frembringelseshøjde over for Manning.

Patent- og Varemærkestyrelsens problemformulering indeholder fejlagtigt et fingerpeg i retning af løsningen. Han begår ikke selv samme fejl ved at opstille kravet "indeholder færre ingredienser", da dette ikke direkte angiver en løsning. Sagsøgtes problemformulering med "et alternativ" vil også kunne godkendes.

Såfremt et lægemiddel falder inden for kravene, vil det krænke, men ved den vurdering skal det objektive tekniske problem ikke indgå.

Bender indeholder ikke én formulering, som fagmanden kan tage udgangspunkt i. Det objektive tekniske problem ud fra Bender som "closest prior art" er at formulere et alternativ til Humira, og vejen dertil er gennem alternative buffere. Inden for rammerne af Bender må fagpersonen derfor ikke skifte andet end buffere.

Sven Frøkjær har vedstået de af ham afgivne erklæringer og har supplerende hertil forklaret bl.a., at han ønsker at berigtige punkt 28 i sin erklæring af 8. februar 2019, således at bufferkombinationen angives som histidin og succinat.

Det er umuligt at vurdere, om konklusionerne i brugsmodellerne er draget med rette, bl.a. fordi der ikke er oplysninger om, hvor mange tests der er lavet, og hvilken spredning resultaterne har. Derudover er der i brugsmodellerne testet en række formuleringer, hvor der muligvis er sket kontaminering, hvilket burde have ført til, at der blev udført nye forsøg. Det er overraskende, at brugsmodellerne vælger en foretrukken pH-værdi, der ligger langt fra Humiras pH 5,2.

PS 20 og PS 80 er grundlæggende den samme type stof, men forskellen består alene i længden af den fedtsyre, der er koblet til stoffet. På denne baggrund bør de opføre sig meget sammenligneligt, hvilket også fremgår af Wangs artikel fra 2007. Brugsmodellerne tester alene det overfladeaktive stof PS 80, og det fremgår af resultaterne i screeningseksperiment 2, at PS 80 ikke havde en væsentlig effekt på stabiliseringen. Der er således ikke belæg for, at brugsmodel '071 vælger PS 20.

Overordnet er målet at lave det bedst mulige lægemiddel, og des færre hjælpestoffer, der anvendes, des mindre testning kræves der. Han ville lægge sig så tæt op ad det allerede godkendte lægemiddel som muligt, da det allerede er grundigt testet, og da myndighederne derfor stiller færre krav til godkendelse. Han ville således kun ændre formuleringen, hvis den var beskyttet af et patent. I en sådan situation ville han hente inspiration i litteraturen.

Histidin og citrat er blandt de mest anvendte buffere, og det er oplagt at vælge en kombination heraf i en alternativ formulering af Humira. Selvom citrat medfører smerte ved injektion, er det meget anvendt.

Læsningen af Bender ville få ham til at teste buffersystemerne fosfat-acetat, fosfat-histidin eller acetat-histidin på baggrund af oplysningerne om det pH-interval, som de fungerer inden for. Han er enig med Anette Müllertz i, at når Bender beskriver, at nogle af buffersystemerne også har en stabiliserende effekt, da vil fagmanden som udgangspunkt vælge disse.

Manning har en mere videnskabelig tilgang til testningen end brugsmodellerne, selvom Manning heller ikke laver et tilstrækkeligt antal tests. Manning indleder med "summary of the Invention", som er en gennemgang af forsøget og de opnåede resultater. Selve konklusionen bygger på det, der fremgår af "summary of the Invention", og indeholder den mere stringente konklusion.

Adalimumab er meget stabilt, hvis formuleringen har den rigtige pH.

Hvis han som videnskabsmand blev præsenteret for Manning, ville han gøre sig bekendt med det overordnede indhold. Da dette overraskede ham, ville han gå nærmere ind i beskrivelsen og konklusionerne, der fortsat indeholdt overraskende resultater, hvorfor han ville foretage en grundig gennemlæsning af hele dokumentet. Han ville herefter opdage, at Mannings overraskende konklusion vedrørende anvendelse af PS 80 frem for PS 20 og F-68 ikke havde støtte i resultaterne indeholdt i blok G, og at Manning i øvrigt heller ikke drog denne konklusion under blok G.

Han forstår Mannings konklusion vedrørende sukkerstoffer således, at mannitol, sorbitol og trehalose fungerer omtrent lige godt, idet mannitol dog fungerer bedst i høje koncentrationer, og at de øvrige fungerer bedre ved lavere koncentrationer.

Det fremgår af Manning, at der er flere anvendelige buffere, og at selv en formulering uden buffer er stabil. Hvis en fagperson skal tage udgangspunkt i og forbedre H11, vil han overveje at udelade nogle af stofferne. Derudover vil han eksempelvis teste PS 20 i stedet for PS 80, samt øge mængden af mannitol eller anvende sorbitol eller trehalose i stedet for mannitol.

Brugsmodellerne definerer en stabilisator funktionelt, idet den skal lette opretholdelsen af den strukturelle integritet. Ifølge brugsmodellerne skal formuleringen indeholde en sukkerstabilisator fra en bestemt gruppe af stoffer, samtidig med at den skal opfylde den funktionelle definition.

I forsøgene med Imraldi indeholdt prøven uden histidin flere aggregater ved t0 end de øvrige, hvilket viser, at den er ustabil. Han vil ikke forvente, at de kvalitative resultater var blevet anderledes, hvis man i stedet for at fjerne histidin ved dialyse havde lavet en formulering uden histidin. Det, at der ved t0 var flere aggregater i den histidinfrie prøve, betyder ikke, at prøven af denne grund var disponeret for en kraftigere stigning, da alle prøverne indeholdt aggregater. Det fremgår ikke, om det efter dialysen var nødvendigt at justere pH-niveauet tilbage til 5,2.

Han har på baggrund af de i brugsmodellerne opstillede kvantitative mål for, om en given adalimumab formulering er tilstrækkelig stabil, når den udsættes for stresstests, konkluderet, at sorbitol ikke fungerer som stabilisator i Imraldi.

Hvis man skal formulere et biosimilært lægemiddel til Humira, vil man udvikle en formulering, der i lighed med Humira er stabilt i 2 år. Det kan ikke afvises, at 1 år også vil være tilstrækkeligt.

Stresstests kan være varme, omrøring eller fryse/tø. Et stof, der klarer sig godt i en stresstest, hvor stoffet udsættes for 40 grader i 4 uger, er ikke nødvendigvis stabilt i 2 år. Det er således heller ikke muligt alene på baggrund af Mannings forsøg at konkludere, om en bufferfri formulering kan være stabil i 1 eller 2 år. Det samme gør sig gældende vedrørende H11, men man må på baggrund af sammenligningen med Humira forvente, at en række af de testede stoffer vil være stabile også over længere tid. Hvis stoffet skal godkendes, skal stresstestene foretages efter ICH-guidelines.

Det fremgår af brugsmodellernes eksempler, at væskeformige farmaceutiske sammensætninger indbefattende en sukkerstabilisator klarer sig særligt godt, hvilket indikerer, at man har testet både farmaceutiske sammensætninger med og uden en sukkerstabilisator.

Daniel Erik Otzen har vedstået de af ham afgivne erklæringer og har supplerende hertil forklaret bl.a., at han har berigtiget sin erklæring af 24. april 2019, da han opdagede en tastefejl i talmaterialet i PLS-analysen. Hans konklusion er uændret.

Brugsmodellerne anvender i eksempel 1 ingen overfladeaktive stoffer, og i eksempel 2 anvendes PS 80 som det overfladeaktive stof. Fagmanden ville være åben over for anvendelse af PS 20 i stedet for PS 80, da de har meget sammenlignelige egenskaber. Det vil være almindeligt at prøve begge.

Den vigtigste faktor ved formulering af et protein er sædvanligvis pH. Det vil være oplagt at vælge fosfat-acetat, fosfat-histidin eller acetat-histidin som buffer, når man ønsker pH 5,2 i en formulering. Dette fremgår også af Bender.

En PLS-analyse er et matematisk værktøj til brug for at analysere en række data med uafhængige variable og kan bruges til at finde sammenhænge. Det vil fremgå af den samlede analyse, om de fundne sammenhænge er signifikante. En PLS-analyse er anvendelig, hvis der er mange forskellige variable, men i blok G, hvor alene det overfladeaktive stof varieres, da vil det være mere validt at se på resultaterne fra denne blok.

Han har lavet en PLS-analyse på Mannings testresultater, idet han dog ikke har medtaget resultaterne fra blok A og blok B, da undersøgelserne ikke er foretaget under samme betingelser som resten. Han kan på den baggrund konkludere, at ingen af de testede overfladeaktive stoffer har en signifikant betydning for adalimumabs stabilitet.

Det er en mangel ved Mannings data, at de ikke indeholder flere tests, og alene små forskelle vil således kunne ændre konklusionerne.

Han kan tiltræde Sven Frøkjærs konklusion om, at sorbitol ikke fungerer som en sukkerstabilisator i Imraldi i brugsmodellernes forstand. Det skyldes, at formuleringen, selv når man fjerner sorbitol, vil opfylde brugsmodellernes krav til formuleringens stabilitet. Det fremgår dog af resultaterne, at sorbitol har en vis stabiliserende effekt.

Tae Heui Lee har vedstået den af ham afgivne erklæring og har supplerende hertil forklaret bl.a., at udviklingen af SB5 blev påbegyndt mellem 2009 og 2010, da lægemidlet skulle være klar på markedet ved udgangen af april 2018, hvor patentbeskyttelsen af Humira ville udløbe. Beskyttelsen af Humira blev efterfølgende forlænget med 6 måneder.

Joint venture-samarbejdet vedrørte udvikling, produktion og markedsføring af såvel SB2, SB3, SB4 og SB5, der alle er blevet markedsført i Europa. I 2012 havde Samsung BioLogics ikke erfaring med fremstilling og markedsføring af lægemidler, men den ekspertise havde Biogen. SB5 skulle markedsføres i hele Europa, og Biogen var fra 2012 udpeget som ansvarlig for markedsføringen i bl.a. Danmark.

Han har ikke kendskab til, hvilke selskaber i Biogen-koncernen, der deltog i samarbejdet. Der deltog ansatte fra Hillerød i joint venture- og tech-transfermøderne, men han husker ikke deltagernes navne. Han er ikke bekendt med, om han samarbejdede direkte med Biogen Denmark A/S, da han opfattede Biogen som en enhed. Deltagerne fra Hillerød var ansvarlige for kvalitetskontrol og dokumentation i forbindelse med den tech-transfer, som fandt sted i perioden fra marts til august 2013.

Der var et tæt samarbejde med udveksling af erfaring og viden, men overordnet havde Samsung Bioepis ansvaret for udvikling af fremstillingsprocessen, formuleringen, de kliniske forsøg og godkendelse af produkterne, mens Biogen havde ansvaret for fremstilling og markedsføring.

Han underviste bl.a. personer fra Biogen i Hillerød i den specifikke teknologi, der vedrørte SB5. Dette fandt sted fra marts til august 2013. Fra 2012-2014 blev de biosimilære lægemidler SB2, SB3 og SB4 produceret i Hillerød.

Hans mail af 14. juni 2013 blev sendt til hans tech-transfer samarbejdspartnere hos Biogen i North Carolina. Formlen nævner ikke adalimumab, da alle involverede i projektet vidste, at lægemidlet skulle indeholde samme mængde som Humira og have samme pH.

Formuleringen fra 2013 blev brugt i de kliniske forsøg, og det er samme produkt, der efterfølgende blev sendt på markedet som Imraldi. Hvis de efterfølgende havde ændret formuleringen, ville det kræve nye tests mv. bl.a. med henblik på ny godkendelse.

Det første parti SB5 til brug for de kliniske forsøg blev produceret i North Carolina i august 2013. I henhold til kontrakten var der mulighed for at flytte produktionen til Hillerød, hvilket skete i januar 2016, da produktionen grundet immaterialretlige forhold ikke kunne fortsætte i North Carolina.

Det var Samsung Bioepis, der tilrettelagde processen for godkendelse af produktet, forestod godkendelse og fik markedsføringstilladelse. Han deltog i møderne vedrørende den kliniske godkendelse af produktet. Samsung Bioepis afholdt udgifterne til godkendelsesprocessen og honorerede også Biogen for deres arbejde med tech-transfer programmet.

Han har ikke deltaget i forhandlingerne og indgåelsen af aftalerne. Han har siden 2017 været involveret i markedsføringen af Imraldi. Merck var ikke involveret i udviklingen af eller produktion af SB5.

Parternes synspunkter

Parterne har i det væsentligste procederet i overensstemmelse med deres påstandsdokumenter, idet de dog begge under sagen har udbygget og uddybet deres anbringender.

Fresenius Kabi Deutschland GmbH har i påstandsdokument af 30. april 2019 bl.a. anført følgende:

> *"Brugsmodellerne er gyldige*
>
> Brugsmodellerne (BR '70 … og BR '71 …) blev prøvet af Patent- og Varemærkestyrelsen ("PVS") inden udstedelsen, og der er følgelig en stærk formodning for Brugsmodellernes gyldighed. For at afkræfte denne stærke formodning skal de sagsøgte godtgøre at Brugsmodellerne er ugyldige. De sagsøgte har således bevisbyrden for Brugsmodellernes ugyldighed.
>
> De sagsøgte har gjort gældende, at Brugsmodellerne er ugyldige på grund af (i) utilladelig udvidelse, (ii) manglende nyhed og (iii) manglende frembringelseshøjde.
>
> <u>Ingen utilladelig udvidelse (brugsmodellovens § 18)</u>
> Fresenius bestrider, at Brugsmodellerne er ugyldige på grund af utilladelig udvidelse. Fresenius henviser særligt til følgende forhold:

- Under sin prøvelse af de respektive ansøgninger om Brugsmodellerne undersøgte PVS *ex officio,* hvorvidt ansøgningerne om Brugsmodellerne indebar en utilladelig udvidelse. PVS' udstedelse af Brugsmodellerne viser, at PVS ikke anså Brugsmodellerne for at indebære en utilladelig udvidelse. PVS har eksplicit bekræftet denne vurdering i sine breve af 29. marts 2019 til Ankenævnet for Patenter og Varemærker … .
- Europæisk patentagent Michael Bech Sommers erklæring I …, afsnit 2, og erklæring III …, afsnit 2.

Frembringelserne i henhold til Brugsmodellerne er nye (brugsmodellovens § 5)
Fresenius bestrider, at Brugsmodellerne er ugyldige på grund af manglende nyhed. Fresenius henviser særligt til følgende forhold:

- Under sin prøvelse af de respektive ansøgninger om Brugsmodellerne undersøgte PVS *ex officio,* hvorvidt frembringelserne i henhold til ansøgningerne om Brugsmodellerne manglede nyhed. PVS' udstedelse af Brugsmodellerne viser, at PVS anså frembringelserne i henhold til Brugsmodellerne for at være nye i forhold til kendt teknik. PVS har eksplicit bekræftet denne vurdering i sine breve af 29. marts 2019 til Ankenævnet for Patenter og Varemærker ….
- Europæisk patentagent Michael Bech Sommers erklæring I …, afsnit 3.1, og erklæring III …, afsnit 3.1.

Frembringelserne i henhold til Brugsmodellerne adskiller sig tydeligt fra kendt teknik ("frembringelseshøjde") (brugsmodellovens § 5)
Fresenius bestrider, at Brugsmodellerne er ugyldige på grund af manglende frembringelseshøjde. Fresenius henviser særligt til følgende forhold:

- Under sin prøvelse af de respektive ansøgninger om Brugsmodellerne undersøgte PVS *ex officio,* hvorvidt frembringelserne i henhold til ansøgningerne om Brugsmodellerne manglede frembringelseshøjde. PVS' udstedelse af Brugsmodellerne viser, at PVS anså frembringelserne i henhold til Brugsmodellerne for at adskille sig tydeligt fra den kendte teknik. For så vidt angår BR ´71 har PVS eksplicit bekræftet denne vurdering i sit brev af 29. marts 2019 til Ankenævnet for Patenter og Varemærker … . For så vidt angår BR ´70 har PVS modificeret sin oprindelige vurdering i sit brev af 29. marts 2019 til Ankenævnet for Patenter og Varemærker … . PVS oplyste således i sit brev til Ankenævnet for Patenter og Varemærker, at PVS anså krav 1-6, 8 og 11-12 for at mangle frembringelseshøjde, men at krav 7 og 9-10 ifølge PVS havde frembringelseshøjde. Under henvisning til bl.a. europæisk patentagent Michael Bech Sommers erklæring III …, afsnit 3.2, gør Fresenius gældende, at BR ´70 skal anses for gyldig i sin helhed. Subsidiært skal krav 7 og 9-10 i BR ´70 som minimum anses for gyldige. Det bemærkes, at BR ´70 fortsat formelt er gyldig i sin helhed.
- Europæisk patentagent Michael Bech Sommers erklæring I …, afsnit 3.2, og erklæring III …, afsnit 3.2.

Brugsmodellerne er krænket
Fresenius har bevisbyrden for, at Brugsmodellerne er krænket. Fresenius skal imidlertid kun sandsynliggøre, at det er tilfældet, se retsplejelovens § 413, nr. 1.

Som forklaret i det følgende er Imraldi® omfattet af beskyttelsesomfanget for begge Brugsmodeller, og de Danske Biogen Selskabers handlinger i forhold til Imraldi® krænker følgelig Fresenius' enerettigheder i henhold til brugsmodellovens § 6:

Træk	**Krav 1 i BR ´70**	**Imraldi®**
1.	Vandig farmaceutisk sammensætning, der omfatter:	Vandig farmaceutisk sammensætning (ubestridt)
2.	(a) adalimumab;	adalimumab (ubestridt)
3.	(b) histidinbuffermiddel eller histidinbuffersystem;	Histidinbuffermiddel/histidinbuffersystem (ubestridt)
4.	(c) sukkerstabilisator valgt fra gruppen, der indbefatter trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol; og	Ubestridt at Imraldi® omfatter sorbitol. Omtvistet hvorvidt dette tekniske træk *de jure* kræver, at sorbitol fungerer som en stabilisator. Omtvistet hvorvidt sorbitol *de facto* fungerer som en stabilisator.
5.	(d) 0,05mg/ml til 2mg/ml overfladeaktivt stof valgt blandt polysorbat 20 og polysorbat 80;	0,8 mg/ml polysorbat 20 (ubestridt)
	hvor sammensætningen:	
6.	har et pH på mellem 5,0 og 6,7;	pH mellem 5.0 og 6.7 (ubestridt); Faktiske pH omkring 5.2 forstået af Fresenius som værende ubestridt.
7.	enten er fri for andre aminosyrer end histidin eller omfatter en eller flere andre aminosyrer end histidin ved en samlet koncentration på højst 0,1mM; og	der er ingen andre aminosyrer (ubestridt)
8.	enten er fri for phosphatbuffermidler eller omfatter et phosphatbuffersystem ved en koncentration på højst 0,1mM;	der er ingen phosphatbuffer (ubestridt)
9.	hvor sammensætningen yderligere omfatter en citratbuffer og	citratbuffer (ubestridt)
10.	hvor sammensætningen omfatter sukkerstabilisatoren ved en koncentration på 50 til 400mM	koncentration af sorbitol mellem 50 til 400 mM (ubestridt)

Træk	Krav 7 i BR ´70	Imraldi®
1.-10.	Vandig farmaceutisk sammensætning ifølge et hvilket som helst af ovennævnte krav,	se ovenfor vedrørende krav 1
11.	hvor det overfladeaktive stof er polysorbat 20	polysorbat 20 (ubestridt)

Træk	Krav 1 i BR ´71	Imraldi®
1.	Vandig farmaceutisk sammensætning, der omfatter:	Vandig farmaceutisk sammensætning (ubestridt)
2.	(a) adalimumab;	adalimumab (ubestridt)
3.	(b) histidinbuffermiddel eller histidinbuffersystem;	Histidinbuffermiddel/histidinbuffersystem (ubestridt)
4.	(c) sukkerstabilisator valgt fra gruppen, der indbefatter trehalose, sucrose, mannitol, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol; og	Ubestridt at Imraldi® omfatter sorbitol. Omtvistet hvorvidt dette tekniske træk *de jure* kræver, at sorbitol fungerer som en stabilisator. Omtvistet hvorvidt sorbitol *de facto* fungerer som en stabilisator.
5.	(d) polysorbat 20;	polysorbat 20 (ubestridt)
	hvor sammensætningen:	
6.	enten er fri for andre aminosyrer end histidin eller omfatter en eller flere andre aminosyrer end histidin ved en samlet koncentration på højst 0,1mM; og	der er ingen andre aminosyrer (ubestridt)
7.	enten er fri for phosphatbuffermidler eller omfatter et phosphatbuffersystem ved en koncentration på højst 0,1mM;	der er ingen phosphatbuffer (ubestridt)
8.	hvor sammensætningen yderligere omfatter en citratbuffer og	citratbuffer (ubestridt)
9.	hvor sammensætningen omfatter sukkerstabilisatoren ved en koncentration på 50 til 400mM.	koncentration af sorbitol mellem 50 til 400 mM (ubestridt)

Som anført ovenfor relaterer parternes uenighed i forhold til krænkelse sig til følgende spørgsmål:

- Kræver det tekniske træk 4 i krav 1 i henholdsvis BR ´70 og BR ´71 *de jure*, at sorbitol fungerer som en stabilisator?
- I så fald, fungerer sorbitol *de facto* som en stabilisator i Imraldi®?

Fresenius gør gældende, at det tekniske træk 4 defineret i krav 1 i henholdsvis BR ´70 og BR ´71 *de jure* alene kræver tilstedeværelsen af en sukkerstabilisator fra den anførte gruppe, der inkluderer sorbitol. Det er sådan den relevante fagmand vil forstå de definerede tekniske træk, se professor Anette Müllertz' erklæring II …, afsnit 4.1. Idet Imraldi® omfatter sorbitol, er det tekniske træk 4 defineret i krav i henholdsvis BR ´70 og BR ´71 til stede i Imraldi®.

Faktisk fungerer sorbitol også som en stabilisator i Imraldi®, se professor Anette Müllertz' erklæring II …, afsnit 4.2. Så selv om det tekniske træk 4 defineret i krav 1 i henholdsvis BR ´70 og BR ´71 skal forstås sådan, at det kræves, at sorbitol *de facto* fungerer som en stabilisator, så er dette tekniske træk stadig til stede i Imraldi®.

Hverken Biogen (Denmark) Manufacturing ApS eller Biogen (Denmark) A/S nyder en forbenyttelsesret (brugsmodellovens § 9)

De sagsøgte har bevisbyrden for, at Biogen (Denmark) Manufacturing ApS og/eller Biogen (Denmark) A/S besidder en forbenyttelsesret. For at løfte bevisbyrden skal de sagsøgte godtgøre eksistensen og omfanget af en sådan ret.
Fresenius bestrider eksistensen og omfanget af den påståede forbenyttelsesret.

Fresenius forstår de sagsøgte således, at de sagsøgte mener, at både "Biogen-koncernen" (inklusiv de Danske Biogen Selskaber) og "Samsung Bioepis-koncernen" besidder en forbenyttelsesret, og at enhver virksomhed inden for disse koncerner nyder en forbenyttelsesret.

En forbenyttelsesret i medfør af brugsmodellovens § 9 tilhører en bestemt fysisk eller juridisk person, ikke en gruppe af selskaber. Fresenius forstår de sagsøgte således, at de sagsøgte ikke desto mindre gør gældende, at § 9 giver retsgrundlag for en forbenyttelsesret, der på en eller anden måde kan ejes af en gruppe af selskaber. For at forstå karakteren og omfanget af dette synspunkt har Fresenius fremsat de processuelle opfordringer C-G med henblik på at få afklaret præcist hvilke aktiviteter ('væsentlige foranstaltninger') specifikt identificerede selskaber måtte have udført før den 23. maj 2014 ("Prioritetsdatoen") med henblik på en erhvervsmæssig udnyttelse i Danmark af frembringelserne beskyttet af BR ´70 henholdsvis BR ´71.

Fresenius har adresseret disse opfordringer samt manglen på tilfredsstillende svar i processkrift 4 af 11. april 2019. Fresenius har noteret sig, at de sagsøgte har valgt ikke at besvare opfordringerne tilfredsstillende i deres efterfølgende processkrift B af 25. april 2019. På denne baggrund bestrider Fresenius, at noget relevant selskab på Prioritetsdatoen havde truffet væsentlige foranstaltninger til

fremstilling, markedsføring og/eller salg af Imraldi® i Danmark, jf. brugsmodellovens § 9, stk. 1, 2. pkt. Det bestrides derfor, at nogen af de Danske Biogen Selskaber i denne sag besidder en forbenyttelsesret i forhold til Brugsmodellerne.

I denne forbindelse bemærkes det, at brugsmodellovens § 9 skal fortolkes snævert, idet bestemmelsen udgør en undtagelse til den eneret indehaveren af Brugsmodellerne nyder, og som er baseret på det grundlæggende "first-to-file" princip.

Selv om det ikke er direkte relevant i denne sag bestrides det også, at noget selskab i "Biogen-koncernen" og/eller "Samsung Bioepis-koncernen" inden Prioritetsdatoen havde truffet væsentlige foranstaltninger til fremstilling, markedsføring og/eller salg af Imraldi® i Danmark og som følge heraf skulle besidde en forbenyttelsesret i medfør af brugsmodelloven.

Selv hvis et eller flere selskaber i "Biogen-koncernen" og/eller "Samsung Bioepis-koncernen" skulle have truffet væsentlige foranstaltninger til fremstilling, markedsføring og/eller salg af Imraldi® i Danmark inden Prioritetsdatoen, gælder en forbenyttelsesret kun for de specifikke selskaber, der har truffet sådanne væsentlige foranstaltninger, og forbenyttelsesretten er ikke overdragelig medmindre betingelserne i § 9, stk. 2 af brugsmodelloven er opfyldt. Disse betingelser er ikke opfyldt i nærværende sag, og de Danske Biogen Selskaber har derfor ikke erhvervet nogen forbenyttelsesret fra en tredjepart inden for eller uden for "Biogen-koncernen" og/eller "Samsung Bioepis-koncernen".

Fresenius bemærker for en klarheds skyld, at de sagsøgte ikke har gjort gældende, at de sagsøgte besidder en forbenyttelsesret som følge af en påstået erhvervsmæssig udnyttelse i Danmark af frembringelserne beskyttet af Brugsmodellerne inden Prioritetsdatoen.

Alle betingelserne for midlertidige afgørelser er opfyldt

Fresenius gør gældende, at alle betingelser i kapitel 40 i retsplejeloven for meddelelse af midlertidige afgørelser er opfyldt.

Betingelsen i § 413, nr. 1 er gennemgået ovenfor.

Betingelsen i § 413, nr. 2 er opfyldt, idet Imraldi® er kommercialiseret i Danmark af de Danske Biogen Selskaber.

Betingelserne i § 413, nr. 3 og § 414, stk. 1 er opfyldt. Fresenius og de Danske Biogen Selskaber er direkte konkurrenter på markedet for biosimilære lægemidler svarende til Humira®. Det er et faktum, uanset om Fresenius markedsfører et produkt, der er omfattet af Brugsmodellerne. Der eksisterer derfor en formodning for, at Fresenius vil lide retstab, hvis Fresenius' anmodning om midlertidigt forbud og påbud ikke meddeles.

Betingelsen i § 414, stk. 2 for at nægte meddelelse af et forbud eller påbud er ikke opfyldt. Efter Fresenius' opfattelse har de sagsøgte gjort gældende, at biosimilære lægemidler svarende til Humira® kan formuleres på mange forskellige måder. Formålet med sagen er at forbyde udnyttelse af Fresenius' beskyttede formulering uden Fresenius' samtykke. De Danske Biogen Selskaber kan følgelig udnytte formuleringer, der ikke er dækket af Fresenius' eller tredjemands enerettigheder.

Under henvisning til § 420, stk. 1 bemærker Fresenius, at de krævede forbud og påbud ikke kan være i strid med nogen ret hos SB. På den baggrund er der ikke noget basis for, at SB kan hovedintervenere.

Fresenius gør gældende, at de krævede forbud og påbud skal meddeles uden sikkerhedsstillelse – subsidiært mod sikkerhedsstillelse efter rettens skøn."

Biogen (Denmark) Manufacturing ApS og Biogen (Denmark) A/S samt Samsung Bioepis UK Limited har i deres sammenfattende processkrift og påstandsdokument af 30. april 2019 bl.a. anført følgende:

"Denne sag drejer sig om Fresenius' påstand om, at fremstilling mv. af produktet Imraldi® krænker brugsmodellerne DK 2018 00070 Y4 ("**BR '070**") … og DK 2018 00071 Y4 ("**BR '071**") … (samlet "**Stridsbrugsmodellerne**"), som begge er registreret i Fresenius' navn. Begge Stridsbrugsmodellerne vedrører formuleringer af lægemidler indeholdende anti-TNFα antistoffet adalimumab.

Stridsbrugsmodellernes krav omfatter formuleringer af adalimumab, som indeholder:

	adalimumab	Histidinbuffer	Sukkerstabilisator valgt fra gruppen, der indbefatter trehalose, sucrose, sorbitol, maltose, lactose, xylitol, arabitol, erythritol, lactitol, maltitol, inositol	Polysorbat 80	Polysorbat 20	Citratbuffer
BR '070	JA	JA	JA	JA (krav 1-6, 8 og 11-12)	JA, som alternativ til polysorbat 80	JA
BR '071	JA	JA	JA + mannitol	NEJ	JA	JA

Hertil kommer træk, der går ud på, at formuleringen skal være i det væsentlige fri for andre aminosyrer end histidin og i det væsentlige fri for phosphatbuffer. Der er også træk, der angår pH og koncentrationen af sukkerstabilisatoren.
Det første lægemiddel indeholdende adalimumab, Humira®, markedsføres af AbbVie Inc. Humira® er det bedst sælgende lægemiddel i verden.

Ved udsigten til, at AbbVies grundpatent og det korresponderende supplerende beskyttelsescertifikat ("**SPC**"), der beskytter adalimumab, ville udløbe i Europa i oktober 2018 har en række biosimilære lægemidler indeholdende adalimumab opnået markedsføringstilladelse fra Det Europæiske Lægemiddelagentur ("**EMA**"), herunder biosimilære lægemidler udviklet af Amgen, Sandoz, Boehringer Ingelheim (senere trukket tilbage), Fujifilm-Kirin Biologics (FKB)/Mylan og Samsung Bioepis/Biogen og senest Fresenius (se nedenfor).

Samsung Bioepis'/Biogens biosimilære version af Humira® hedder Imraldi®. Arbejdet med at udvikle Imraldi® påbegyndte lang tid før prioritetsdatoen for Stridsbrugsmodellerne. Imraldi® blev udviklet som led i et samarbejde mellem selskaber i Biogen-koncernen ("**Biogen-koncernen**") og Samsung Bioepis-koncernen (**"Samsung Bioepis-koncernen"**).

Ved anlæggelsen af denne sag var SB indehaver af den europæiske markedsføringstilladelse for Imraldi® […], som efterfølgende er overdraget til et søsterselskab ved navn Samsung Bioepis NL B.V. Selskaber i Biogen-koncernen varetager markedsføringen og salget af Imraldi® i Europa. I Danmark har Imraldi® opnået en markedsandel på ca. 50%.

AbbVie og adalimumab har igennem mange år nydt gavn af beskyttelse fra IP-rettigheder, og Fresenius – som ikke har udviklet Humira® – forsøger nu at forstyrre, hvad der burde være et frit biosimilar-marked. Det er således først efter anlæggelsen af denne sag, at Fresenius har opnået markedsføringstilladelse til sit eget lægemiddel indeholdende adalimumab. Fresenius' biosimilære version af Humira® hedder Idacio®. Idacio® opnåede markedsføringstilladelse den 3. april 2019, men Idacio® markedsføres for indeværende ikke på det danske marked.
Denne sag er anlagt den 16. oktober 2018. Til at begynde med påberåbte Fresenius sig den danske del af det europæiske patent EP 3 148 510 … (det europæiske patent benævnes herefter "**EP '510**"), som Fresenius også er den registrerede ejer af. EP '510 og Stridsbrugsmodellerne tilhører den samme patentfamilie.
Der verserer parallelle retssager mellem parterne vedrørende EP '510 i et antal jurisdiktioner i Europa, men endnu foreligger ingen retsafgørelser.
Først den 3. december 2018 blev Stridsbrugsmodellerne inddraget under denne sag … og Stridsbrugsmodellerne blev faktisk først endeligt registrerede af Patent- og Varemærkestyrelsen ("**Styrelsen**") den 13. december 2018.

Den 21. december 2018 meddelte Fresenius så de Sagsøgte, at Fresenius ikke længere ville påberåbe sig EP '510 under sagen … .

De sagsøgte har indbragt afgørelsen om at registrere Stridsbrugsmodellerne for Ankenævnet for Patenter og Varemærker ("**Ankenævnet**") …, hvor disse ankesager verserer.

Styrelsen har afgivet indlæg til Ankenævnet dateret den 29. marts 2019 … . Det fremgår af disse indlæg, at det er Styrelsens opfattelse, at krav 1-6, 8 og 11-12 ifølge BR '070 ikke adskiller sig tydeligt fra kendt teknik. Det fremgår endvidere,

at Styrelsen nu ser markant anderledes på registrerbarheden af begge Stridsbrugsmodeller i lyset af den kendte teknik, idet Styrelsen på en række væsentlige punkter foretager en anden bedømmelse, end Styrelsen gjorde i forbindelse med sin oprindelige prøvning.

De Sagsøgte har på denne baggrund henstillet til Ankenævnet og Styrelsen, at Styrelsen genoptager sagsbehandlingen af begge Stridsbrugsmodeller … . Uanset at der således er væsentlig usikkerhed om begge Stridsbrugsmodellers gyldighed, skal Sø- og Handelsretten under denne sag tage stilling til, om Stridsbrugsmodellerne kan håndhæves overfor de Sagsøgte, sådan at de Sagsøgte midlertidigt vil blive forhindrede i at drage fordel af en indsats, som er påbegyndt længe før Stridsbrugsmodellernes prioritetsdato.

Tvistepunkter
Til støtte for deres principale påstand i nærværende sag vil Biogen og SB gøre gældende, at Stridsbrugsmodellerne er ugyldige som følge af utilladelig udvidelse (dvs. *added matter*) og som følge af manglende nyhed og frembringelseshøjde i forhold til den kendte teknik. Hertil kommer, at Imraldi® ikke krænker krav 1 (eller noget andet krav) i Stridsbrugsmodellerne, og at de Sagsøgte under alle omstændigheder har forbenyttelsesret.

Utilladelig udvidelse
Kravene ifølge Stridsbrugsmodellerne afviger så markant fra EP '510 stamansøgningen som indleveret …, at det synes som om, at Fresenius har twistet både EP '510 og i endnu højere grad Stridsbrugsmodellerne nærmest til ukendelighed i et forsøg på at få kravene til potentielt at dække formuleringen af Imraldi® - som Fresenius kendte inden udstedelse af EP '510 og registrering af Stridsbrugsmodellerne.

Der mangler således basis for flere af de enkeltstående træk i kravene ifølge Stridsbrugsmodellerne.

Hertil kommer, at kombinationen af disse træk overhovedet ikke fremgår af EP '510 stamansøgningen som indleveret. Fresenius har så at sige benyttet EP '510 stamansøgningen som et "reservoir" og har i kravene sammensat en kombination af [et] enkeltstående træk, som ikke er beskrevet i EP '510 stamansøgningen. Dette udgør under alle omstændigheder utilladelig udvidelse, som medfører, at Stridsbrugsmodellerne er ugyldige.

Manglende nyhed og frembringelseshøjde
Det var på prioritetsdatoen for Stridsbrugsmodellerne (23. maj 2014 ("**Prioritetsdatoen**") kendt at lave formuleringer af adalimumab, og det er på den baggrund ikke overraskende, at de Sagsøgte har identificeret flere relevante modhold, som man har påberåbt sig fx under den indsigelsessag mod udstedelsen af EP '510, som verserer ved Det Europæiske Patentkontor ("**EPO**") …. Det omfatter blandt andre dokumenterne Rast …, Dai … og Fraunhofer …, som de Sagsøgte har fremlagt også under denne sag.

De Sagsøgte har yderligere fremlagt dokumentet Manning … som modhold både under sagen ved EPO og under denne sag.

Manning angår i det væsentlige samme problem som Stridsbrugsmodellerne, nemlig at udvikle alternative adalimumab formleringer til Hu[m]ira®. På side 88 i Manning … beskrives følgende formulering (formuleringen herefter benævnt "**Manning H11**"):

Form No.	API	protein	citrate	phosphate	succinate	HIS	ACETATE	Gly	Arg	mannitol	NaCl	PS80
Form No.	API	protein	citrate	phosphate	succinate	HIS	ACETATE	Gly	Arg	mannitol	NaCl	PS80

De Sagsøgte gør gældende, at Manning H11 er nyhedsskadelig for alle krav ifølge begge Stridsbrugsmodeller.

Manning H11 indeholder mannitol i stedet for de sukkerstabilisatorer, som ved specifik benævnelse er inkluderet i krav 1 i BR '070. Listen af sukkerstabilisatorer i kravet er open-ended som følge af ordvalget *"omfatter"* og *"… valgt fra gruppen der indebefatter …"* og yderligere er det udtrykkeligt beskrevet i Manning, at mannitol kan udskiftes med sorbitol eller trehalose, som er specifikt nævnt i krav 1 i BR '070.

Manning H11 indeholder endvidere det overfladeaktive stof polysorbat 80 ("**PS80**") i stedet for polysorbat 20 ("**PS20**"), som er det eneste overfladeaktive stof inkluderet i krav 7, 9 og 10 i BR '070 og i alle krav i BR '071. Manning indeholder imidlertid også en udtrykkelig beskrivelse af, at PS80 kan udskiftes med PS20.

Hvis ikke Manning H11 er nyhedsskadelig for Stridsbrugsmodellerne, er det under alle omstændigheder klart, at der ikke er frembringelseshøjde, hvilket de Sagsøgte redegør nærmere for … nedenfor.

Styrelsen har allerede konkluderet, at krav 1-6, 8 og 11-12 ifølge BR '070 savner frembringelseshøjde i forhold til Manning. Styrelsen har udtalt, at det var almindelig fagmandsviden at udskifte mannitol med en af de i kravene ifølge BR '070 specifikt nævnte sukkerstabilisatorer. Det er allerede på dette grundlag klart, at der ikke under denne sag kan bestå nogen formodning for gyldigheden af disse krav ifølge BR '070.

Hvad angår frembringelseshøjden for de krav, som er begrænset til PS20, nemlig krav 7, 9 og 10 ifølge BR '070 og alle krav ifølge BR '071, har Styrelsen udtalt, at det objektive tekniske problem, som løses ifølge disse krav, er anvisningen af en alternativ overfladeaktiv forbindelse i stabile vandige formuleringer af adalimumab. Her er spørgsmålet, om fagmanden i lyset af Manning H11 ville udskifte PS80 med PS20.

Styrelsen når i denne sammenhæng frem til (i strid med den holdning Styrelsen indtog i forbindelse med sin oprindelige prøvning), at der er et udsagn i Manning, som indebærer, at fagmanden ikke ville udskifte PS80 med PS20.

De Sagsøgte fremlægger under denne sag en omfattende bevisførelse, som klart afkræfter Styrelsens opfattelse. Det drejer sig om sagkyndige erklæringer fra professor Frøkjær … og professor Otzen ….

Styrelsen har ikke haft mulighed for at inddrage denne bevisførelse i sin vurdering.

De Sagsøgtes bevisførelse i denne henseende er så overbevisende, at der ikke længere består nogen rimelig formodning for, at Stridsbrugsmodellerne er gyldige over Manning.

De Sagsøgte har endvidere fremlagt dokumentet Bender … .

De Sagsøgte er først for ganske nylig blevet opmærksomme på Bender, så dette modhold indgår ikke endnu i hverken sagerne for Ankenævnet eller for EPO. Ingen patentmyndighed har derfor endnu taget stilling til betydningen af modholdet Bender i forhold til hverken EP '510 eller Stridsbrugsmodellerne.

Der kan således heller ikke bestå nogen formodning for, at Stridsbrugsmodellerne er gyldige over Bender.

Fresenius skal på denne baggrund sandsynliggøre på anden vis end ved henvisning til en formodning for gyldighed, at Stridsbrugsmodellerne er gyldige.

Bender henviser til Humira® formuleringen og anfører videre, at dokumentet angår "*further suitable liquid formulations for Adalimumab based on obvious alternative buffer systems*" (side 2, under overskriften Summary). Formuleringstilgangen, som beskrives I Bender, er konsistent med det, som de Sagsøgtes eksperter, professor Frøkjær og professor Otzen, har anført i deres erklæringer, og det der fremgår af afsnit 12 om den tekniske baggrund.

Bender beskriver "*alternative Adalimumab compositions*", som omfatter 9 forskellige buffer systemer, hvoraf et af dem er et histidin-citratbuffersystem.

De alternative sammensætninger beskrevet i Bender er gengivet i tabellen nedenfor:

Indholdsstof	**Bredt interval**	**Foretrukkent interval**
pH	4.9 – 6.5	4.9 – 5.5
Adalimumab	20 – 130 mg/ml	45 – 55 mg/ml
Sodium chloride	1 – 10 mg/ml	6.0 – 6.4 mg/ml
Mannitol*	11.0 – 137.2 mM	54.9 – 76.9 mM
Polysorbate 20 eller 80	0.1 – 5 mg/ml	0.5 – 2 mg/ml
Buffer (1-9 på side 6 og 7)	0.5 – 30 mM	0.6 – 30 mM

* I Bender angives mængden af mannitol i mg/ml, men angives her omregnet til enheden brugt i Stridsbrugsmodellerne.

Bender anfører, at "*suggested buffer alternatives are commonly used in liquid formulations*", og at "*[a]ll suggested alternatives provide sufficient buffer capacities, show good long term stability, and have a good safety record*." Det beskrives, hvordan hvert buffersystem kan laves, og det pH interval over hvilket, den er effektiv. PS20 or PS80 er lige foretrukne.

Bender foregriber således direkte og entydigt hvert træk i Stridsbrugsmodellerne BR '070 og BR '071, og i hvert fald er det klart, at Stridsbrugsmodellerne ikke har frembringelseshøjde over Bender.

Fresenius har under denne sag fremlagt sagkyndige erklæringer fra professor Anette Müllertz … og europæisk patentagent Michael Bech Sommer ….
Det er bemærkelsesværdigt, at Styrelsens indlæg i sagerne for Ankenævnet … udtrykkeligt går i rette med blandt andet det objektive tekniske problem formuleret af Michael Bech Sommer.

Uheldigvis er spørgsmålene til professor Annette Müllertz baseret på dette objektive tekniske problem (jf. afsnit 3.3 af professor Müllertz' erklæring …, hvor hun behandler det objektive tekniske problem, som består i at tilvejebringe "… *a viable formulation that allows for fewer excipients*" og tilsvarende afsnit 3.8 i hendes anden erklæring …, og det er på denne baggrund klart, at Fresenius' bevisførelse til støtte for Stridsbrugsmodellernes gyldighed allerede af denne grund ikke kan tillægges nogen vægt under denne sag.

Fresenius' bevisførelse baserer sig endvidere på den samme fejlagtige læsning af Manning, som Styrelsen har foretaget. Når der korrigeres for denne fejlagtige læsning, må man falde tilbage på, at Styrelsen indledningsvist i sin vurdering af registrerbarheden af Stridsbrugsmodellerne udtalte, at det er almindelig fagmandsviden at udskifte PS80 med PS20 …, hvilket også er konsistent med professorerne Frøkjærs og Otzens vurdering af fagmandens viden og endvidere med en fornuftig læsning af Manning selv.

Samlet set er der hermed ikke det fornødne grundlag for, at Sø- og Handelsretten skulle kunne lægge til grund, at Fresenius er indehaver af gyldige rettigheder, der kan begrunde midlertidige forbud i overensstemmelse med Fresenius' påstande.

Imraldi® krænker ikke Stridsbrugsmodellerne
Selv hvis Stridsbrugsmodellerne skulle blive anset for at være gyldige, skal Fresenius sandsynliggøre, at fremstillingen mv. af Imraldi® krænker Stridsbrugsmodellerne.

Det er i denne sammenhæng blandt andet nødvendigt at godtgøre eller sandsynliggøre, at Imraldi® indeholder en sukkerstabilisator i Stridsbrugsmodellernes forstand. Fresenius har ikke løftet sin bevisbyrde. Data fra stabilitetstests udført

af Samsung Bioepis […] viser tværtimod, at Imraldi® ikke indeholder en sådan sukkerstabilisator.

Fresenius har gjort gældende, at trækket om en sukkerstabilisator i Stridsbrugsmodellernes krav 1 er opfyldt i Imraldi®, eftersom Imraldi® indeholder sorbitol, der indgår i den gruppe af bestanddele, som Stridsbrugsmodellerne angiver, at sukkerstabilisatoren, blandt andet, kan vælges ud fra.
Dette bestrides.

Det er ikke tilstrækkeligt at en formulering indeholder eksempelvis sorbitol – sorbitol skal også faktisk fungere som en sukkestabilisator, som defineret i Stridsbrugsmodellerne, i den pågældende farmaceutiske sammensætning. Det er klart fra flere passager i Stridsbrugsmodellerne, at trækket om en "sukkerstabilisator" i Stridsbrugsmodellernes krav 1 skal således forstås funktionelt. Fungerer den pågældende bestandel (ex. sorbitol) ikke som sukkerstabilisator, som defineret i Stridsbrugsmodellerne, krænker den pågældende formulering ikke Stridsbrugsmodellerne.

Om sorbitol fungerer som en stabilisator i Imraldi® afhænger, som det fremgår af …, af et antal faktorer, herunder koncentrationen af sorbitol, det specifikke protein og de øvrige indholdsstoffer. Som det også forklares af professor Frøkjær, viser de Sagsøgtes eksperimenter, at sorbitol ikke fungerer som en sukkerstabilisator i Stridsbrugsmodellernes forstand i Imraldi®. Sorbitol er indeholdt i Imraldi® som toniceringsmiddel og udøver sin funktion i sammensætningen i overensstemmelse hermed. De sagsøgtes eksperimenter viser, at det alene er histidin-bestanddelen, som er ansvarlig for den stabiliserende effekt i Imraldi®-sammensætningen.

Eftersom Imraldi® således ikke indeholder en sukkerstabilisator som defineret i Stridsbrugsmodellerne, krænker Imraldi® ikke krav 1 (eller noget andet krav) i Stridsbrugsmodellerne.

Forbenyttelsesret
De Sagsøgte gør yderligere gældende, at Biogen og SB under alle omstændigheder har en forbenyttelsesret, idet man inden Prioritetsdatoen havde truffet væsentlige foranstaltninger til at fremstille, markedsføre og sælge Imraldi®, herunder i Danmark.

Samsung Bioepis og Biogen udviklede Imraldi® (dengang kendt som SB5) før Prioritetsdatoen (23. maj 2014) og således helt uafhængigt af og uden kendskab til EP ’510 og Stridsbrugsmodellerne.

Den endelige formulering (som blev brugt i de kliniske forsøg og som der efterfølgende er opnået markedsføringstilladelse til) blev fastlagt den 14. juni 2013 (Bilag AD (E415)). Denne formulering har ikke ændret sig efterfølgende.

Følgende handlinger var foretaget inden Prioritetsdatoen (23. maj 2014); (i) Samsung Bioepis og selskaber i Biogen-koncernen havde indgået aftaler om udvikling, fremstilling og markedsføring af SB5 (herunder i Danmark); (ii) Samsung Bioepis havde allerede udviklet formuleringen af SB5 og planlagt de kliniske forsøg, som var undervejs; (iii) det formulerede medicinske produkt til brug for de kliniske forsøg i Fase I og Fase III var blevet fremstillet af selskaber i Biogen-koncernen i USA og importeret til Storbritannien (i marts 2014) for derefter at blive sendt til Tyskland til brug for forsøgene (tidligt i maj 2014); (iv) i alt 19 forsøgspersoner var blevet doseret med dette formulerede produkt før Prioritetsdatoen; og (v) Samsung Bioepis og Biogen havde sådanne forventninger til, at Fase I forsøgene ville være positive, at man allerede havde opnået regulatorisk godkendelse til at udføre det meget større Fase III forsøg parallelt, og man påbegyndte administrering af SB5 til den første patient i Fase III forsøget kun nogle få dage efter Prioritetsdatoen. Dataene fra forsøgene blev efterfølgende brugt i ansøgninger til EMA om at opnå markedsføringstilladelse til Imraldi®.

Der var herved truffet væsentlige og meget omkostningstunge (tocifret millioner USD) foranstaltninger med henblik på fremstillingen, markedsføringen og salget af Imraldi® i Danmark. Intet har ændret sig siden Prioritetsdatoen. Biogen-koncernen og Samsung Bioepis-koncernen har udelukkende fortsat med at gøre det, de allerede gjorde og havde planlagt at gøre – at fremstille, markedsføre og sælge SB5/Imraldi®. Stridsbrugsmodellerne har ikke haft indflydelse på dette.

Betingelserne for forbenyttelsesretten efter Brugsmodellovens § 9, stk. 1, 2. pkt., er således opfyldte. Foranstaltningerne har tilsigtet udnyttelse i form af fremstilling, markedsføring og salg i Danmark, og retten til fortsat udnyttelse (forbenyttelsesretten) er af et tilsvarende omfang.

Da væsentlige foranstaltninger var foretaget af både Samsung Bioepis-koncernen og Biogen-koncernen på Prioritetsdatoen til fremstilling, markedsføring og salg af Imraldi® i Danmark, eksisterer der ifølge Brugsmodelslovens § 9 en forbenyttelsesret for dem begge.

De almindelige betingelser for meddelelse af foreløbige forbud er ikke opfyldt

Endeligt vil Biogen og SB gøre gældende, at betingelsen for meddelelse af midlertidigt forbud om formålets forspildelse ikke er opfyldt, og at meddelelse af midlertidigt forbud efter omstændighederne vil være et uforholdsmæssigt retsmiddel."

Sø- og Handelsrettens begrundelse og resultat

Under denne sag har Fresenius i sine endelige påstande under henvisning til brugsmodellerne BR 2018 0070 og BR 2018 0071 anmodet om bl.a. midlertidigt forbud mod de to sagsøgte Biogen-selskabers produktion og salg mv. af lægemidlet Imraldi, som er et biosimilært lægemiddel til det originale produkt Humira fra selskabet AbbVie. De sagsøgte Biogen-selskaber har med støtte fra

Samsung Bioepis UK Limited påstået, at anmodningen om forbud ikke skal fremmes.

Sagens tvistepunkter omfatter spørgsmål om brugsmodellernes gyldighed, herunder om utilladelig udvidelse efter brugsmodellovens § 18 og manglende nyhed og frembringelseshøjde efter § 5, samt i givet fald spørgsmål om krænkelse. Endvidere har de sagsøgte gjort gældende, at de under alle omstændigheder har en forbenyttelsesret, jf. brugsmodellovens § 9, idet man inden prioritetsdagen havde truffet væsentlige foranstaltninger til at fremstille, markedsføre og sælge Imraldi i Danmark.

Retten skal om spørgsmålet om forbenyttelsesret udtale følgende:

Selskabsforhold/aftaleforhold
Det er fremgået af sagens oplysninger, at udviklingen af SB5, senere markedsført som Imraldi som en biosimilær udgave af det patentbeskyttede biologiske adalimumab-præparat Humira, der i forvejen var på markedet, blev indledt af selskabet Samsung Electronics i 2009-2010.

Om de efterfølgende aftalemæssige forhold bemærkes, at Samsung Bioepis Co., Ltd. den 27. februar 2012 blev stiftet som et joint venture-selskab på grundlag af en aftale fra december 2011 mellem Samsung Biologics Co., Ltd og Biogen Idec Therapeutics Inc (senere Biogen Therapeutics Inc.). Stiftelsen skete med det formål, at selskabet skulle forestå udvikling, fremstilling og markedsføring af biosimilære lægemiddelprodukter. Den 29. februar 2012, to dage efter stiftelsen, indgik Samsung Bioepis Co., Ltd. som "purchaser" en "Manufacturing Agreement" med Biogen Idec MA, Inc. (Biogen Inc.) som "supplier". Af aftalens pkt. 3.4 "Production Sites" fremgår blandt andet, at "Supplier shall Manufacture Bulk Drug Substances at its own Facilities." I "Schedule 1" til aftalen er "Facilities" defineret som "… Supplier's facilities in Cambridge, Massachusetts, in Research Triangle Park, North Carolina, and in Denmark … (each, a **"Facility"**).

Den 18. september 2012 indgik Samsung Bioepis Co., Ltd. en "Quality Agreement" med Biogen Idec MA, Inc. (Biogen Inc.) og Biogen Idec, Denmark, Manufacturing ApS, der i 2015 skiftede navn til Biogen (Denmark) Manufacturing ApS (sagsøgte 1), hjemmehørende i Hillerød. I afsnit 2, "Definitions" fremgår blandt andet, at "Manufacture or Manufacturing shall mean activities directed to making, producing, manufacturing, processing, filling, finishing, packaging, labeling, quality assurance testing and release, shipping or storage of a product, including Products and other Biosimilar Pharmaceutical Products." Af afsnit 3 om "Roles and Responsibilities" fremgår, at de to Biogen-aftaleparter har ansvaret for at sikre, at produkterne bliver "… manufactured, packaged for storage and shipping, quality control tested and released in compliance with applicable cGMP and all other applicable laws and regulations". Af afsnit 5 om

"Manufacturing Activities" fremgår, at de to Biogen-aftaleparter skal "…Manufacture Products at the Facilities in accordance with cGMPs, the applicable Regulatory Approvals, as may be amended from time to time, the agreed Specifications and the Master Batch Records". Ved et addendum til "Quality Agreement", blandt andet underskrevet af direktør Charlotte Kornbo på vegne Biogen Idec, Denmark, Manufacturing ApS, er SB5 oplistet som et af aftalens "Products", betegnet "BIIB606" ("Biogen Idec Code"), "Adalimumab" ("Description"), "SB5" ("Samsung Bioepis Code"), mens det under "Biosimilar Information" var anført "Humira (Abbott) - RA; TNF Inhibitor".

Med ikrafttræden den 13. december 2013 indgik Samsung Bioepis Co., Ltd. en "Development and Commercialization Agreement" med Biogen Idec International Holding Ltd. Af aftalen fremgik, at Biogen-koncernen skulle forestå markedsføring af det senere Imraldi®-produkt i Europa og herunder i Danmark.

I interne Biogen-bilag fra 21. januar 2014 og 3. juni 2014 (bilag AY og AZ) er markedsforhold, kommercialiseringsstatus- og organisation etc. i forhold lancering og salg af SB5/Imraldi beskrevet, herunder for Danmark.

Øvrige omstændigheder
Af Tae Heui Lee's erklæring af 15. februar 2019 og vidneforklaring under hovedforhandlingen er det fremgået, at han, der er "director" i det som et joint venture stiftede selskab Samsung Bioepis Co., Ltd, siden maj 2012 har været "project manager" for produktet SB5, der i Europa nu er lanceret som "Imraldi" (2018). Om målsætningen for SB5-projektet er det fremgået, at Samsung Bioepis Co., Ltd. havde fokus på at være først med en lancering af sit biosimilære produkt SB5 på det europæiske marked, når patent- og SPC-beskyttelsen for Humira forventeligt udløb i april 2018. Der blev i dette perspektiv – både på Samsung-side og Biogen-side - anvendt meget betydelige ressourcer på SB5-projektet, som på forskellige planer blev fremskyndet, blandt andet således at fase I og fase III- forsøg blev afviklet parallelt.

På tidspunktet for den hævdede prioritetsdato for de to udstedte brugsmodeller den 23. maj 2014 var såvel fase I som fase III-forsøgene ansøgt og godkendt og lige omkring prioritetsdatoen indledt med brug af en produktformulering, som - uden kendskab til det senere EP '510 og de senere udstedte brugsmodeller - var blevet endeligt valgt året før (14. juni 2013), og som senere uændret indgik i produktet Imraldi. Det formulerede produkt var til brug for forsøgene blevet fremstillet af Biogen-selskaber i USA og var før prioritetsdatoen til rådighed for udførelsen af forsøgene, der skulle forestås af firmaet Parexel International, med hvem Samsung Bioepis Co., Ltd. havde indgået aftaler i september og november 2013.

Rettens overvejelser

Det er på den beskrevne baggrund, der støttes af en række øvrige oplysninger i sagen, samt når yderligere henses til de krav til dokumentation, der forud for en markedsføringstilladelse stilles inden for det foreliggende erhvervsområde i form af forskning, herunder kliniske forsøg, udvikling og myndighedsbehandling, ubetænkeligt at lægge til grund, at der på prioritetsdatoen var truffet sådanne "væsentlige foranstaltninger til erhvervsmæssig udnyttelse", som denne betingelse må forstås i henhold til brugsmodellovens § 9, stk. 1, 2. pkt.

På grundlag af bevisførelsen lægger retten endvidere til grund, at de "væsentlige foranstaltninger", som fastslået ovenfor, var truffet til erhvervsmæssig udnyttelse her i landet. Retten har herved lagt afgørende vægt på, at der allerede før den hævdede prioritetsdato den 23. maj 2014 var truffet strategiske beslutninger i Samsung- og Biogenkoncernen om markedsføring af SB5-produktet i Europa, herunder Danmark, at Danmark i det tidlige aftaleforløb mellem Samsung og Biogen, jf. Manufacturing Agreement" af 29. februar 2012, specifikt var angivet som produktionssted (sammen med to amerikanske lokaliteter), og at sagsøgte Biogen (Denmark) Manufacturing ApS var part i "Quality Agreement" af 18. september 2012, indgået med Samsung Bioepis Co., Ltd., hvilken aftale specifikt omfattede SB5. Det bemærkes hertil, at repræsentanter fra Biogen (Denmark) Manufacturing ApS ifølge forklaringen, afgivet af Tae Heui Lee, deltog i udviklingsmøder hos Samsung Bioepis Co., Ltd. Det må tillægges betydning, at produktion af Imraldi med henblik på kommercielt salg senere faktisk blev placeret hos Biogen (Denmark) Manufacturing ApS.

Retten har ved afgørelsen således ikke tillagt det nogen afgørende betydning, at de "væsentlige foranstaltninger" (brugsmodellovens § 9, stk. 1, 2. pkt.) ikke havde fundet sted her i landet, men har fundet det afgørende, at de "væsentlige foranstaltninger" fandt sted med henblik på udnyttelse her i landet, hvor det under de anførte omstændigheder ikke har nogen betydning, at Danmark ikke var eneste land, hvor frembringelsen var tiltænkt udnyttet.

Retten har under hensyn til de anførte aftalemæssige omstændigheder og det beskrevne udviklingsforløb i en internationalt baseret branche, der er karakteriseret ved blandt andet store krav til investeringer, udvikling og forskning, og hvor slutprodukternes tiltænkte anvendelse kan være verdensomspændende, ikke fundet, at de to danske selskabers positioner som datterskaber i Biogenkoncernen modsiger, at der i Danmark består en forbenyttelsesret. Retten bemærker hertil, at selskaberne netop er udstyret med rettighederne og faciliteterne til at forestå den oprindeligt planlagte erhvervsmæssige udnyttelse af Imraldi her i landet.

Under de anførte omstændigheder samt når henses til de rimelighedshensyn, herunder hensyn til beskyttelse mod værdispild og tab af investeringer, som til-

sigtes varetaget med bestemmelsen, finder retten, at der i medfør af brugsmodellovens § 9, stk. 1, 2. pkt., er etableret en forbenyttelsesret her i landet, som vil være til hinder for, at Fresenius Kabi Deutschland GmbH's forbuds- og påbudspåstande han nyde fremme.

Det følger af det, der er anført om forbenyttelsesret ovenfor, at retten allerede af denne grund vil nægte anmodningerne fremme. Retten finder dog efter sagens karakter, omfang og forløb anledning til at bemærke, at retten endvidere finder det godtgjort, at begge de omtvistede brugsmodeller savner gyldighed som følge af utilladelig udvidelse, jf. brugsmodellovens § 18. Det følger således af brugsmodellovens § 18, patentlovens § 13 og artikel 123, stk. 2, i Den Europæiske Patentkonvention, at ændringer i en ansøgning ikke må foretages således, at brugsmodelregistrering søges for noget, som fagmanden under anvendelse af sin fagmandsviden på prioritetsdagen ikke kunne udlede direkte og utvetydigt, enten implicit eller explicit, af den oprindelige ansøgning. Testen for, om noget kan udledes af en ansøgning på denne kvalificerede måde, svarer til testen for nyhed i brugsmodellovens § 5, stk. 1, jf. herved afgørelsen fra Enlarged Board of Appeal i EPO den 8. april 2004 i sagen G 0001/03. Retten finder, at i hvert fald det træk i brugsmodellernes krav 1, hvorefter sammensætningen yderligere indeholder en citratbuffer, savner basis i stamansøgningen som indleveret, EP 3 148 510, hvor der hverken i den generelle definition af "buffer" eller "bufferopløsning", som blandt andet omfatter citrat, eller i ansøgningen i øvrigt findes en tilstrækkelig kvalificeret angivelse af en udførelsesform svarende til brugsmodellernes krav 1, herunder med en citratbuffer.

Konklusionen bliver herefter som anført, at retten nægter at fremme anmodningerne om midlertidige forbud og påbud.

Sagsomkostninger
Efter sagens udfald skal Fresenius Kabi Deutschland GmBh til Biogen (Denmark) Manufacturing ApS og Biogen (Denmark) A/S betale 3.795.000 kr. ekskl. moms. Sagsomkostningerne er fastsat til dækning af advokatudgift med 3.500.000 kr. og af øvrige udgifter med 295.000 kr.

Efter sagens udfald skal Fresenius Kabi Deutschland GmBh endvidere til Samsung Bioepis UK Limited betale 4.115.000 kr. inkl. moms. Sagsomkostningerne er fastsat til dækning af advokatudgift med 3.750.000 kr. og af øvrige udgifter med 365.000 kr.

Der er ved fastsættelse af beløbene til dækning af advokatudgift lagt vægt på forbudssagens karakter, økonomiske værdi og omfang, herunder at der har været omfattende skriftveksling mellem parterne, og at hovedforhandlingen strakte sig over 7 dage.

Udgifterne til patentkyndig bistand kan alene kræves godtgjort som sagsomkostning, hvis særlige forhold gør sig gældende. Der er ikke påvist sådanne særlige forhold i den foreliggende sag. Sø- og Handelsretten har derimod fundet udgifterne til sagkyndig bistand fra professor Daniel Erik Otzen og professor Sven Frøkjær som rimelige og påkrævede for sagens forsvarlige udførsel.

THI BESTEMMES:

De af Fresenius Kabi Deutschland GmbH mod Biogen (Denmark) Manufaturing ApS og Biogen (Denmark) A/S nedlagte påstande om forbud og påbud nægtes fremme.

Fresenius Kabi Deutschland GmbH skal inden 14 dage til Biogen (Denmark) Manufacturing ApS og Biogen (Denmark) A/S betale sagsomkostninger med 3.795.000 kr.

Fresenius Kabi Deutschland GmBh skal inden 14 dage til Samsung Bioepis UK Limited betale sagsomkostninger med 4.115.000 kr.

Sagsomkostningerne forrentes efter rentelovens § 8 a.

Vejledning

Retten har truffet afgørelse i sagen.

Hvis du er utilfreds med afgørelsen, kan du kære (klage over) afgørelsen til landsretten. Fristen for at kære er 4 uger fra afgørelsens dato. Kære har ikke opsættende virkning. Det betyder, at afgørelsen gælder, mens landsretten behandler sagen.

Du kan kære afgørelsen på minretssag.dk ved at trykke på knappen "Opret appel" og derefter vælge "Kære" og følge vejledningen der. Du skal betale en retsafgift på 400 kr. for at kære afgørelsen.

Den, der overtræder et forbud eller et påbud, kan straffes med bøde eller fængsel indtil 4 måneder og kan dømmes til at betale erstatning.

Et forbud/påbud skal følges op af et sagsanlæg fra den part, som har anmodet om forbuddet/påbuddet. Sagen skal anlægges inden 2 uger efter rettens afgørelse. Hvis sagen ikke bliver anlagt, kan retten ophæve afgørelsen.

Du kan få mere vejledning på domstol.dk.

Publiceret til portalen d. 20-06-2019 kl. 10:01
Modtagere: Sagsøger Fresenius Kabi Deutschland GmbH, Sagsøgte BIOGEN (DENMARK) MANUFACTURING ApS, Advokat (H) Jakob Krag Nielsen, Advokat (H) Nicolai Lindgreen, Sagsøgte BIOGEN (DENMARK) A/S, Hovedintervenient Samsung Bioepis UK Limited, Advokat (H) Klaus Ewald Madsen, Sagkyndig dommer Ulla Callesen Klinge, Sagkyndig dommer Karin Verland