Nos. 18-2321, 18-2350

United States Court of Appeals for the Federal Circuit

JANSSEN BIOTECH, INC.,

Plaintiff-Appellant,

– v. –

CELLTRION HEALTHCARE CO., LTD., CELLTRION, INC., HOSPIRA, INC.,

Defendants-Cross-Appellants.

On Appeal from the U.S. District Court for the District of Massachusetts in No. 1:17-cv-11008, Honorable Mark L. Wolf, U.S. District Judge

BRIEF FOR APPELLANT

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DECEMBER 10, 2018

FORM 9. Certificate of Interest **Form 9**
Rev. 10/17

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Janssen Biotech, Inc. **v.** Celltrion Healthcare Co., Ltd.

Case No. 18-2321, 18-2350

CERTIFICATE OF INTEREST

Counsel for the:
☐ (petitioner) ■ (appellant) ☐ (respondent) ☐ (appellee) ☐ (amicus) ☐ (name of party)

Janssen Biotech, Inc.

certifies the following (use "None" if applicable; use extra sheets if necessary):

1. Full Name of Party Represented by me	2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:	3. Parent corporations and publicly held companies that own 10% or more of stock in the party
Janssen Biotech, Inc.	Janssen Biotech, Inc.	Johnson & Johnson

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court **(and who have not or will not enter an appearance in this case)** are:

Patterson Belknap Webb & Tyler LLP: Lachlan Campbell-Verduyn, Andrew D. Cohen, Kathleen M. Crotty, Jamison Davies, Gregory L. Diskant, Aron Fischer, Daniel A. Friedman, Eugene M. Gelernter, Jason S. Gould, Benjamin F. Jackson, David Kleban, Hui Li, Nathan Monroe-Yavneh, A. Robert Quirk, Irena Royzman, Viviane Scott

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Rev. 10/17

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47. 4(a)(5) and 47.5(b). (The parties should attach continuation pages as necessary).

None

12/10/2018
Date

/s/ Gregory L. Diskant
Signature of counsel

Please Note: All questions must be answered

Gregory L. Diskant
Printed name of counsel

cc: James F. Hurst, Esq.

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STATEMENT OF RELATED CASES

There was an earlier appeal in this case, No. 17-1120, from an order by the district court granting summary judgment that U.S. Patent No. 6,284,471 (the '471 patent) is invalid for obviousness-type double patenting. The '471 patent is no longer part of this case and is not the subject of this appeal. The appeal in No. 17-1120 was dismissed as moot in a non-precedential decision in view of the decision in a different appeal, *In re Janssen Biotech, Inc.*, 880 F.3d 1315 (Fed. Cir. 2018), upholding a decision by the Patent Trial and Appeal Board that affirmed a rejection of the '471 patent. *See Janssen Biotech, Inc. v. Celltrion Healthcare Co.*, No. 17-1120, 2018 WL 2072723 (Fed. Cir. Jan. 23, 2018). Chief Judge Prost and Circuit Judges Reyna and Wallach were on the panel in No. 17-1120.

Counsel is not aware of any pending case that would directly affect, or be directly affected by, the outcome of this case.

STATEMENT OF JURISDICTION

The district court had jurisdiction over this action for patent infringement under 28 U.S.C. §§ 1331, 1338(a). The district court entered final judgment of noninfringement on July 31, 2018 (and an amended judgment on August 23, 2018). Appx20-21. Janssen filed a timely notice of appeal on August 23, 2018. Appx8233-8234. This Court has jurisdiction over this appeal under 28 U.S.C. § 1295(a)(1).

ABBREVIATIONS

The patent-in-suit	
’083 Patent	U.S. Patent No. 7,598,083

Parties	
Janssen	Plaintiff-Appellant Janssen Biotech, Inc.
Celltrion	Defendants-Cross-Appellants Celltrion Healthcare Co., Ltd., Celltrion, Inc. and Hospira, Inc., collectively.

References	
GSK	WO 2004/078955, filed by GlaxoSmithKline Biologicals S.A.
Life Techs	WO 98/15614, filed by Life Technologies, Inc.

INTRODUCTION

Janssen's '083 Patent discloses a cell culture medium composed of a unique combination of 52 essential ingredients specially designed for growing eukaryotic cells that can be used to make biotechnology products. Before Janssen's invention, there was no other cell culture medium with this particular combination of ingredients. The claimed medium has proven to be highly effective for growing large volumes of eukaryotic cells for extended periods of time.

During Janssen's development of its medium, it shared its then-proprietary formula with its contract manufacturer, HyClone, under a confidentiality agreement. Recognizing the superior quality of Janssen's formula, HyClone copied Janssen's medium and later supplied a version of its copy to Celltrion, the defendant in this case. Celltrion relied on that copy to create the media for its biosimilar version of Janssen's biologic drug Remicade®. Celltrion's media contain all 52 of the ingredients required by claim 1 of the '083 Patent.

Of those 52 ingredients in Celltrion's media, 40 are in concentrations literally within the concentration ranges recited in claim 1. As testing proved, the remaining twelve ingredients are present in concentrations that are not substantially different from the claimed ranges. Celltrion's own expert witness did not dispute this. Celltrion's media accordingly infringe claim 1 under the doctrine of equivalents ("DOE"). Nonetheless, shortly before trial, the district court granted

summary judgment of noninfringement on the ground of ensnarement, holding that a hypothetical claim that expanded the claimed concentration ranges so as to literally cover Celltrion's cell culture media was obvious and that Janssen accordingly is barred from asserting infringement under the DOE.

The district court's ensnarement ruling is seriously flawed, the result of reversible legal errors that are fatal to its analysis. Principal among them is the district court's repeated—and unabashed—reliance on hindsight in concluding that the hypothetical claim was obvious. First, the district court stated it was permitted to use hindsight to select two obscure references, GSK and Life Techs, as the basis for its obviousness analysis. It said so explicitly. According to the district court, it was "not required" to consider the "motivation to select a particular prior art" reference as a "starting point" and could instead focus on two references selected from the sea of prior art references solely because of their similarity (in hindsight) to the hypothetical claim. Appx49. In so doing, the district court ignored this Court's repeated admonitions that obviousness requires a showing of "reasons why one of ordinary skill in the art would have been motivated to ***select the references***" used in an obviousness analysis. *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 n.4 (emphasis added) (quoting *In re Rouffet*, 149 F.3d 1350, 1359 (Fed. Cir. 1998)).

This error was particularly egregious because both sides' experts agreed that a skilled artisan seeking to develop an improved cell culture medium would have had no reason to select either the GSK or Life Techs reference. Instead, the experts agreed that an artisan would start elsewhere—with one of the so-called "classical" cell culture media. Without relying upon Janssen's invention to provide a hindsight-based roadmap for analysis, there was no reason for an artisan to consider, let alone select, GSK or Life Techs for modification.

Second, the district court compounded its error by believing, and stating explicitly, that it was permissible to use hindsight to consider only the differences between these two references and the hypothetical claim, and that it could ignore the claim as a whole. That is, using its knowledge of the hypothetical claim, the court considered only the modifications to GSK and Life Techs that would be needed to recreate the hypothetical claim. The court defended this approach by stating that "it is not impermissible use of hindsight to analyze the differences" between the hypothetical claim and the prior art and to ignore the other ingredients in the formula. Appx63. This also violated black letter law. "Focusing on the obviousness of substitutions and differences instead of the invention as a whole … [is] a legally improper way to simplify the difficult determination of obviousness." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*,

802 F.2d 1367, 1383 (Fed. Cir. 1986). It contravenes 35 U.S.C. § 103 by not addressing the invention "as a whole."

Third, the district court again used hindsight to modify the references in such a way as to arrive at the hypothetical claim. In the prior art references, two ingredients (GSK) or five ingredients (Life Techs), and 17 preferred concentrations (GSK) or 12 preferred concentrations (Life Techs), were different from the formula of the hypothetical claim. For instance, the prior art references contain perfectly acceptable iron chelates that are different from the highly unusual iron chelate found in the hypothetical claim, ferric ammonium citrate ("FAC"). The court pointed to no legally cognizable reason why an artisan would have been motivated to modify the iron chelates in the references and replace them with FAC—other than a laser-like focus on recreating the hypothetical claim with the benefit of hindsight.

In short, the district court (at Celltrion's urging) ignored motivation altogether—finding obviousness where there was no motivation to select the prior art references, no motivation to focus only on the differences between the hypothetical claim and those references, and no motivation to modify those differences to recreate the hypothetical claim. But motivation is required as part of the analysis expressly "[t]o preclude hindsight in this analysis." *Rolls-Royce, PLC v. United Tech. Corp.*, 603 F.3d 1325, 1338 (Fed. Cir. 2010). In place of

motivation, the district court used hindsight knowledge of the hypothetical claim as a road map to the prior art, mixing-and-matching elements to support its conclusion that the hypothetical claim would have been obvious. Because it ignored motivation and instead relied on hindsight, Celltrion's ensnarement defense should have been rejected as a matter of law.

Finally, the district court erred in granting summary judgment to Celltrion because it did not view the facts in the light most favorable to Janssen. The district court brushed aside evidence that the prior art taught away from using FAC as an ingredient in a cell culture medium and it minimized strong objective indicia of non-obviousness—compelling evidence that Celltrion's supplier copied Janssen's patented formula.

STATEMENT OF QUESTIONS PRESENTED

1. Did the district court err in ruling on summary judgment that a hypothetical claim covering Celltrion's cell culture media would have been obvious in view of the GSK and Life Techs references and in dismissing Janssen's DOE claim of infringement on that basis, where there was no reason—other than hindsight derived from Janssen's invention—for a person of ordinary skill to (a) select those references for modification, (b) focus only on the differences between those references and the hypothetical claim, and (c) modify those differences to achieve the formula of the hypothetical claim?

2. Because Celltrion failed to offer any evidence of motivation, did the district court err by not rejecting Celltrion's obviousness-based ensnarement defense as legally baseless and by declining to grant summary judgment of no ensnarement in favor of Janssen?

3. In any event, did the district court err in not drawing reasonable inferences in Janssen's favor, *e.g.*, on teaching away from using ferric ammonium citrate ("FAC") and on objective evidence of copying of Janssen's invention, while nonetheless concluding that there were no fact issues precluding summary judgment in favor of Celltrion?

STATEMENT OF THE CASE

Janssen alleges that the cell culture media Celltrion uses to make its biosimilar version of Janssen's biologic drug Remicade® infringe claim 1 of the '083 Patent under the DOE. In response, Celltrion raised an ensnarement defense, asserting that a hypothetical claim literally reading on its cell culture media would have been obvious and moved for summary judgment on that basis.

Because undisputed evidence warrants summary judgment in Janssen's favor on ensnarement as a matter of law, Janssen gave timely notice under Rule 56(f), Fed.R.Civ.P., that summary judgment in its favor was appropriate. Appx866-867.

The district court granted Celltrion's summary judgment motion and declined to grant summary judgment in favor of Janssen. Because the district court's rulings are clearly erroneous, Janssen now appeals.

STATEMENT OF FACTS

A. The '083 Patent

The '083 Patent discloses and claims optimal cell culture media for growing cells. Cell culture media are chemical compositions of nutrients, vitamins and other chemical building blocks that are used to cultivate living cells *in vitro*. These media are used in the biotechnology industry to grow living cells that have been genetically engineered to produce a therapeutic protein of interest, such as antibodies for treating particular diseases.

Janssen, through its predecessor, Centocor, is a pioneer in using biotechnology to create biologic drugs, such as Remicade®, which is approved for treating rheumatoid arthritis, Crohn's disease and other serious illnesses.

In 2003, a team of Janssen scientists led by Dr. David Epstein undertook to develop new, improved media that could grow eukaryotic cells in the high volumes needed for commercial production. At the time, there was concern about potential health risks from a then-common ingredient in cell culture media, fetal bovine serum. As a result, Dr. Epstein's team focused on creating a serum-free medium. Appx2539.

The ’083 invention is the result: a serum-free medium that is the product of extensive research and testing by Janssen scientists. The Janssen inventors developed a unique combination of ingredients that includes 52 essential ingredients and 9 optional ingredients. The media of the invention “are optimized for biopharmaceutical production.” Appx173/col.1:65-67. They “can sustain high cell growth and viability,” Appx177/col.9:45-46, and provide “high monoclonal antibody titers and specific productivity” in large scale bioreactors. Appx177/col.10:9-11. The experimental success of Janssen’s preferred embodiment, referred to as MET 1.5, is reported in Examples 1-3 and Figures 1-3 of the ’083 Patent. Appx177/col.9:40-col.10:47; Appx170-172.

Claim 1 of the ’083 Patent is drafted specifically to cover a novel “composition … suitable for producing a final volume of cell culture media” that comprises 52 chemical ingredients, each with a recited concentration range. Appx177-178/col.10:49-col.11:48. For nine additional ingredients, the specified concentration ranges have a lower limit of zero, making those ingredients optional, rather than mandatory.

B. Development of the ’083 Media

Dr. Epstein and his team began their development process by selecting one of the so-called “classic” cell culture media as the starting point. Appx1578/pp.84:4-85:25. Classical cell culture media can be thought of as starter

kits for the development of complete cell culture media. They cannot be used "as is" because a complete medium requires adding at least serum (needed to promote cell growth) or a replacement for serum. But they provide the widely-acknowledged starting points for cell culture scientists seeking to develop new media. As Dr. Epstein explained, "[w]e started with DMEM/F12," one of the classic cell culture media, not "from scratch." Appx1581/pp.211:23-212:3.

After selecting DMEM/12 as the starting point, the Janssen team conducted experiments considering a variety of ingredients for possible addition to, or subtraction from, that formula. Appx1581-1582/pp.212:4-214:17; Appx2539-2540. Then, they conducted small-scale experiments to find the combination of ingredients and concentrations that would provide an optimal cell culture medium for growing cells. *Id.* After a months-long iterative experimental process, the Janssen team decided on a unique combination of ingredients and concentrations that had never been used for any cell culture medium. Among the novel features of their invention was their decision to go against conventional wisdom by including FAC as an iron chelate.

Based on its in-house testing, Janssen knew that its formulation worked well on a small scale. Janssen then hired HyClone, a commercial manufacturer of cell culture media, under a confidentiality agreement to make large batches for testing in large-scale bioreactors. Appx1687-1709. The test

results were impressive. They showed that Janssen's preferred embodiment, MET 1.5, could sustain cells at high viability for nearly a month, and promote high cell density—greater than 20 million cells per milliliter—for much of that time. Testing also showed that MET 1.5 yielded significant amounts of secreted monoclonal antibody at levels well-suited for biopharmaceutical production. Experiments described in the '083 Patent showed that Janssen's cell culture medium could "sustain high cell growth and viability," and provide "high monoclonal antibody titers and specific productivity." Appx177/col.9:45-46; *id.*/col.10:9-11.

Janssen's scientists were thrilled. They exchanged congratulatory emails about their "[e]xtremely good results," the "highest harvest titer in perfusion ever observed." The results were "pretty darned good. Congratulations." Appx2540. Adding an exclamation point to these kudos, Janssen's contract manufacturer, HyClone, offered Janssen "[c]ongratulations on your successful design!" Appx1711-1712.

On October 27, 2005, Janssen filed U.S. Patent Application 11/260,788, which claimed the benefit of its provisional application filed on October 29, 2004. This application claimed Janssen's novel combination of 52 required elements, all in specified concentration ranges. It encountered no prior art rejections and issued as the '083 Patent on October 6, 2009.

C. HyClone Copied Janssen's Patented Formulation

When Janssen hired HyClone to generate larger batches of its medium for testing, HyClone was marketing its own off-the-shelf medium called ADCF-Mab, which lacked nine of the ingredients in Janssen's formula. Appx109. Janssen tested ADCF-Mab and concluded that it produced "lousy growth." Appx938, Appx1686.

After receiving Janssen's unique formula under a confidentiality agreement and congratulating Janssen on its "successful design," Appx1711-1712, HyClone created a new product called Cell Boost 5 (CB5) as a supplement to its ADCF-Mab product. Appx939; Appx1725-1733; Appx1736-1737/pp.37:18-39:3. HyClone promoted that combination of ADCF-Mab and CB5 to its customers. In combination, the resulting media had ***every required ingredient*** and ***every optional ingredient*** in Janssen's formula. More than that, it included each ingredient in ***exactly the same chemical form*** as in Janssen's MET 1.5 media (*e.g.*, in the same salt form). Appx939; Appx1745-1757 at Appx1746-1749. Dr. Whitford, the HyClone scientist who had access to Janssen's formula and was instrumental in developing CB5, boasted that, for a given cell line, the ADCF-Mab/CB5

combination "worked better than any other media in the world." Appx1742/p.109:1-3.[1]

As the district court recognized, "a reasonable factfinder could conclude that HyClone copied [Janssen's] MET 1.5 formulation," Appx112, because of its "novel combination of ingredients and concentrations." Appx113.

D. Celltrion's Development of Its Infringing Media

Celltrion is a Korean manufacturer of biosimilars. In 2008, Celltrion decided to pursue a biosimilar version of Janssen's biologic drug Remicade. To do so, Celltrion needed suitable cell culture media for producing antibodies whose attributes matched Remicade's as closely as possible.

Celltrion retained HyClone to help it find suitable media. Among the choices Celltrion tested was the ADCF-Mab/CB5 combination that HyClone developed after gaining access to Janssen's confidential formula. Appx1737/pp.35:24-37:2.

Celltrion conducted extensive experiments with the ADCF-Mab/CB5 combination. It fiddled with adding and subtracting ingredients, and it explored different concentrations. After nearly a year of testing and experimentation, Celltrion chose to use its tweaked ADCF-Mab/CB5 combination to make the

[1] Janssen sued HyClone for infringing the '083 Patent in a separate lawsuit that is now stayed, pending the outcome of this case.

media accused of infringement in this case. Appx2954-2967; Appx1761-1762/pp.60:22-63:18.

E. Prior Proceedings in This Case

In 2014, Celltrion notified Janssen of its application under the Biologics Price Competition and Innovation Act of 2010 ("BPCIA") for a biosimilar version of Remicade. In response, Janssen notified Celltrion under 42 U.S.C. § 262(*l*)(3)(A) that the '083 Patent was a potentially infringed patent. After obtaining additional information, Janssen commenced this lawsuit, asserting infringement under 35 U.S.C. § 271(e)(2)(C)(ii).

1. The Evidence of Infringement

Discovery revealed that Celltrion's media have ***every one*** of the 52 essential ingredients required by claim 1 of the '083 Patent in ***exactly the chemical forms*** claimed. Forty of those ingredients are in concentrations that fall within the literal language of the claimed ranges. For the remaining twelve ingredients, any differences in concentration are insubstantial. Celltrion's expert Dr. Glacken did not contend otherwise. As Dr. Glacken acknowledged, he did "not opine in [his] expert report about insubstantiality of the differences." Appx8238-8249 at Appx8242-8243/pp.201:17-202:03. In light of this important concession, the district court asked directly, and Celltrion confirmed that its expert would not assert that the concentration differences are substantial:

> THE COURT: So he's not going to say, "I believe the differences are substantial"?
>
> CELLTRION'S COUNSEL: Right….

Appx2756. Celltrion offered no evidence that the concentration differences are substantial, but said it would nonetheless challenge the sufficiency of Janssen's proof under the DOE.

But the evidence of equivalence was overwhelming. Janssen's expert Dr. Butler opined, based on experiments he had conducted in the regular course of his scientific research, that the concentration differences between Celltrion's media and claim 1 were insubstantial, subject to experimental confirmation. Dr. Wurm, another Janssen expert, conducted well-controlled experiments that confirmed Dr. Butler's opinion. Using the performance measures recited in the '083 Patent, Dr. Wurm's testing proved, both on an ingredient-by-ingredient basis and for the media as a whole, that the concentrations in Celltrion's media produce substantially the same result as the concentrations recited in claim 1. Appx951-1005; Appx8250-8349. In denying Celltrion's *Daubert* challenge to this evidence, the district court described Drs. Butler and Wurm as "eminent scientists" "rather than professional witnesses" whose "testimony grows out of extensive pre-litigation relevant research each has done." Appx2773; Appx2766.

2. Celltrion's Ensnarement Theory

After the denial of its *Daubert* motion, Celltrion moved for summary judgment of noninfringement based on ensnarement. It argued that a hypothetical claim that covers the accused cell culture media was obvious over the GSK and Life Techs references. Celltrion's hypothetical claim is almost identical to claim 1 of the '083 Patent. It includes the same ingredients in the same chemical forms. The only difference is that twelve concentrations ranges have been slightly enlarged to literally cover Celltrion's accused media.

Celltrion did not assert that the hypothetical claim is anticipated. Instead, it argued that the hypothetical claim was obvious in view of two references that would never have been considered without impermissible hindsight—the GSK and Life Techs references. Those references disclose cell culture media that have 96 and 88 ingredients, respectively. But the ingredients and concentration ranges in those references do not match the 52 essential ingredients and concentration ranges of the hypothetical claim. Celltrion's position was that a POSA could have substituted other ingredients for two ingredients in GSK and five in Life Techs, and could have modified the concentration of 17 ingredients in GSK and 12 in Life Techs, to arrive at the unique formulation of the hypothetical claim. Celltrion did not identify a reason or motivation for a POSA to do any of this.

In response, Janssen argued that Celltrion's obviousness theory was baseless as a matter of law, warranting summary judgment in Janssen's favor on ensnarement under Rule 56(f), Fed.R.Civ.P. Appx866-867. Janssen demonstrated that there was no reason or motivation for a POSA to look to GSK or Life Techs in developing a cell culture medium, and if a POSA looked to those references, there was no reason or motivation to make the modifications that would be needed to create the hypothetical claim.

3. The Evidence on Obviousness

Discovery revealed widespread agreement among the experts on key issues relevant to the obviousness inquiry.

a. Cell Culture Media is an Experimental Science

Both sides' experts agreed that the science of cell culture media—like all biological sciences—is experimental. Developing a cell culture medium for a particular purpose is an iterative, experimental process whose results cannot be predicted with a reasonable degree of certainty. Finding the precise combination of ingredients and concentrations that will work for a given purpose can require extensive experimentation. Appx1125-1127; Appx2954-2967; Appx8355-8356.

As Celltrion's Dr. Glacken explained, there are "100s of possible components, each with different optimal concentrations," and "[a]lmost an infinite number of possible formulations." Appx1123-1144 at Appx1125. Ingredients, and

concentrations of ingredients, may interact with each other in unpredictable ways. Appx1879-1880; Appx1890; Appx2892. The scientific challenge is identifying the right combination of ingredients, in the right concentrations, for a particular application. That is because the performance of a specific combination of ingredients in specific concentrations is "always the sum of everything, always." Appx2841/pp.156:21-157:3.

The experimental nature of this science is reflected in the experience of Samsung Bioepis, which also manufactures a biosimilar of Remicade. Bioepis had to engage in "extensive experimentation and the expenditure of much effort and financial resources" over "many years" to develop suitable cell culture media. Appx1320-1324 at Appx1321. Likewise, even after being provided HyClone's copy, Celltrion devoted over a year to screening, testing, modifying and more testing before settling on the accused media to grow its biosimilar version of Remicade®. Appx2954-2967; Appx2584-2585.

b. The Steps Skilled Artisans Take in Developing Cell Culture Media

There was no disagreement among the experts about the iterative experimental steps that skilled artisans follow in trying to create new serum-free cell culture media. Celltrion's Dr. Glacken set them forth explicitly in his expert report. Dr. Butler did not disagree.

Step 1: Selecting a Classical Medium as a Starting Point

According to Dr. Glacken, the first step for a skilled artisan involves selecting a "basal medium as a potential starting point, which are typically mixtures of various media, for example, DMEM/F12 or eRDF." Appx1338-1339. As Dr. Glacken testified: "[W]hat many folks do and … what ['083 inventor] Epstein said he did … and what I have done is, you will look at commercial media, ***the classics***, DMEM, F12, DMEM/F12, RPMI and look at combinations of those." Appx1094/p.72:4-8 (emphasis added).

The "classics" Dr. Glacken referred to are classical cell culture media developed in the mid-20th century. The classics are not complete cell culture media; rather, they are basal (or base) media, starting points for development. In particular, the classics cannot grow cells without adding growth factors—either serum or chemical replacements for serum. In that sense, classical media are starter kits for creating cell culture media. The first classics were created by early pioneers such as Harry Eagle, Nobel Laureate Renato Dulbecco and Richard Ham and were named after them: Eagle's Minimum Essential Media (MEM), Dulbecco's Modified Eagle's Medium (DMEM), and Ham's F12. Appx1441-1448. Other classical media are combinations of earlier classics. DMEM/F12,

which is a combination of DMEM and F12, has become "the most widely utilized basal synthetic medium." Appx1479; Appx1445-1448.

The inventors of '083 Patent started with the most widely used classic, DMEM/F12. Appx1578/pp.84:4-85:25.

Dr. Glacken's report cited Jayme 1997, a review of the classical media. A summary table from Jayme is reproduced on the following pages. The table lists classical cell culture media that a skilled artisan could select as a starting point, including their respective ingredients and concentrations. As noted, these classic formulas are not complete cell culture media. Rather, they are all starting points for further development.

Table 1. Comparative biochemical composition of basal nutrient formulations[a]

Component	MEM	F–12	DMEM	DMEM/F12	RPMI 1640	RDF	eRDF
Inorganic salts							
$CaCl_2$ (anhyd)	200.00	33.22	200.00	116.60			
$CaCl_2 \cdot 2H_2O$						77.90	108.77
$Ca(NO_3)_3 \cdot 4H_2O$					100.00	49.58	
$CuSO_4 \cdot 5H_2O$		0.0024		0.0013		0.00062	0.00075
$FeSO_4 \cdot 7H_2O$		0.83		0.417		0.208	0.222
$Fe(NO_3)_3 \cdot 9H_2O$		0.10		0.05		0.025	
KCl	400.00	223.60	400.00	311.80	400.00	358.00	373.00
$MgSO_4$ (anhyd)	97.67	57.22	97.67	48.84	48.84	49.35	66.20
$MgCl_2$ (anhyd)				28.64			
$MgCl_2 \cdot 6H_2O$						30.48	
NaCl	6800.00	7599.00	6400.00	6995.50	6000.00	6505.00	6435.00
$NaHCO_3$	2200.00	1176.00	3700.00	2438.00	2000.00	1050.00	1050.00
$NaH_2PO_4 \cdot H_2O$	140.00		125.00	62.50		31.20	
Na_2HPO_4 (anhyd)		142.00		71.02	800.00		
$Na_2HPO_4 \cdot 12H_2O$						1100.00	1220.00
$ZnSO_4 \cdot 7H_2O$		0.86		0.43		0.22	0.23
Sub-total	9837.67	9232.83	10922.67	10073.80	9348.84	9251.96	9253.42
Amino Acids							
L-Alanine		8.90		4.45		2.23	6.68
L-Arginine·HCl	126.00	211.00	84.00	147.50	200.00	194.00	582.00
L-Aspartic acid		13.30		6.65	20.00	13.30	39.90
L-Asparagine·H_2O		15.01		7.50	50.00	31.50	94.50
L-Cysteine·HCl·H_2O		35.12		17.56		8.80	105.40
L-Cystine						36.00	
L-Cystine·2HCl	31.00		63.00	31.29	65.00		
L-Glutamic acid		14.70		7.35	20.00	13.20	39.70
L-Glutamine	292.00	146.00	584.00	365.00	300.00	333.00	1000.00
Glycine		7.50	30.00	18.75	10.00	14.30	42.80
L-Histidine·HCl·H_2O	42.00	21.00	42.00	31.48	15.00	25.00	75.00
L-Hydroxyproline					20.00	10.50	31.50
L-Isoleucine	52.00	4.00	105.00	54.47	50.00	52.50	157.50
L-Leucine	52.00	13.10	105.00	59.05	50.00	55.10	165.30
L-Lysine·HCl	73.00	36.50	146.00	91.25	40.00	65.80	197.30
L-Methionine	15.00	4.50	30.00	17.24	15.00	16.40	49.20
L-Phenylalanine	32.00	5.00	66.00	35.48	15.00	24.80	74.30
L-Proline		34.50		17.25	20.00	18.40	55.30
L-Serine		10.50	42.00	26.25	30.00	28.40	85.10
L-Threonine	48.00	11.90	95.00	53.45	20.00	36.90	110.80
L-Tryptophan	10.00	2.00	16.00	9.02	5.00	6.10	18.40
L-Tyrosine						29.00	87.00
L-Tyrosine·2Na·$2H_2O$	52.00	7.81	104.00	55.79	29.00		
L-Valine	46.00	11.70	94.00	52.85	20.00	36.30	108.90
Sub-total	871.00	614.04	1606.00	1110.02	994.00	1051.53	3126.58

Table 1. Continued.

Component	MEM	F–12	DMEM	DMEM/F12	RPMI 1640	RDF	eRDF
Vitamins							
p-Aminobenzoic acid					1.00	0.51	0.51
Biotin		0.0073		0.0035	0.20	0.10	0.10
D-Ca Pantothenate	1.00	0.50	4.00	2.24	0.25	0.67	0.67
Folic acid	1.00	1.30	4.00	2.65	1.00	1.81	1.81
Niacinamide	1.00	0.036	4.00	2.02	1.00	1.50	1.50
Pyridoxal HCl	1.00		4.00	2.00		1.00	1.00
Pyridoxine HCl		0.06		0.03	1.00	0.50	0.50
Riboflavin	0.10	0.037	0.40	0.22	0.20	0.21	0.21
Thiamine HCl	1.00	0.30	4.00	2.17	1.00	1.60	1.60
Vitamin B12		1.40		0.68	0.005	0.34	0.34
Sub-total	5.10	3.64	20.40	12.02	5.66	8.24	8.24
Miscellaneous							
Choline chloride	1.00	14.00	4.00	8.98	3.00	6.14	12.29
D-Glucose	1000.00	1802.00	4500.00	3151.00	2000.00	1700.00	3423.00
Glutathione (reduced)					1.00	0.50	0.50
HEPES						1190.00	1190.00
Hypoxanthine (Na salt)		4.77		2.39		1.00	1.00
i-Inositol	2.00	18.00	7.20	12.60	35.00	23.40	46.80
Linoleic acid		0.084		0.042		0.021	0.021
Lipoic acid		0.21		0.105		0.052	0.052
Phenol red	10.00	1.20	15.00	8.10	5.00	6.56	5.00
Putrescine·2HCl		0.161		0.081		0.04	0.04
Pyruvate (Na salt)		110.00		55.00		55.00	110.00
Thymidine		0.70		0.365		0.18	0.18
Sub-total	1013.00	1951.13	4526.20	3238.67	2044.00	2982.89	4788.88
Total Formulation	11726.77	11801.64	17075.27	14434.51	12392.50	13294.62	17177.12

[a] All biochemical quantities are expressed in milligrams per liter. Sub-totals for each category are rounded to two decimal places. Selected media represent the most frequently-used, glutamine-containing derivative of the referenced formulation. MEM is based upon reference #8; Nutrient Mixture F–12 upon reference #9; DMEM upon reference #11; DMEM/F12 upon a 1:1 mixture of the parent formulations, as defined in reference #14; RPMI 1640 upon reference #13; RDF and eRDF formulations are based upon concentrations defined in reference #18.

Appx1478-1482.

Steps 2 & 3: Selecting Ingredients to Test

After a skilled artisan chooses a starting point, the next steps, according to Dr. Glacken, involve selecting ingredients to test. A skilled artisan would "[a]ssemble a list of potential active components" and "[s]elect ingredients

that can provide the active components from the assembled list to formulate a candidate medium." Appx1338-1339.

Even when starting with a classical medium, an artisan is not limited to any particular combination of ingredients. Based on experience and need, ingredients can be added and subtracted from the starting point. Moreover, serum or other chemically derived growth factors must be added so that cells can grow and survive. At the time of the '083 Patent, scientists typically were creating growth factors with combinations of chemicals, rather than natural serum, because of perceived safety concerns with animal-derived growth factors. They sought to create serum-free media capable of supporting cell growth at high cell densities and quality. Appx1015; Appx1453-1454.

These serum-free media start with ingredients selected from the components of classical media, Appx1338-1339; Appx8352-8356, and add serum-replacing ingredients such as transferrin or transferrin-replacing ingredients, to function as growth factors in place of serum. Transferrin is a natural protein that can transport iron into cells. Researchers often use synthetic replacements for transferrin, including iron chelates, forms of iron that have claw-like ligands bound to the iron. Appx1043-1046. Numerous potential transferrin replacements have been identified, but results in any particular cell line and cell culture medium are

mixed and unpredictable. Appx1112/pp.179:16-180:6; Appx1157-1159; Appx2419.

Steps 2 & 3 in Dr. Glacken's development plan refer to "active components" and "ingredients that can provide the active components." Appx1338-1339. That is because some active components of cell culture media can be supplied by different salt forms of the same chemical, *e.g.*, the three calcium-containing ingredients listed in the first three rows of the above chart. Appx1480-1481. Thus, the form of the ingredient, as well as the ingredient itself, must be selected. In Steps 2 & 3 of the development process, the choices for a skilled artisan are staggeringly large. With 60-90 ingredients in a given medium, even setting aside the different salt forms of the same active ingredient, there is a near infinity of possible unique combinations of ingredients. Appx935; Appx1125.

Steps 4 & 5: Selecting and Testing Concentrations of Each Ingredient

According to Dr. Glacken, the last steps a skilled artisan would follow involve "[d]evelop[ing] an experimental design where the concentrations of the ingredients are varied in the medium to determine the optimal amount(s)," and "[e]xecut[ing] the designed experiments using a matrix-based experiment…." Appx1338-1339. In other words, the artisan would select the concentrations of the assembled ingredients and iteratively test them. At this stage of development there

are also endless unique possible combinations of different concentrations—even if the artisan just tested (as Dr. Glacken suggests) no more than three possible concentrations of each ingredient. Appx936; Appx1403.

4. The Cited References

The GSK and Life Techs references, Appx1177-1226; Appx1586-1643, do not disclose classical cell media that a POSA might use to create new cell culture media. Rather, both references are directed to cell culture media supplements, *i.e.*, additives designed to improve a cell culture medium. Each reference discloses, as an example, a complete serum-free cell culture medium for use with these supplements.

The experts and the inventors all agreed that a skilled artisan would not have selected such a medium as a starting point for developing a new cell culture medium. Appx1047-1048; Appx1062-1064. As Dr. Glacken explained, a POSA would start with "commercial media, ***the classics***, DMEM, F12, DMEM/F12, RPMI and look at combinations of those." Appx1094/p.72:3-12 (emphasis added); Appx1338-1339. Then the POSA would begin the experimental steps of modifying the basic formula by adding or subtracting ingredients and testing the result at different concentrations. That is how the inventors of the '083 Patent worked, "start[ing] with DMEM/F12." Appx1581/pp.211:21-212:8. Janssen's expert Dr. Butler agreed. Appx1024.

Dr. Glacken was particularly clear that one would not start with a complete serum-free medium as described in GSK and Life Techs. Indeed, although he was well-familiar with the classics—DMEM, F12, DMEM/F12, RPMI—Dr. Glacken could not remember ever hearing about the GSK or Life Techs media before this litigation, Appx1093-1094/pp.69:17-71:13, and testified that they would not provide a proper starting point. "[Y]ou don't start with a—you know, necessarily start with a serum free medium that you saw in [a] paper somewhere." Appx1094/p.72:10-12. One might consider the information in the reference for what it was worth, but in Dr. Glacken's experience "I didn't start with a complete serum-free media … as a starting point…. [T]hat's not what I've done in the past." Appx1097/pp.82:20-83:12. Dr. Butler agreed: "I do not believe that a POSA would have selected the [complete serum-free] medium disclosed" in GSK or Life Techs. Appx1062; *see also* Appx1047.

GSK: The GSK reference describes "exogenous animal-free growth factors" that can be added as supplements to a cell culture medium. Appx1062; Appx1178. GSK teaches that the supplements described in the reference can be added to any media, such as an "exemplary" serum-free medium that "comprises all or most of the common ingredients listed in Table 3." Appx1198. Table 3 lists 96 ingredients with concentration ranges and preferred concentrations for each ingredient. Appx1192-1201. Forty-four of the ingredients in Table 3 are not

required by the hypothetical claim. Two ingredients required by the hypothetical claim are not mentioned in Table 3: ammonium metavanadate (NH_4VO_3), a trace-metal containing ingredient, and Janssen's choice of a transferrin replacement, the iron chelate ferric ammonium citrate ("FAC"). Celltrion argued that NH_4VO_3 (a required ingredient in the hypothetical claim) is interchangeable with sodium metavanadate ($NaVO_3$), which is in Table 3, and that FAC (also required by the hypothetical claim) could replace ferric fructose, also in Table 3. Appx1201.

The concentration ranges in the hypothetical claim partially overlap the concentration ranges in GSK's Table 3. For seventeen ingredients, the preferred concentrations in GSK fall outside the concentration ranges of the hypothetical claim.

Life Techs: The Life Techs reference also is directed to media supplements. These can be used with "[a]ny basal medium," *i.e.*, not specific to any medium. Appx1048; Appx1598. Life Techs' Table 1, which Celltrion cited, lists a medium of 88 ingredients, with a concentration range and preferred concentration for each. Thirty-six of those ingredients are not required by the hypothetical claim. Five ingredients that are required by the hypothetical claim are not listed in Table 1: manganese sulfate hydrate ($MnSO_4•H_2O$), sodium selenite (Na_2SeO_3), tin chloride dihydrate ($SnCl_2•2H_2O$), ammonium metavanadate (NH_4VO_3), and FAC. The first four are trace metal-containing ingredients; FAC is

a transferrin replacement. Celltrion argued that the four trace metals are interchangeable with ingredients listed in Table 1: manganese chloride tetrahydrate ($MnCl_2 \cdot 4H_2O$), selenous acid (H_2SeO_3), anhydrous tin chloride ($SnCl_2$), and sodium metavanadate ($NaVO_3$). Celltrion also asserted that FAC could replace ferric citrate chelate, listed in Table 1.

The concentration ranges in the hypothetical claim partially overlap the concentration ranges in Life Techs' Table 1. There is no overlap at all for one ingredient, putrescine hydrochloride. For twelve ingredients, the preferred concentration ranges in Life Techs fall outside the concentration ranges of the hypothetical claim. Appx1050-1051.

5. Celltrion's Position on Obviousness

Celltrion argued that it would have been obvious to modify two ingredients and 17 concentrations in GSK, and five ingredients and 12 concentrations in Life Techs, to arrive at the hypothetical claim.

In response, Janssen demonstrated that this theory was entirely based on hindsight. In particular, Janssen argued that there was no reason—other than hindsight—for a POSA to select GSK or Life Techs as a starting point for development. If a POSA did select those references, there was no reason—other than hindsight—to focus only on the differences between those references and the hypothetical claim. And if a POSA did focus on the differences, there was no

reason—other than hindsight—to modify the differences in such a way as to arrive at the hypothetical claim.

Celltrion did not offer any evidence of motivation. Instead, Celltrion's position was that there was no need to show motivation at all. It focused on GSK and Life Techs simply because (with the benefit of hindsight) those compositions are similar to the hypothetical claim, and it focused (again in hindsight) only on the differences between those references and the hypothetical claim because that supposedly is all an obviousness analysis requires. In that way, Celltrion purported to reduce the choices down to just the GSK and Life Techs references, and then to just two ingredients in GSK and five in Life Techs. Using hindsight, Celltrion argued that modifying those ingredients to arrive at the hypothetical claim was "'mere substitution of one element for another known in the field' that does 'no more than yield a predictable result.'" Appx337 (quoting *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 416 (2007)). But as Janssen showed, even if one focused only on the differences between GSK and Life Techs and the hypothetical claim, the ingredients were not all interchangeable. Celltrion's expert, Dr. Glacken, acknowledged that the iron chelate FAC—which is required by the claim and not present in GSK or Life Techs—is not interchangeable with any ingredients in those media, and that using FAC does not lead to predictable results.

Appx1112/pp.179:19-180:6. Celltrion needed to provide some reason or motivation to use FAC and it provided none.

For the concentration differences, Celltrion's only argument was that concentration ranges in the hypothetical claim generally overlapped with ranges in the prior art and so obviousness should be presumed. But that presumption does not apply here because the ranges in the prior art are "so broad as to encompass a very large number of possible distinct compositions"—in fact, a nearly infinite number. *In re Peterson*, 315 F.3d 1325, 1330 n.1 (Fed. Cir. 2003). Celltrion offered no evidence of any reason or motivation to modify the concentrations of GSK and Life Techs to arrive at concentrations within the hypothetical claim.

F. The District Court's Decision

The district court granted Celltrion's motion for summary judgment of non-infringement based on ensnarement and denied Janssen's request for judgment in its favor under Rule 56(f). Appx22-134.

The district court's reliance on GSK and Life Techs: In selecting the GSK and Life Techs references, the district court ignored undisputed evidence from both sides' experts that a skilled artisan would not have chosen the complete serum-free media from those references as a starting point in developing an improved cell culture medium, and instead would have been motivated to start with one of the classical media.

The district court believed that it could disregard this evidence, and decades of decisions from this Court, because it supposedly was not required to identify a reason why an artisan would select GSK or Life Techs for modification from the sea of prior art references. The court found it sufficient that—in hindsight—these references were similar to the hypothetical claim, even if an artisan actually would have started work elsewhere. Appx48. According to the court, "it is not required" to consider "motivation to select a particular prior art [reference] that was a preferable starting point compared with other [references] in the art." Appx49. This was permissible, the court concluded, because *KSR* encourages "a 'flexible' inquiry based on the facts of the case, not a framework of 'rigid rule[s].'" Appx48. This erroneous legal analysis was essential to the court's outcome.

The district court's reliance on the differences between the hypothetical claim and the prior art: After using hindsight to select GSK and Life Techs, the district court improperly—and admittedly—used hindsight again to consider only the ingredients in those references that are different from ingredients in the hypothetical claim. Appx66-70. It did so by asserting that 35 U.S.C. § 103 requires analysis only of "the differences between the claimed invention and the prior art," ignoring section 103's explicit command to consider the invention "as a whole." Based on this, the court concluded, again contrary to decades of decisions

by this Court, that "it is not impermissible use of hindsight to analyze the differences between the claimed composition and a composition in the prior art that was directed to the same problem." Appx63.

Thus, in considering GSK, the court focused on only two ingredients—sodium metavanadate and ferric fructose—and ignored the other 94 ingredients in the GSK formula, including the other 50 ingredients that are required by the hypothetical claim. It assumed that a POSA seeking to develop an improved medium would not consider modifying other ingredients in GSK. It identified no motivation for a POSA to modify those two particular ingredients, and only those two ingredients, let alone to substitute ammonium metavanadate and FAC in their place. The district court's analysis of Life Techs was similar. Thus, the court ignored uncontradicted evidence that an artisan interested in modifying either GSK or Life Techs could create "[a]lmost an infinite number of possible formulations," Appx1125, most well removed from the hypothetical claim. Again, this error was fatal to the district court's analysis. The district court identified no evidence, and Celltrion provided none, that a POSA intent on modifying either reference would focus only on the ingredients that the court selected with hindsight, let alone be motivated to modify them.

The district court's analysis of the differences between the hypothetical claim and the prior art: After wrongly narrowing its obviousness

analysis to GSK and Life Techs alone, and then to only the differences between the hypothetical claim and those references, the district court continued to substitute hindsight for motivation. The court's errors were driven by its clearly erroneous conclusion that cell culture media was not an experimental science, but rather one in which "experimentation would not have been needed" to know whether a particular combination of ingredients and concentrations would provide a cell culture media "capable of growing cells in volumes and conditions suitable for biopharmaceutical production." Appx39.

Based on that incorrect proposition, the court accepted Celltrion's contention that the ingredient differences between the claim and the prior art all involved interchangeable ingredients that would yield predictable results, so that hindsight sufficed and motivation was unnecessary. Appx89-94. This finding was unsupported by the record. Celltrion's case depended on the substitution of FAC as a transferrin replacement instead of ferric fructose (in GSK) or ferric citrate (in Life Techs). Appx67-68. But as the district court recognized elsewhere, the record shows that iron chelates are not interchangeable. Rather, their "efficacy would vary based on the cell line being grown," so that it was necessary that they be "tested to determine which [iron chelate] would work best for a given cell line." Appx101 (citations omitted). This is the exact opposite of an interchangeable ingredient yielding a predictable result.

Equally in error, the district court ignored the concentration differences between the prior art and the hypothetical claim. Using hindsight, it simply noted that concentration ranges overlapped, which supposedly made the differences in ranges presumptively obvious. Appx74-75. In doing so, the district court brushed aside this Court's warning that the presumption is inapplicable where, as here, "the disclosed range is so broad as to encompass a very large number of possible distinct compositions." *Peterson*, 315 F.3d at 1130 n.1. And it ignored undisputed evidence that results of different concentrations, especially multiple different concentrations in combination, are not predictable, but require testing and non-obvious invention. Again, these decisions were critical to the court's holding.

The district court's rejection of the "teaching away" and copying evidence: Although the district court stated that it was required to view the evidence in the light most favorable to Janssen, it consistently did the opposite. For example, it rejected Dr. Butler's testimony that the art taught away from using FAC because Dr. Butler said that "one would have been dissuaded" from using FAC as a transferrin replacement, rather than that FAC's performance was "so flawed" that no artisan would ever use it as a transferrin replacement. Appx96-99 (citations omitted). Likewise, the court acknowledged that "a reasonable factfinder could conclude that HyClone copied the MET 1.5 formulation" of the '083 Patent,

Appx112-113, but nonetheless rejected the copying evidence instead of viewing it in the light most favorable to Janssen. Appx114; Appx121.

SUMMARY OF ARGUMENT

The district court impermissibly relied on hindsight in holding that the hypothetical claim was obvious in view of GSK and Life Techs. The district court should have granted summary judgment of no ensnarement in favor of Janssen. At a minimum, it was error to grant summary judgment of noninfringement in favor of Celltrion.

The district court erred at the outset in using hindsight gained from the '083 Patent (and the hypothetical claim) to select GSK and Life Techs as the basis for its obviousness analysis. On the undisputed evidence, without knowledge of the '083 Patent, there was no reason for a skilled artisan to choose those references. On the undisputed evidence, a skilled artisan wanting to develop a new cell culture medium would have been motivated to start elsewhere—with one of the classical media.

The district court compounded that error by again using hindsight gained from the '083 Patent to consider only the differences between GSK and Life Techs and the hypothetical claim. On the undisputed evidence, a POSA who selected GSK and Life Techs would have been equally motivated to consider

changing any or all 96 ingredients in GSK, and any or all 88 ingredients in Life Techs, and the concentration ranges for all of those ingredients.

Finally, the district court also identified no motivation for a skilled artisan who (with hindsight) selected GSK and Life Techs and then (with hindsight) focused only on the differences between those references and the hypothetical claim, to replace their transferrin substitutes with FAC or modify multiple different concentrations to arrive at a combination of ingredients and concentrations within the hypothetical claim. The only reason to do so was, once again, hindsight.

Celltrion's position, accepted by the district court, was that there was no need to identify a reason or motivation to start with GSK and Life Techs, or to modify only the ingredients in those references that differed from the hypothetical claim, or to modify even those ingredients so as to recreate the hypothetical claim. This was error. On the undisputed evidence, the district court should have granted summary judgment of no ensnarement in favor of Janssen.

At a minimum, the court erred in granting summary judgment of noninfringement in favor of Celltrion and should have given Janssen the opportunity to present all of its evidence, including evidence of teaching away and of HyClone's copying, at trial.

ARGUMENT

STANDARD OF REVIEW

"This court reviews a grant of summary judgment under the standard of review of the regional circuit." *Enfish, LLC v. Microsoft Corp*., 822 F.3d 1327, 1334 (Fed. Cir. 2016). The First Circuit "review[s] a grant of summary judgment de novo; in doing so, [the court] consider[s] the facts in the light most favorable to the nonmoving party, drawing all reasonable inferences in his favor. Issues of law are reviewed de novo." *Buchanan v. Maine*, 469 F.3d 158, 162 (1st Cir. 2006) (citations omitted). "Summary judgment is only appropriate if 'there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law.'" *Enfish*, 822 F.3d at 1334 (quoting Fed.R.Civ.P. 56(a)).

THE ENSNAREMENT DOCTRINE

Ensnarement is a noninfringement defense in a DOE case that relies on an obviousness analysis. (Ensnarement can also be based on anticipation, but there is no such claim here.) The prior art limits the application of the DOE so that a patentee cannot obtain coverage by equivalents of subject matter that would have been obvious over the prior art. *Wilson Sporting Goods Co. v. David Geoffrey & Assocs.*, 904 F.2d 677, 684 (Fed. Cir. 1990). Thus, "[a] doctrine of equivalents theory cannot be asserted if it will encompass or 'ensnare' the prior art." *Jang v. Boston Sci. Corp.*, 872 F.3d 1275, 1285 (Fed. Cir. 2017) (citation omitted).

"A helpful first step in an ensnarement analysis is to construct a hypothetical claim that literally covers the accused device." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1324 (Fed. Cir. 2009). "Next, the district court must assess the prior art introduced by the accused infringer to determine whether the patentee has carried its burden of persuading the court that the hypothetical claim is patentable over the prior art." *Id.* at 1325. "[A] court also must apply standards of patentability consistent with [the Federal Circuit's] jurisprudence regarding anticipation and obviousness." *Conroy v. Reebok Int'l, Ltd.*, 14 F.3d 1570, 1577 (Fed. Cir. 1994); *accord Wilson Sporting Goods*, 904 F.2d at 684 (hypothetical claim approach "allows use of traditional patentability rules").

Whether a hypothetical claim is patentable—and therefore whether the prior art limits the application of the DOE—is a question of law for the Court predicated on underlying factual findings. *Intendis GmbH v. Glenmark Pharms., Inc.*, 822 F.3d 1355, 1363 (Fed. Cir. 2016). "The burden of producing evidence of prior art to challenge a hypothetical claim rests with an accused infringer, but the burden of proving patentability of the hypothetical claim rests with the patentee." *Jang*, 872 F.3d at 1285 (citation omitted).

Celltrion's hypothetical claim is identical to claim 1 of the '083 Patent except that the concentration ranges for 12 ingredients have been slightly broadened to literally cover the accused media.

I. THE DISTRICT COURT IMPROPERLY USED HINDSIGHT, AND IGNORED MOTIVATION, THROUGHOUT ITS OBVIOUSNESS ANALYSIS

The Supreme Court has repeatedly warned against the "distortion caused by hindsight bias." *KSR*, 550 U.S. at 421; *see also Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966). This Court's decisions are replete with similar warnings. An obviousness analysis must avoid "even a hint of hindsight." *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013).

"To preclude hindsight in the analysis," there must be "evidence from before the time of the invention in the form of some teaching, suggestion or even mere motivation … to make the variation or combination." *Rolls-Royce*, 603 F.3d at 1338. This evidence need not appear in a published reference, but it must be present. *See KSR*, 550 U.S. at 419. The requirement for motivation provides "the best defense against hindsight-based obviousness analysis." *Ecolochem, Inc. v. So. Cal. Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000).

A. The District Court Erred by Using Hindsight to Select the GSK and Life Techs References

The district court used hindsight to select the GSK and Life Techs references as the starting point for its obviousness analysis—not because a POSA would have been motivated to select them, but because of their closeness to the hypothetical claim. It made no effort to disguise what it was doing, stating that it

was "not required" to identify a "motivation to select a particular prior art [reference] that was a preferable starting point compared with other [references] in the art…." Appx49; *see also* Appx62. This was error.

Obviousness requires a showing of "reasons one of ordinary skill in the art would have been motivated to ***select the references***" used in an obviousness analysis. *Polaris*, 882 F.3d at 1069 n.4 (emphasis added) (quoting *Rouffet*, 149 F.3d at 1359); *see also Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1273 (Fed. Cir. 2018) (same). As this Court has explained, an obviousness analysis under "*KSR* assumes a starting reference point or points in the art, from which a skilled artisan might identify a problem and pursue potential solutions." *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). What reference(s) a skilled artisan would choose as a starting point is guided by what skilled persons would have done "in the normal course of research and development." *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011).

Here, undisputed evidence shows that in the normal course of research and development a POSA would have been motivated to select a classical medium as a starting point for development, not GSK or Life Techs. That is what Janssen's inventors did; it is what Celltrion's expert has done; it is what both sides' experts said a POSA would have done. *See* pages 17-19, *supra*. As Dr. Glacken explained, "you will look at commercial media, ***the classics***, DMEM, F12,

DMEM/F12, RPMI and you look at combinations of those." Appx1094/p.72:3-12 (emphasis added); *accord* Appx1578/pp.84:8-85:25; Appx1024.

Both sides' experts agreed that the media described in GSK and Life Techs are not classical media that a POSA would have used as a starting point in research and development. Appx1047; Appx1062; Appx1097/pp.82:20-83:12. Rather, they are complete serum-free media in which classics have already been modified and optimized for a particular application. Appx1047-1048; Appx1062-1064. GSK and Life Techs would only provide a starting point for development if an artisan had hindsight knowledge of the hypothetical claim and was working backwards to recreate it.

Rather than identify a reason to select GSK and Life Techs as "reference … points" from which a skilled artisan could "pursue potential solutions," *Eisai*, 533 F.3d at 1359, the district court said there was no need to do so except in so-called "lead compound" cases involving chemical compounds.[2] Appx49; *see also* Appx40-42. In the lead compound cases, this Court has analyzed the motivation to select a reference and concluded, as a matter of law, that the starting point for an artisan making a chemical compound is a lead compound, *i.e.*, a compound selected because of its potential efficacy, not its chemical structure.

[2]*See, e.g.*, *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-92 (Fed. Cir. 2012); *Eisai*, 533 F.3d at 1359; *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007).

But those cases are just a specialized application of a general principle.[3] There is ***always*** a requirement that an obviousness analysis identify a reason to select a reference from the analogous prior art references. On particular facts, that reference may be the closest prior art, but only if there is a reason to select it.

For example, *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317 (Fed. Cir. 2016), involved marine generators. Like the district court here, the district court in *WBIP* treated the obviousness issue "as an inquiry into whether a person of skill, with two (and only two) references sitting on the table in front of him, would have been motivated to [modify] … the references in a way that renders the claimed invention obvious." *Id.* at 1337. That was incorrect:

> Whether a skilled artisan would be motivated to make a combination includes whether he would ***select particular references*** in order to combine [or modify] their elements**.**

Id. (emphasis added). As this Court explained, "***[t]he real question is whether that skilled artisan would have plucked one reference out of the sea of prior art***" and then modified it. *Id.* (emphasis added); *see also Polaris,* 882 F.3d at 1069 n.4

[3]Recognizing that the lead compound analysis reflects a general principle, this Court has extended its rule to chemical compositions, such as the hypothetical claim. *See Unigene*, 655 F.3d at 1361-62 ("[T]he term 'reference composition' is more appropriate than 'lead compound' when considering obviousness for a chemical composition."); *UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1324 (Fed. Cir. 2018) (approving application of a lead compound analysis for a compound separated from a prior art mixture).

(there must be a reason why a skilled artisan "would have been motivated to select the references and to [modify] them") (patent on all-terrain vehicles) (citation omitted); *Continental Can Co., USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1271 (Fed. Cir. 1991) (vacating summary judgment of obviousness for failure to prove that a skilled artisan "would be motivated to select and combine features from each source") (patent on plastic bottles).

Nothing in the district court's decision justifies its selection of GSK and Life Techs for analysis. The district court stated that a validity challenger is not required "'to prove obviousness by starting with a prior art commercial embodiment and then providing motivation to alter that commercial embodiment.'" Appx43-44 (quoting *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737 (Fed. Cir. 2013)). That is true, but irrelevant. The obviousness analysis need not start with a "prior art commercial embodiment," but there must a reason for a POSA to select the prior art references used in an obviousness analysis. The reason cannot consist of hindsight knowledge of the patent claim and a desire to recreate it.

The district court also purported to justify relying on GSK and Life Techs by finding that those references are analogous art—"'from the same field of endeavor' in which the inventors of the '083 patent were working" and "'reasonably pertinent' to the problem the inventors set out to solve." Appx63-64

(quoting *Sci. Plastic Prods., Inc. v. Biotage AB*, 766 F.3d 1355, 1359 (Fed. Cir. 2014)). But identifying analogous art only frames the inquiry; it does not answer it. The "analogous art" defines the universe of prior art under § 102 that "qualif[ies] as prior art for an obviousness determination." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). The need for motivation then "picks up where the analogous art test leaves off …." *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1290 (Fed. Cir. 2006) (citation omitted). The issue is not whether GSK and Life Techs are analogous art, but rather whether a skilled artisan would have a reason to "pluck[] [those] reference[s] out of the sea of [analogous] prior art." *WBIP*, 829 F.3d at 1337.

Finally, the district court fell back on the axiom that "obviousness is a 'flexible' inquiry …, not a framework of 'rigid rule[s].'" Appx48 (quoting *KSR*, 550 U.S. at 415, 419). But the flexibility of the inquiry is not a reason to jettison the requirement of a reason for a skilled artisan to select the references. *See Rolls-Royce*, 603 F.3d at 1338 (collecting post-*KSR* cases on motivation). Negating the need for motivation, as the district court did here, would eliminate a "critical safeguard against hindsight." *Yamanouchi Pharm. Co. v. Danbury Pharm., Inc.*, 231 F.3d 1339, 1344 (Fed. Cir. 2000).[4]

[4]The district court stated in a footnote that if it needed to identify a reason to select references "it would conclude that the GSK or Life Techs media would have been

As a matter of law, the district court erred at the outset by using hindsight knowledge gained from the '083 Patent, rather than a preexisting motivation, in selecting GSK and Life Techs as the starting point for its analysis.

B. The District Court Erred by Using Hindsight to Focus Only on the Differences Between the References and the Hypothetical Claim

Even if a skilled person were motivated to start with and then modify the GSK and Life Techs media, the district court improperly used hindsight gained from the '083 Patent to consider only whether the differences between GSK and Life Techs and the hypothetical claim were obvious. The court admitted that there was no reason other than hindsight to focus on the differences. It justified doing so by stating that "§ 103 expressly focuses the court on 'the differences between the claimed invention and the prior art.'" Appx63. Based on that incomplete quotation from § 103, the district court concluded that "it is not impermissible use

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more suitable lead compounds than [a classic basal media such as] DMEM/F-12 …." Appx49 n.4. This was supposedly because the media in those references were complete serum-free formulas optimized for a particular use, while the classical media all required (at the least) the creation of a customized serum replacement. But that untenable argument was rejected by the experts on both sides who said one would start instead with a classic media. Celltrion did not argue this position and there is no evidence to support it. In any event, the court's fact finding was inappropriate on summary judgment when courts are required to view the evidence in the light most favorable to the non-movant. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986).

of hindsight to analyze the differences between the claimed composition and a composition in the prior art that was directed to the same problem." *Id*.

In fact, that is a classic impermissible use of hindsight. Section 103 directs the court to the proper question: whether "the differences between the claimed invention and the prior art are such that the claimed invention ***as a whole*** would have been obvious …." 35 U.S.C. § 103 (emphasis added). The "differences between the prior art and the claims at issue" is one of the *Graham* factors, 383 U.S. at 17, but "***the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious***." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1537 (Fed. Cir. 1983) (emphasis added). "Consideration of differences … is but an aid in reaching the ultimate determination of whether the claimed invention as a whole would have been obvious." *Id*. "Focusing on the obviousness of substitutions and differences instead of the invention as a whole … [is] a legally improper way to simplify the difficult determination of obviousness." *Hybritech*, 802 F.2d at 1383; *see also UCB*, 890 F.3d at 1324 ("[D]ifferences cannot be considered in isolation—the claims must be considered as a whole.").

Additionally, courts "must analyze and consider the references as whole …." *Vandenberg v. Dairy Equip. Co*., 740 F.2d 1560, 1564 (Fed. Cir. 1984); *see Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368, 1377 (Fed. Cir. 2012) (same); *see also* MPEP § 2141.02(VI) ("A prior art reference must be

considered in its entirety, i.e., as a whole ….") (emphasis in original). Looking at the references as a whole, there must be a reason for a skilled artisan to "***select the elements*** from the cited prior art references for [modification] in the manner claimed." *Beckson Marine, Inc. v. Nfm, Inc.*, 292 F.3d 718, 728 (Fed. Cir. 2002) (emphasis added). Here, instead, the district court improperly "stitch[ed] together an obviousness finding from discrete portions of prior art references without considering the references as a whole." *In re Enhanced Sec. Research, Inc.*, 739 F.3d 1347, 1355 (Fed. Cir. 2014).

The district court ignored almost all of the 96 ingredients in GSK and almost all of the 88 ingredients in Life Techs. In particular, the court ignored all of the overlapping ingredients between those references and the hypothetical claim. In doing so, the district court assumed that the *only* ingredients in GSK and Life Techs that a POSA would consider modifying were the ones not found in the hypothetical claim. But without hindsight, a POSA would not know which ingredients those were. Obviousness requires a showing—without hindsight knowledge of the invention—that "a person of ordinary skill in the art 'would have selected these components for [modification] in the manner claimed.'" *Polaris*, 882 F.3d at 1069 n.4 (citation omitted). There was no such showing here. Out of the dozens of ingredients in the two references, why modify, for example, ferric

fructose (in GSK) or ferric citrate (in Life Techs), and replace them with FAC? No reason at all, other than a hindsight-driven effort to recreate the hypothetical claim.

In leading the district court to legal error, Celltrion made no attempt to identify any reason for a skilled artisan to focus only on the differences between the references and the claimed invention. Celltrion's expert Dr. Glacken said, "I don't feel it's necessary" to identify a reason. Appx1112/pp.178:13-179:13. Neither did the district court. But "[i]t is improper to take concepts from [prior art references] and change them in light of the now-known template of the patented [product], without some direction in the prior art that would render it obvious to do so." *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1378 (Fed. Cir. 2011).

To the extent that GSK or Life Techs provided a motivation to modify any of the elements of their media, both references simply state that the supplements they disclose can be used with any cell culture media and (in Life Techs) that the trace metals could be varied. Appx1598-1600; Appx1605; Appx1189; Appx1198. That provides no reason for a skilled person to focus anywhere in particular. *See* Appx934-937; Appx1048-1061; Appx1064-1072. As Dr. Glacken has written, there are "100s of possible components, each with different optimal concentrations," leading to "[a]lmost an infinite number of possible solutions." Appx1125.

When GSK and Life Techs are considered as a whole and without hindsight, a skilled artisan who selected those references for development would need to consider modifying ***any and all*** of the 96 ingredients in GSK and 88 ingredients in Life Techs, and their concentration ranges, with no signposts calling attention to any particular ingredients. "This court and obviousness law in general recognizes an important distinction between combining known options into 'a finite number of identified, predictable solutions,' *KSR,* 550 U.S. at 421, … , and 'merely throwing metaphorical darts at a board' in hopes of arriving at a successful result,' …." *Leo Pharm. Prods., Inc. v. Rea*. 726 F.3d 1346, 1357 (Fed. Cir. 2013). Here, there is no finite number of solutions; rather, the number approaches infinity.

Other than hindsight, there is no reason for the experimental process of addition and subtraction artificially to hold constant the 50 ingredients in GSK that ***matched*** the '083 Patent and change only the two that ***differed***. Or to hold constant 47 ingredients in Life Techs and change only five. Rather, in the normal course of development, there would be no such preconditions. The same is true for concentrations.

To illustrate, consider the development of the '083 Patent and Celltrion's media. The '083 inventors started with the DMEM/F12 medium and made additions and subtractions based on their research. Additions included FAC and NH_4VO_3, ingredients that do not appear in either GSK or Life Techs.

Subtractions included pyridoxal•HCl and sodium bicarbonate, ingredients that do appear in GSK and Life Techs. Meanwhile, based on its research, Celltrion made different choices in modifying the HyClone media (copied from Janssen) from which it started. Its additions included galactose, which is in neither GSK nor Life Techs, and its deletions included two of the optional amino acids in the '083 formula, sodium hypoxanthine and thymidine. Such addition and subtraction is the fundamental nature of media development. Without hindsight, an artisan working with the GSK or Life Techs media would do the same—and have no reason either to focus (*e.g.*, in GSK) on FAC and NH_4VO_3 or to leave the other ingredients untouched.

In fact, an artisan considering modifying the GSK or Life Techs formulas would have a vast number of different combinations to consider. Conservatively assuming just a binary decision for each ingredient (either retaining the ingredient or eliminating/replacing it), a skilled artisan who considered only the 52 ingredients in the GSK or Life Techs references alleged to render the hypothetical claim obvious would have to choose among 2^{52} alternative combinations of ingredients—and only one of these endless different combinations would be the unique combination of the hypothetical claim. "[T]he breadth of the[] choices and the numerous combinations indicate that these disclosures would

not have rendered the claimed invention [even] obvious to try." *Leo*, 726 F.3d at 1356-57.

The district court committed reversible error by using hindsight rather than motivation to focus only on the differences between the prior art and the hypothetical claim.

C. The District Court Improperly Used Hindsight in Finding the Differences Between the References and the Hypothetical Claim To Be Obvious

The district court erred yet again in using hindsight as a substitute for a reason or motivation to (1) replace ferric fructose (in GSK) or ferric citrate (in Life Techs) with FAC as a transferrin substitute, and (2) select concentrations within the ranges in the hypothetical claim.[5] The district court did not identify a reason to do any of this. Neither did Celltrion's expert. The most Celltrion's expert could say was that a skilled person modifying GSK or Life Techs "could" or "might" wind up with the hypothetical claim. Appx1105/pp.140:23-141:3; Appx1107/p.149:12-17; Appx1116/p.215:12-20. But "obviousness concerns whether a skilled artisan not only ***could have made*** but ***would have been motivated to make*** the combinations or modifications of prior art to arrive at the claimed

[5]For purposes of this appeal, Janssen does not dispute that the different salt forms of trace metals in GSK (vanadium) and Life Techs (manganese, selenium, tin and vanadium) are interchangeable with the salt forms of those metals found in the hypothetical claim.

invention." *Belden, Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (emphasis in original). Because the record shows no motivation to make these changes, Celltrion's ensnarement case fails—once again—as a matter of law.

The principal error in the district court's analysis of the differences between the prior art references and the hypothetical claim stemmed from its clearly erroneous conclusion that this is an art where "experimentation would not have been needed." Appx39. Based on that false premise, the court viewed the substitution of ingredients and changes in concentration as so routine that an artisan "would have had the ability and motivation to combine familiar ingredients" in "predictable concentrations" and to have "predicted the combination's successful results" in creating a "cell culture media capable of growing cells in volumes and conditions suitable for biopharmaceutical production." Appx27; Appx39. This was error.

1. FAC

The district court did not identify any problem or drawback with using ferric fructose (in GSK) or ferric citrate (in Life Techs) as a transferrin replacement. Nothing in those references identified a problem with those ingredients, let alone a reason to search for substitutes. Indeed, the ingredients are used in the preferred, working examples in GSK and Life Techs. Celltrion identified no need to improve upon those ingredients and no evidence that FAC

would be better. *See Leo*, 726 F.3d at 1354. There was no reason or motivation for an artisan to replace those ingredients, let alone to replace them with FAC in particular.

In fact, Janssen went against conventional wisdom in selecting FAC as a transferrin replacement in the '083 Patent. That decision was the contribution of Dr. Susan Lenk, one of the inventors. No reference described using FAC as a transferrin replacement in a complete serum-free medium other than for experimentation, and the reported experimental results—of which Dr. Lenk was aware—were not encouraging. Nonetheless, based on her own experiments using FAC, Dr. Lenk had the insight to include FAC in the media to replace transferrin. Appx2539-2540; Appx1574-1575/pp.25:2-26:8.

The district court stated that ferric fructose, ferric citrate and FAC all could be used to replace transferrin in serum-free media and that it did not matter how they compared—or whether FAC was inferior—because "[i]nfringement under the doctrine of equivalents and obviousness are separate legal inquiries." Appx87-88. That is true, but not the point. For an obviousness analysis, the court needed to—but did not—identify a problem with ferric fructose or ferric citrate or at least a motivation to replace these completely acceptable transferrin substitutes, used in working examples, with FAC. Iron chelates (such as ferric fructose, ferric citrate and FAC) are not interchangeable.

In fact, as Dr. Butler explained, the prior art references that Dr. Glacken cited in his report demonstrate that FAC was considered "inferior" to other "preferable" transferrin replacements. Appx97. The district court accepted that conclusion as the teaching of the art ("FAC was not the 'best performing factor,'" Appx101), but brushed that aside as insufficient to demonstrate "teaching away," Appx101-102. But "even if a reference is not found to teach away, its statements regarding preferences are relevant to a finding regarding whether a skilled artisan would be motivated to combine that reference with another reference." *Polaris*, 882 F.3d at 1069. The art provided no affirmative motivation to use the "inferior" FAC as a transferrin replacement—which undoubtedly explains why FAC was not included in the formula of any publicly available cell culture media before the '083 inventors demonstrated its efficacy.

In particular, in ¶¶ 158-162 and 257 of his report, Dr. Glacken cited Keenan (Appx1157-1159), as supposedly demonstrating that the use of FAC as a transferrin replacement was "within the scope of knowledge of POSA." Appx1554. Keenan tested seven iron-containing compounds, including FAC, as potential transferrin replacements. In the first round of experiments, only four of the seven potentials made the cut. FAC, along with two others, was rejected because it "stimulated a maximum of 74-75% of the growth obtained by transferrin," compared to the 92-100% growth demonstrated by the other four.

Appx1158. In other words, FAC failed to demonstrate growth equivalent to transferrin. Keenan hypothesized that "[t]his may reflect the reduced potential biological accessibility of ferric iron [*e.g.*, FAC] as compared to ferrous ion." Appx1159. Indeed, Keenan's experiments ultimately demonstrated that "only [three potential iron sources] appeared as suitable replacements for transferrin." *Id*. FAC was not one of them. Citing published work by Metcalf, Keenan also reported that FAC would not "support high levels of growth" in "suspension," the most prevalent cell culture system and the one for which the '083 Patent was developed. *Id.* None of this would have motivated an artisan to select FAC to replace the completely acceptable transferrin substitutes in GSK and Life Techs.

The district court spent most of its attention on its own analysis of the Keenan reference, but then briefly cited two other references as supposedly demonstrating that the "combined teachings" of the prior art were that FAC was a suitable source of chelated iron. Appx102-103. The two references, the Kitano book chapter (a review article) and the '162 patent, included no experimental data about iron chelates. These random prior art references did not reflect the "combined teachings" of the prior art. Most notably, the court's review omitted the Field '140 patent, even though Dr. Glacken expressly discussed Field (along with Keenan) as demonstrating a POSA's "scope of knowledge" about FAC. Appx1507-1508; Appx1554. The '140 patent reports, based on multiple

experiments, that "in agitated [*i.e.*, suspension] culture … [FAC] concentrations of >1 mg/l are toxic," and that, in even lower concentrations, "myeloma cells failed to thrive and died." Appx2419.[6]

Finally, even if an artisan perceived a problem (for some reason) with the use of ferric fructose (in GSK) or ferric citrate (in Life Techs), and even if he were motivated (for some reason) to replace those transferrin replacements with FAC, the artisan would had have no reasonable expectation of success with using FAC as a transferrin replacement in creating a media capable of high volume biopharmaceutical production. Biotechnology is an "unpredictable art." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009). As Dr. Glacken explained, the literature demonstrates that different iron chelates may "perform differently … for a given cell line." Appx1112/p.180:2-6; *see also* Appx1044-1046. FAC's performance cannot be predicted without experimentation. At a minimum, the disputed facts about FAC's supposed suitability as a transferrin replacement, viewed in the light most favorable to Janssen, should have precluded summary judgment in Celltrion's favor.

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[6]Janssen agreed during oral argument on Celltrion's summary judgment motion that the court could disregard Field and focus on Keenan because Janssen had not discussed Field in its brief. Appx2238-2240. But the court then went beyond Keenan and purported to review the "combined teachings" of the art, Appx102-103, while ignoring Field, one of the two references cited by Dr. Glacken in ¶257 as demonstrating a POSA's knowledge. That makes consideration of Field appropriate here. *See* Appx68; Appx72.

2. Concentration Ranges

GSK and Life Techs disclose a concentration range for each of their 80-plus ingredients, most partially overlapping the ranges of the hypothetical claim. At the same time, the preferred concentrations for 17 ingredients in GSK and 12 ingredients in Life Techs are completely outside the ranges required by the hypothetical claim. Appx936-937.

Celltrion offered no evidence why it would have been obvious to modify the preferred concentrations of GSK or Life Techs to move them into the ranges of the hypothetical claim. Nor did it offer any evidence—either opinion evidence or testing evidence—that the preferred concentrations of the prior art references were equivalent to the concentration ranges of the hypothetical claim. And it likewise made no effort to demonstrate that, in this experimental art, there was any reason for an artisan ***simultaneously*** to modify the concentrations of 17 (GSK) or 12 (Life Techs) entirely different ingredients—and at the same time to replace two (GSK) or five (Life Techs) still different ingredients—so as to wind up with the exact concentrations and ingredients of the hypothetical claim. Dr. Glacken was instructed by Celltrion that such an analysis was unnecessary and he provided none. Appx1119/pp.226:2-227:4; Appx1368.

The district court agreed that no such analysis was necessary and that the concentration ranges in the hypothetical claim were obvious. Appx71-80. The

court's ruling relied solely on the principle that "partially overlapping concentration ranges establish a prima facie case of obviousness" that "'shifts the burden to the [patentee] to show that his invention would not have been obvious.'" Appx74 (quoting *Peterson*, 315 F.3d at 1329, 1330). That principle is inapplicable here.

First, the concentration range for putrescine hydrochloride in Life Techs does not overlap at all with the concentration range for that ingredient in the hypothetical claim, making the presumption inapplicable for that ingredient.

Second, considering the claim and the references properly, *i.e.*, as a whole, the partially overlapping ranges do not create a presumption of obviousness because there are also two (GSK) or five (Life Techs) ingredient differences between the prior art media and the media of the hypothetical claim. *See Abbott Labs. v. Dey, LP*, 287 F.3d 1097, 1106 (Fed. Cir. 2002) (overlapping ranges do not create *prima facie* obviousness where "other limitations of the claim" are different).

Third, and most fundamentally, the combination of many different concentration ranges, each one broad in itself and in combination almost infinitely broad, gives rise to no presumption at all. The presumption with respect to overlapping ranges arises for "ranges that are not especially broad, [which] invite routine experimentation to discover optimum values, rather than require

nonobvious invention …." *Peterson*, 315 F.3d at 1330 n.1. In that circumstance, the "normal desire of scientists or artisans to improve upon what is already generally known ***provides the motivation*** to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *Id.* at 1330 (emphasis added).

Under *Peterson* and its progeny, this approach should not apply where, as here, the range in the prior art is "so broad as to encompass a very large number of distinct compositions." 315 F.3d at 1330 n.1; *see also Genetics Institute v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011) ("[T]he typical desire of scientists to find an optimum value within a narrow disclosed range, does not apply" where the prior art ranges are "so broad as to encompass a very large number" of possibilities.). This Court recently reaffirmed this principle in *E.I. duPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018).

The district court identified three ways in which a patentee can rebut the presumption of obviousness for overlapping ranges:

> [B]y producing evidence that "[1] the [claimed] range is critical … [or] [2] achieves unexpected results relative to the prior art range," or [3] by "showing that the prior art teaches away from the claimed invention."

Appx74-75 (quoting *Peterson*, 315 F.3d at 1329) (bracketed numbers added). That was error. As this Court recently reemphasized, there are four ways, not three, in which the patentee may rebut that presumption: "***Fourth, we have reasoned that disclosure of very broad ranges may not invite routine optimization***." *duPont*, 904 F.3d at 1006 (emphasis added) (citing *Peterson*, 315 F.3d at 1330 n.1; *Genetics Institute*, 655 F.3d at 1306). In *Genetics Institute*, this Court held that a reference identifying 68,000 protein variants made up of 2,332 amino acids "'disclosed [a] range so broad as to encompass a very large number of possible distinct compositions' thus 'requir[ing] nonobvious invention' …." 655 F.3d at 1306 (quoting *Peterson*, 315 F.3d at 1330 n.1).

Here, as in *Genetics Institute*, the prior art references disclose an extremely broad range, requiring non-obvious invention and making any presumption of obviousness inapplicable. As Dr. Butler explained, "[i]n order to arrive at the concentration ranges of [the hypothetical claim], it would have been necessary to modify each of the concentration ranges [of the prior art]." Appx1052. With a large number of concentrations as possible candidates for modification, and a large range of concentrations for each ingredient, the number of possible combinations is vast. Appx1102/p.118:6-25; Appx1115/pp.212:17-213:2.

The district court said it was not "required" to focus on the preferred concentrations because it could consider all the concentrations taught in the art. Appx72 n.8. But Dr. Glacken made clear that in this art a POSA would go straight to the preferred concentrations and work from there. He testified that "one common way" to look at concentrations was to use the preferred concentrations in the prior art. Appx1115/p.211:1-11. That approach would yield a formula with 17 (GSK) or 12 (Life Techs) concentrations outside of the hypothetical claim and no particular reason to modify any of them.

Alternatively, Dr. Glacken suggested an artisan might study three concentrations in the prior art: high, middle and low. Appx1115/p.211:1-11. Using that approach, and focusing just on the limited universe of ingredients whose preferred concentration is outside the hypothetical claim, an artisan might experiment with three variations of each concentration—the preferred concentration, one higher and one lower. By definition, two of these three concentrations would fall outside the hypothetical claim. To test all three versions of 17 (GSK) or 12 (Life Techs) concentrations, all in combination, would require studying endless unique combinations (anywhere from 3^{12} to 3^{17} different combinations). *See* Appx936. Of those many different combinations, only one combination would result in a formulation with all 17 or 12 concentrations falling within the concentration range of the hypothetical claim. *See id.* The typical

desire of scientists to find an optimum value within a narrow disclosed range does not apply here. *Genetics Institute*, 655 F.3d at 1306.

Finally, even if there were a motivation to make the precise combination of changes in the prior art concentrations so as to bring them within the hypothetical claim, there was no showing of a reasonable likelihood of success. The function of particular ingredients in cell culture media is poorly understood even alone, much less in combination. It is impossible without experimentation to know the effect of changing the concentrations on the combination as a whole. *See* Appx1879-1880; Appx1890; Appx2892. In his experiments demonstrating infringement, Dr. Wurm tested a much simpler problem, the effect of a single change in concentration on the formula as a whole. Even so, he explained, the effect of just one concentration difference on the performance of a complex multi-ingredient cell culture medium is not predictable. It is "always the sum of everything, always." Appx2841/pp.156:21-157:3.

II. THE DISTRICT COURT FURTHER ERRED BY VIEWING THE EVIDENCE IN THE LIGHT MOST FAVORABLE TO CELLTRION

The district court said it viewed the record on summary judgment in the light most favorable to the non-movant. *See, e.g.*, Appx27-28; Appx47 n.3; Appx52; Appx108. In reality, it viewed the evidence in the light most favorable to Celltrion.

A. The District Court Improperly Viewed the Evidence on Teaching Away in the Light Most Favorable to Celltrion

Whether the prior art "teaches away from the claimed invention" is a "question[] of fact." *Meiersonne v. Google, Inc.*, 849 F.3d 1379, 1382 (Fed. Cir. 2017). Yet, the district court made a fact finding on this issue without viewing the evidence in the light most favorable to Janssen.

Dr. Butler—whom the court called an "eminent scientist[]" with "extensive pre-litigation relevant research," Appx2766—concluded that Keenan "teaches away from using FAC as a transferrin replacement" and "dissuade[s]" one of skill from using FAC. Appx1043-1046. Keenan's findings would "discourage[]" a POSA from using FAC as a transferrin replacement, and thus "teach away" from the hypothetical claim. *See Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1381 (Fed. Cir. 2015) ("A reference teaches away from a claimed invention when a person of ordinary skill, 'upon reading the reference, would be discouraged from following the path [that is criticized], or would be led in a direction divergent from th[at] path ….'") (citation omitted).

Without hearing at trial from Dr. Butler, the court decided that it could interpret what Keenan teaches a POSA on its own, as supposedly merely expressing a "prefer[ence]" for other potential transferrin replacements. Appx97-98. Viewing the evidence in the light most favorable to Janssen, this was an issue for trial, not summary judgment.

B. The District Court Improperly Viewed the Copying Evidence in the Light Most Favorable to Celltrion

The district court agreed that a reasonable fact finder could find that HyClone "copied the MET 1.5 formulation," the preferred embodiment of the '083 Patent, "because of [its] novel combination of ingredients and concentrations," Appx112-113. Although the district court purported to review this evidence in the light most favorable to Janssen, it did not do so. Instead, it speculated about evidence that did not exist and downplayed evidence that did. As a result, it erroneously concluded that the question of copying was "close," Appx110, and could be disregarded on summary judgment.

Without any supporting evidence, the court speculated that it would be "unsurprising" if HyClone scientists independently developed their formula because they supposedly had "access to" GSK and Life Techs. Appx110-111. This is baseless; there is no evidence that HyClone knew about GSK or Life Techs. Moreover, the testimony of Celltrion's expert—certainly when viewed most favorably to Janssen—shows that HyClone would never have developed a medium based on those references and instead would have developed a medium based on "classical" media. Meanwhile, the court minimized HyClone's recognition of the value of Janssen's invention and the success of its copy, evidence bearing directly on its motivation for copying. The court described Dr. Whitford—the HyClone scientist who knew Janssen's confidential formula and supervised development of

HyClone's copy—as testifying that the copy was just another cell culture medium that "might be superior to other media for producing certain cell lines, but would not have been considered universally more effective." Appx109. Here's Dr. Whitford's actual testimony: "For a given clone … ***it could have worked better than any other media in the world***." Appx1742/p.109:1-3 (emphasis added).

This combination of speculation and minimization did not excuse the court from hearing live evidence. If HyClone claims to have independently created its medium, or to have based it on GSK or Life Techs, its witnesses should say so in court—where their credibility can be judged.

Copying involves issues of intent, and the summary judgment standard is "particularly rigorous when the disputed issue turns on a question of motive or intent." *Lipsett v. Univ. of Puerto Rico*, 864 F.2d 881, 895 (1st Cir. 1988); *see also KangaROOS U.S.A., Inc. v. Caldor, Inc.*, 778 F.3d 1571 (Fed. Cir. 1985) (same). The crucial question of copying could not be decided without "the benefit of observing [HyClone witnesses'] testimony on direct, as well as cross-examination." *Alza Corp. v. Mylan Labs, Inc.*, 391 F.3d 1365, 1374 (Fed. Cir. 2004).

After wrongly concluding the question of copying was "close," the district court then improperly discounted that evidence for two reasons. First, the court noted that the copyist was HyClone, Celltrion's supplier of cell media, not

Celltrion. Appx114-118. But copying by a major commercial manufacturer of cell culture media in a competitive industry is powerful evidence of nonobviousness, whether the copyist is a defendant or not. *See SynQor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1377 (Fed. Cir. 2013) ("copying by competitors"). The significance of copying does not turn on the identity of the copyist.

Second, the district court stated that Janssen presented no other objective evidence of nonobviousness. Appx118-121. But copying alone is sufficient. *E.g.*, *Akamai Techs. v. Cable & Wireless Internet Servs., Inc.*, 344 F.3d 1186, 1196 (Fed. Cir. 2003) ("substantial evidence relating to secondary considerations" consisting only of copying). Moreover, the copying evidence itself reflects praise for the invention and financial success. HyClone "congratulat[ed]" Janssen for its "successful design," Appx1711-1712, and its copy is itself a "'form of flattering praise for inventive features.'" *WBIP*, 829 F.3d at 1336 (citation omitted). Meanwhile, HyClone's copy is purchased in high volume by Celltrion to support its biosimilar business.

CONCLUSION

This Court should reverse the grant of summary judgment for Celltrion and remand this case with directions to enter partial summary judgment on ensnarement in favor of Janssen. At a minimum, this Court should reverse the grant of summary judgment in view of disputed fact issues.

Respectfully submitted,

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ADDENDUM

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

Janssen Biotech, Inc., Plaintiff,	)	
v.	)	**C.A. No. 17-11008-MLW**
Celltrion Healthcare Co., Ltd. et al Defendant.	)	

JUDGMENT

WOLF, D. J.

In accordance with the Court's Memorandum and Order (Docket No. 393) dated July 30, 2018 allowing the Defendant's Motion for Summary Judgment, it is hereby ordered:

Judgment for the DEFENDANT on all counts.

By the Court,

July 31, 2018
Date

/s/ Christine M. Bono
Deputy Clerk

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

JANSSEN BIOTECH, INC., Plaintiff,	)	
v.	)	C.A. No. 17-11008-MLW
CELLTRION HEALTHCARE CO., LTD., ET AL., Defendants.	)	

AMENDED JUDGMENT

WOLF, D.J.

In accordance with the August 23, 2018 Order allowing defendants' Motion to Amend the Judgment, it is hereby ORDERED:

Judgment for the DEFENDANTS on plaintiff's Counts 1, 2, 3, 4, and 5, plaintiff's counterclaim Counts 1 and 2, and defendants' first counterclaim. Defendants' second counterclaim is DISMISSED without prejudice.

By the Court,

August 23, 2018
Date

/s/ Christine M. Bono
Deputy Clerk

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

JANSSEN BIOTECH, INC., Plaintiff, v. CELLTRION HEALTHCARE CO., LTD., ET AL., Defendants.	)	C.A. No. 17-11008-MLW

MEMORANDUM AND ORDER

WOLF, D.J. July 30, 2018

Table of Contents

I. INTRODUCTION

Plaintiff Janssen Biotech, Inc. ("Janssen") makes Remicade, a biologic medicine whose active ingredient is a monoclonal antibody called infliximab. Defendants Celltrion Healthcare Co. and Celltrion, Inc. (collectively, "Celltrion") and Hospira, Inc. ("Hospira") produce a biosimilar infliximab drug that is sold under the trade names Inflectra and Remsima in the United States and abroad. Janssen now alleges that defendants infringe U.S. Patent No. 7,598,083 (the "'083 patent"), under the doctrine of equivalents, in the process of making their biosimilar products.

Producing the infliximab antibody requires use of a composition called a cell culture medium. The '083 patent claims cell culture media and is titled "Chemically Defined Media Compositions." See '083 patent (Docket No. 227-13). The patent was issued on October 6, 2009, and claims a priority date of October 29, 2004. The invention "provides chemically defined compositions useful in the culture of eukaryotic cells" in bioreactors. Id., col. 4. The cells, in turn, produce biopharmaceuticals. Id. "Chemically defined" media, which are "free of animal-derived components and proteins and contain only known chemical compounds," avoid problems of contamination associated with the use of such components in "conventional" media, which can cause patient infections and disease. Id., col. 1.

Infliximab antibodies are biopharmaceuticals. However, the '083 patent does not mention infliximab and Janssen does not use an embodiment of the claimed invention to produce Remicade.

Initially, Janssen focused on its allegation that the defendants infringed its U.S. Patent No. 6,284,471 (the "'471 patent") covering the infliximab antibody. In 2016, this court invalidated the '471 patent for obviousness-type double patenting. See Janssen Biotech, Inc. v. Celltrion Healthcare Co., Ltd., 211 F. Supp. 3d 364, 366 (D. Mass. 2016). The Federal Circuit, in effect, affirmed that decision when it affirmed the decision of the Patent and Trademark Office ("PTO") that upon reexamination, the '471 patent was unpatentable for obviousness-type double patenting. See In re Janssen Biotech, Inc., 880 F.3d 1315, 1318 (Fed. Cir. 2018); see also Janssen Biotech, Inc. v. Celltrion Healthcare Co., Ltd., 2018 WL 2072723, at *1 (dismissing as moot the appeal of this court's decision invalidating the '471 patent).

The focus of this case then shifted to the '083 patent, which had previously received little attention. Claim 1 of the '083 patent claims a "soluble composition[] suitable for producing a final volume of cell culture media" and lists 61 ingredients for the media and a concentration range for each. The parties agree that only 52 of the 61 ingredients are "required" by the claim because nine of the ingredients recite a concentration range with a low end of zero. In addition, claim 1 is a "comprising" claim,

meaning that an accused medium could include additional unnamed ingredients and still infringe the patent.

Third-party HyClone Laboratories, Inc. ("HyClone") makes the cell culture media that Celltrion uses to produce its infliximab product. These media products are referred to as the Celltrion Production Media and the Celltrion Growth Media (the "accused media" or "accused products"). Janssen alleges that Celltrion infringes claim 1 of the '083 patent by employing HyClone to manufacture the media under Celltrion's direction and control as its agent and by inducing HyClone to infringe the patent.[1] Janssen alleges that Hospira is liable for Celltrion's actions as a joint venturer and induces Celltrion to infringe the patent by, among other things, ordering Inflectra from Celltrion.

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[1] A party is liable for direct infringement under 35 U.S.C. §271(a) when it "[a]cts through an agent (applying traditional agency principles) or [b] contracts with another" to do the infringing act. See Akamai Techs., Inc. v. Limelight Networks, Inc., 797 F.3d 1020, 1022-23 (Fed. Cir. 2015). Induced infringement under §271(b) requires both an affirmative act that encourages infringement and specific intent; that is, "knowledge that the induced acts constitute patent infringement." Global-Tech Appliances, Inc. v. SEB S.A., 563 U.S. 754, 766 (2011). The court has previously denied Celltrion's motion for summary judgment on the issues of direct and indirect infringement. See C.A. No. 15-10698, Docket No. 332, Dec. 22, 2016 Hearing Tr. at 6-7.

Although Janssen originally asserted defendants infringed claim 2 of the '083 patent as well, it withdrew that allegation at the June 12, 2018 hearing on defendants' motion for summary judgment. See June 12, 2018 Tr. at 12-13.

Janssen does not allege literal infringement of the '083 patent. Rather, as indicated earlier, Janssen argues only that Celltrion's accused media infringe claim 1 under the doctrine of equivalents. It is undisputed that the accused media contain all 52 ingredients required by claim 1, as well as additional ingredients. However, several of the claimed ingredients are present in the accused media in amounts that fall outside the literal concentration ranges recited the claim. Janssen argues that the amounts of those ingredients used by Celltrion are not substantially different from the amounts claimed in claim 1 and, therefore, the accused media infringe the patent.

The defendants deny the allegations and have moved for summary judgment of non-infringement on the grounds that Janssen's asserted scope of equivalents would ensnare the prior art. The court heard arguments on the motion for summary judgment on June 12 and 13, 2018, and took it under advisement.

For the reasons explained in this Memorandum, the motion for summary judgment is being allowed. The ensnarement defense prevents the patentee from obtaining under the doctrine of equivalents coverage that could not be lawfully obtained from the PTO by literal claims. In essence, the court finds that no reasonable factfinder could conclude that the hypothetical claims that Janssen relies upon to avoid ensnarement would have been patentable because they were obvious rather than inventive. The

evidence, viewed in a light most favorable to Janssen, is barely sufficient to allow a reasonable factfinder to conclude that HyClone copied Janssen's patented medium. However, the factual dispute concerning copying is immaterial. Undisputed and strong evidence compels the conclusion that a person of ordinary skill in the art (a "POSA") would have had the ability and motivation to combine familiar ingredients from prior art cell culture media compositions in predictable concentrations to create what Janssen claims as its hypothetical invention. Moreover, the POSA would have predicted the combination's successful results. Therefore, ensnarement bars Janssen from prevailing under the doctrine of equivalents.

II. ENSNAREMENT

Ensnarement is a defense to patent infringement that bars a patentee from prevailing on a doctrine of equivalents theory of infringement. Ensnarement is a legal issue for the court to decide either on a pretrial motion for summary judgment or on a motion for judgment as a matter of law after trial. See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1324 (Fed. Cir. 2009) (citing Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 39 n.8 (1997)).

When considering ensnarement on a motion for summary judgment, the traditional summary judgment standard applies. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 426-27 (2007). The

court may grant summary judgment if "the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). A fact is material if it has the potential to "affect the outcome of the suit under the governing law." Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 247-48 (1986). A factual dispute is genuine if "the evidence is such that a reasonable [factfinder] could return a verdict for the nonmoving party." Id. at 248. If material facts underlying the ensnarement defense are genuinely disputed, the court must conduct a bench trial to resolve them. See DePuy, 567 F.3d at 1322, 1324.

The ensnarement defense is "a legal limitation on the doctrine of equivalents," similar to prosecution history estoppel. Id. at 1322. It prevents the patentee from "obtain[ing], under the doctrine of equivalents, coverage which he could not lawfully have obtained from the PTO by literal claims." Wilson Sporting Goods Co. v. David Geoffrey & Assocs., 904 F.2d 677, 684 (Fed. Cir. 1990). The ensnarement defense provides that even if the accused media are found to infringe under the doctrine of equivalents, "there can be no infringement if the asserted scope of equivalency of what is literally claimed would encompass the prior art." Id. at 683. In other words, the patentee cannot assert a right to a monopoly over equivalents that is so broad that such claims, if included in the patent application, would not have been patentable

over prior art. Janssen bears the burden to prove "it is entitled to the range of equivalents which it seeks" and, therefore, must prove its theory of infringement does not ensnare the prior art. Jang v. Bos. Sci. Corp., 872 F.3d 1275, 1287 (Fed. Cir. 2017).

To determine whether Janssen's asserted doctrine of equivalents theory of infringement would ensnare the prior art, the parties correctly agree that the court should conduct a "hypothetical claim" analysis. The hypothetical claim analysis is a two-step process that is often used by courts to determine ensnarement. First, the patentee must "construct a hypothetical claim that literally covers the accused device," which involves expanding the claim limitations to encompass the features of the accused product. Id. at 1285. Second, "prior art introduced by the accused infringer is assessed to determine whether the patentee has carried its burden of persuading the court that the hypothetical claim is patentable over the prior art." Id. To determine whether the hypothetical claims would have been patentable, the court applies traditional anticipation and obviousness analyses. See Wilson, 904 F.2d at 684; Conroy v. Reebok Int'l, Ltd., 14 F.3d 1570, 1577 (Fed. Cir. 1994). In the instant case, Celltrion does not assert that the hypothetical claims would have been anticipated by prior art under 35 U.S.C. §102, but only that they would have been obvious under 35 U.S.C. §103.

The parties agreed to adopt two hypothetical claims that expand the reach of claim 1 to encompass the formulations of the Celltrion Production Media ("CPM") and Celltrion Growth Media ("CGM"). See Jang, 872 F.3d at 1285. The hypothetical claims are in Exhibit 1 to this Memorandum. See Ex. 1 (columns titled "Hypothetical Range (mg) - CGM" and "Hypothetical Range (mg) - CPM"). The hypothetical claims include all 61 ingredients listed in claim 1 of the '083 patent (the 52 required ingredients plus the nine optional ingredients), but with the claimed concentration ranges extended where necessary to match the concentrations used in the Celltrion Production Media and Celltrion Growth Media.

In addition, the parties agreed that two references produced by defendants, which were not considered by the PTO during examination of the '083 patent, constitute the closest prior art for purposes of the patentability analysis. See June 12, 2018 Tr. at 24, 27; Resp. to Celltrion SMF (Docket No. 262-1) ¶¶33-34, 38-39. These references are: (1) International Patent Application No. WO 2004/078955, filed by Glaxo-SmithKline Biologicals S.A. and published September 16, 2004 ("GSK"), see GSK application (Docket No. 227-18); and (2) International Patent Application No. WO 98/15614, filed by Life Technologies, Inc. and published April 16, 1998 ("Life Techs"), see Life Techs application (Docket No. 227-17). Therefore, at trial, Janssen would be required to prove that if it submitted the expanded hypothetical claims to the PTO in

2004, the PTO would have found the claims nonobvious and patentable over the GSK and Life Techs references.

III. OBVIOUSNESS

Obviousness is a statutory bar to patentability. The Patent Act states, in pertinent part:

> A patent for a claimed invention may not be obtained ... if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.

35 U.S.C. §103(a). Therefore, "[t]he test for obviousness is what the combined teachings of the [prior art] references would have suggested to those having ordinary skill in the art." In re Mouttet, 686 F.3d 1322, 1333 (Fed. Cir. 2012) (concluding that invention would have been obvious because a person ordinarily skilled in the art "would . . . have recognized that [one claimed component] could have been combined with [another] to predictably yield [the claimed invention]").

Although obviousness is a question of law, it requires consideration of four factual issues known as the "Graham factors": (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) any relevant secondary considerations, including commercial success, long felt but unsolved needs, failure of others, copying, and unexpected

results. See Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966); see also DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360 (Fed. Cir. 2006). "[T]he strength of each of the Graham factors must be weighed" to determine if the invention would have been obvious. WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1328 (Fed. Cir. 2016); see Graham, 383 U.S. at 36.

In KSR v. Teleflex, the Supreme Court affirmed in 2007 that the Graham factors continue to "define the controlling inquiry" for obviousness. 550 U.S. at 399. In KSR the Court described the "expansive and flexible" nature of the inquiry and how it applies in different circumstances. Id. at 415. It explained that "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." Id. at 416. Accordingly, "when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result" to avoid being held to have been obvious. Id. The Court further stated that "when a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability." Id. For example, as the Supreme Court wrote in

Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 335 (1945), "[r]eading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening of a jigsaw puzzle. It is not invention." As the PTO has written, "[e]xemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results." U.S. Patent & Trademark Office, Manual of Patent Examination Procedures §2143 (9th ed. 2018) ("MPEP").

However, "[a] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR, 550 U.S. at 418. Therefore:

> [a]lthough common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

Id. Where, as in the instant case, "all claim limitations are found in a number of prior art references, the factfinder must determine what the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references." DyStar, 464 F.3d at 1363

(quotations omitted). If a POSA would "have had reason to combine the teachings of the prior art references to achieve the claimed invention, and . . . a reasonable expectation of success from doing so," the invention would have been obvious. In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1068-69 (Fed. Cir. 2012).

In KSR, the Supreme Court rejected a "rigid" application of the teaching, suggestion, or motivation test ("TSM test") under which the Federal Circuit had required that an express motivation to combine known elements be found in the prior art in order to prove the combination would have been obvious. 550 U.S. at 419-20. The Court held that a determination of obviousness does not require "precise teachings directed to the specific subject matter of the challenged claim." Id. at 418. Rather, the court may consider "the inferences and creative steps that a person of ordinary skill in the art would employ." Id. It may, therefore:

> look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.

Id. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." Id. at 420.

In KSR, the Supreme Court applied this flexible analysis to the invention at issue, which was an adjustable automobile pedal with an electronic sensor, mounted on the pedal's pivot point, that transmitted the pedal's position to a computer that controlled the throttle. The Court found that it would have been obvious to a POSA to combine the prior art "Asano" mechanical adjustable pedal with a pivot-mounted electronic sensor suggested in other references, because "[the] marketplace . . . created a strong incentive to convert mechanical pedals to electronic pedals, and the prior art taught a number of methods for achieving this advance." Id. at 424. It held that the Federal Circuit "considered the issue too narrowly by, in effect, asking whether a pedal designer writing on a blank slate would have chosen both Asano and a modular sensor similar to the ones used in the [prior art pedal]." Id. The Court held that "[t]he proper question" was "whether a pedal designer of ordinary skill, facing the wide range of needs created by developments in the field of endeavor, would have seen a benefit to upgrading Asano with a sensor." Id. In addition, the patentee failed to demonstrate that the prior art taught away from using or upgrading the Asano pedal, and provided no evidence of secondary considerations of nonobviousness. See id. at 425-26. Therefore, the Court held the claimed invention would have been obvious. See id. at 426-27.

Defendants argue that the hypothetical media are comparable to the invention in KSR, because they are combinations of known ingredients in predictable concentration ranges that yield only predictable results and, therefore, the formulations would have been obvious. Janssen, however, contends that the court must apply two alternative frameworks for deciding the issue of obviousness - either the "obvious to try" framework or the "lead compound" framework. In particular, it asserts that under the "obvious to try" framework, for the compositions to have been obvious, the inventors must have selected them from a small number of predictable solutions to a known problem. In addition, Janssen argues that under the "lead compound" framework, for GSK or Life Techs to render the hypothetical claims obvious, a POSA must have necessarily used the media disclosed in those references as a "starting point" in the development process. For the reasons explained below, the court finds that it is not necessary or appropriate to apply either of Janssen's proposed frameworks to determine whether the hypothetically claimed composition of known ingredients would have been obvious to a POSA.

The "obvious to try" framework is described in KSR, although it was not applied in that case. In KSR, the Supreme Court held that the Federal Circuit made several analytical errors, including but not limited to its conclusion that a claim "cannot be proved obvious by merely showing that the combination of elements was

'obvious to try.'" 550 U.S. at 421. The Court explained that in certain situations, the fact that a combination was "obvious to try" may justify a finding of obviousness:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

Id. (emphases added). In other words, when there are a "easily traversed, small and finite number" of options for solving a known problem, such that only a limited amount of testing would be required to lead a POSA to the successful combination, this "might support an inference of obviousness." Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008).

In other circumstances, an inference of obviousness cannot be drawn from what would have been "obvious to try." See Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720, 725 (Fed. Cir. 1990) ("[W]e have consistently held that 'obvious to try' is not to be equated with obviousness under 35 U.S.C. 103."). If, in a particular field:

> what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful ... [or] what was "obvious to try" was to explore a new

> technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it[,]

the fact that a claimed invention was "obvious to try" will not necessarily lead to a conclusion of obviousness. In re O'Farrell, 853 F.2d at 903; see also In re Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009) ("[W]here a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness."). For a solution that was "obvious to try" to have been legally obvious, the experiments necessary to arrive at the claimed invention must not have been "equivalent to the trial and error procedures often employed to discover a new [composition] where the prior art gave no motivation or suggestion to make the new [composition] nor a reasonable expectation of success." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1365 (Fed. Cir. 2007)(emphasis in original). Therefore, for an obvious-to-try solution to be obvious under §103, the POSA would have to have been motivated to test the known options with a reasonable expectation of succeeding with at least one of them. Id. at 1366 (finding claimed salt form of pharmaceutical composition was obvious because prior art motivated POSA to test "a small[] group" of options, including the claimed salt form, with a reasonable expectation of success).

Janssen argues that the court must apply the "obvious to try" framework and find the hypothetical claims nonobvious because there is an "infinite" number of different combinations of ingredients and concentrations that can be used in cell culture media, all of which would have been "obvious to try." Therefore, it contends that trying to choose the precise combination that would result in the hypothetical media would be like throwing darts at a board filled with numerous combinatorial possibilities. See In re Kubin, 561 F.3d at 1359. However, the Court in KSR merely held that it was "error" for the Federal Circuit to "conclude . . . that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.'" 550 U.S. at 421 (emphasis added). It did not hold that the framework must be applied to find an invention obvious, particularly where, as explained below concerning the instant case, experimentation would not have been needed for a POSA to have had a reasonable expectation that the claimed combination of ingredients would accomplish the inventors' goal of creating an animal-component free cell culture media capable of growing cells in volumes and conditions suitable for biopharmaceutical production. See '083 patent (Docket No. 227-13) at col.1-2, 4. If a POSA would have predicted the results of the "mere substitution of one element for another known in the field" or the "use of prior art elements according to their established functions," without having to "try"

numerous options, the combination may be obvious even if the number of options was not small. KSR, 550 U.S. at 416-17, 421.

Janssen also argues that on the facts of this case, the court must use a "lead compound" analysis, meaning that defendants must show, as a threshold matter, that a POSA would have selected GSK or Life Techs as a "lead compound" - meaning a preferable starting point - in order for the claimed media to be held obvious, even though the instant case involves a composition rather than a compound. However, in the circumstances of this case, the lead compound analysis is neither required nor the most appropriate framework to apply.

In cases involving patentability of new chemical compounds, obviousness "generally turns on the structural similarities and differences between the claimed compound and the prior art compounds." Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1285-86, 1291 (Fed. Cir. 2012); see also Eisai Co. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1356-57 (Fed. Cir. 2008). "Whether a new chemical compound would have been prima facie obvious over particular prior art compounds ordinarily follows a two-part inquiry." Otsuka, 678 F.3d at 1291.

> First, the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts. . . . The second inquiry in the analysis is whether the prior art would have supplied one of ordinary skill in the art with a reason or

> motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success.

Id. at 1291-92.

"Obviousness based on structural similarity" between a prior art and new compound can, therefore, be proved by "identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound." Eisai, 533 F.3d at 1357. The Federal Circuit has held that the "lead compound" is one a POSA would have favored over other compounds. See, e.g., Otsuka, 678 F.3d at 1291-92 (requiring "a reason to select [the proposed lead compound] from the panoply of known compounds in the prior art" as a one that is "most promising to modify in order to improve upon its activity and obtain a compound with better activity"). The motivation to select and modify the lead compound need not be explicit in prior art because "close or established structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007). Therefore, "it is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship . . . to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old." Eisai, 533

F.3d at 1357 (quotations omitted). "Once such a prima facie case [of obviousness] is established, it falls to the applicant or patentee to rebut it, for example with a showing that the claimed compound has unexpected properties." Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301 (Fed. Cir. 2007).

As indicated earlier, the '083 patent claims a chemical composition, not a compound. Janssen has identified only one case in which the Federal Circuit applied the lead compound analysis to a mixture, such as the composition in the instant case, see Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1352, 1361-62 (Fed. Cir. 2011). However, the court in Unigene limited the "lead compound" test to factual circumstances not present here. In addition, in Unigene, the Federal Circuit stated that "[w]here the patent at issue claims a chemical compound, a lead compound is often used" in analyzing obviousness. Id. at 1361 (emphasis added). This suggests that the lead compound framework is not required or always most appropriate even in cases involving a compound. In any event, this court finds that the lead compound framework is neither required nor the most appropriate test in the circumstances of this case.

In Unigene, the court considered whether a claimed formulation was obvious over a "previously FDA-approved formulation," or "reference composition," that it was designed to imitate, called Miacalcin. Id. The Federal Circuit affirmed the

district court's use of the lead compound analysis, comparing its use of Miacalcin as a "reference composition" to the use of a "lead compound." It stated:

> In the context of a composition or formulation patent where the patented formulation was made to mimic a previously FDA-approved formulation, the functional and pharmaceutical properties of the "lead compound" can be more relevant than the actual chemical structure (though not always mutually exclusive). Thus, the term "reference composition" is more appropriate than "lead compound" when considering obviousness for a chemical composition that the infringer [and inventor] deliberately imitate[d].

Id. (emphasis added). Therefore, Unigene held that the lead compound framework for analysis may be appropriate in analyzing formulations when there is a clear reference formulation that the inventor sought to imitate, not that it must be applied to all chemical compositions in fields where development proceeds from a particular starting point. In the instant case, the claimed composition was not "made to mimic a previously FDA-approved formulation." Id. at 1362. It was designed to provide a range of media compositions that could effectively grow cells and produce antibodies for biopharmaceutical production, among other things, without the need for animal components. See '083 patent (Docket No. 227-13) at col.1-2, 4.

After Unigene, the Federal Circuit clarified that in cases involving compositions, rather than compounds, "[n]othing in the statute or our case law requires [a challenger] to prove

obviousness by starting with a prior art commercial embodiment and then providing motivation to alter that commercial embodiment." Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 737 (Fed. Cir. 2013); accord Ex Parte Abdul Gaffar, 2015 WL 7720188, at *3 (P.T.A.B. June 13, 2016) ("There is no requirement . . . that the obviousness analysis for a composition or formulation claim must [] be based on a motivation to modify a particular reference composition."); Auxilium Pharms., Inc. v. Watson Labs., Inc., 2014 WL 9859224, at *13 (D.N.J. 2014) (rejecting argument that "the obviousness inquiry in this [pharmaceutical composition] case should begin with the identification of a 'reference composition' (or commercial embodiment) that a POSA would have used as a starting point during the relevant time period").

Janssen also argues that the court must apply the "lead compound" analysis because of the Federal Circuit's recent decision in UCB Inc. v. Accord Healthcare, Inc., 890 F.3d 1313 (Fed. Cir. 2018). However, UCB does not control the instant case either.

The patent in UCB claimed a chemical compound that had been purified from a "racemic mixture," not a composition.[2] Id. at 1318.

[2] A racemic mixture is a 50-50 mixture of two "compounds that have the same chemical structure - i.e., the same atoms are connected to each other in the same way - but differ in orientation in three-dimensional space," meaning they are mirror-images of each other.

The inventors had discovered that one of the compounds in the racemic mixture, when isolated from the mixture, was "unexpectedly more potent" than the racemic mixture for treating epilepsy. Id. Therefore, the court found the purified compound inventive over a reference disclosing the racemic mixture, which "d[id] not explicitly disclose the [purified compound] or its characteristics." Id. at 1323. In other words, the inventors discovered an unexpected property of a known compound when it was isolated from a known mixture. The invention was not, like the composition in this case, a combination of ingredients with known properties.

The district court agreed with the patentee that it "must apply a 'lead compound' analysis . . . because the claims at issue disclose[d] a chemical compound," even though the claimed compound "can be derived from a racemic mixture." UCB, Inc. v. Accord Healthcare, Inc., 201 F. Supp. 3d 491, 541 (D. Del. 2016), aff'd, 890 F.3d 1313 (emphasis added). The Federal Circuit affirmed the district court's decision, holding that it did not err by applying the lead compound analysis. See UCB, 890 F.3d at 1328 ("Appellants

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Id. at 1318. "Although [the two mirror-image compounds] often have identical physical properties, such as density and boiling point, they can exhibit different pharmacological properties in the human body." Sumitomo Dainippon Pharma Co. v. Emcure Pharms. Ltd., 887 F.3d 1153, 1155 (Fed. Cir. 2018).

argue that the district court erred by using a lead compound analysis because this case merely involves purification (not structural modification) of a known compound. We disagree."). However, the Federal Circuit also held that while it was permissible to apply the lead compound test in the circumstances of UCB, the district court was not required to do so. See id. at 1329 ("Appellants argue that because Aventis did not apply a lead compound analysis, no such analysis is required in this case. We agree.").

The Federal Circuit explained that "[a] lead compound analysis is not required in analyzing obviousness of a chemical compound when, in the inventing process, there was no lead compound." Id. Janssen misinterprets this statement as requiring application of the lead compound analysis whenever there is a particular starting point used "in the inventing process." Id. Janssen then argues that the lead compound analysis is required here because the lead inventor of the '083 patent, David Epstein, testified that he started with a classic basal medium called DMEM/F-12. See Epstein Dep. (Docket No. 262-19) at 26-30, 211-12. Janssen also cites the testimony of defense expert Dr. Michael Glacken, who opined that a POSA developing a new cell culture medium would "typically" start with a "basal medium" such as DMEM/F-12. See Dr. Glacken Reply Report (Docket No. 262-17) ¶17. Therefore, according to Janssen, the lead compound analysis is

required here, and the court must adopt DMEM/F-12, the starting point for developing the '083 medium, as the lead composition, rather than GSK or Life Techs.[3] Janssen asserts that under its theory of the case, the hypothetical claimed compositions would not have been obvious because a POSA would not have been motivated to make the numerous modifications to DMEM/F-12 or another basal medium that would be necessary to arrive at the claimed media. See Otsuka, 678 F.3d at 1292.

However, the Federal Circuit's statement that "[a] lead compound analysis is not required in analyzing obviousness of a chemical compound when, in the inventing process, there was no lead compound" does not mean that the lead compound analysis is required whenever evidence shows an inventor or POSA would begin development with a particular composition or product. UCB, 890 F.3d at 1329. As indicated earlier, in UCB, the district court

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[3] Considering the evidence in the light most favorable to Janssen, for the purposes of this analysis, the court assumes that the GSK and Life Techs media are not "basal" media in the sense contemplated by Drs. Epstein and Glacken. However, the parties' experts and the references themselves suggest that the media are in fact considered "basal media." See Reply to SMF (Docket No. 315) ¶15 ("The medium in Table 1 of Life Techs is an example of a 'basal medium' to which the Life Tech[s] additives can be added . . . ."); Life Techs application (Docket No. 227-17) at 17 (Table 1 listing "basal medium component[s]"); Dr. Glacken Report (Docket No. 221-4) ¶252 (describing GSK as disclosing "a basal cell culture medium"). This factual issue is not material because, as previously explained, the lead compound analysis is not required.

applied the lead compound analysis because the claims were directed to a chemical compound, not because the typical "inventing process" began with a "starting point." See UCB, 201 F. Supp. 3d at 541. In addition, choosing an obviousness framework based on the path the inventors took would be inconsistent with the axiom that a POSA's motivations may be different from the inventors'. See Alcon Research, Ltd. v. Apotex Inc., 687 F.3d 1362, 1369 (Fed. Cir. 2012) ("We have repeatedly held that the motivation to modify a prior art reference to arrive at the claimed invention need not be the same motivation that the patentee had."); cf. KSR, 550 U.S. at 419 ("In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim."). As the court reiterated in UCB, an obviousness challenge "may be based on the closest prior art, which may not have been a lead compound that the inventor had in mind." 890 F.3d at 1329. Therefore, contrary to Janssen's contention, UCB does not require that the court apply the lead compound analysis to the composition claimed here.

Indeed, requiring application of the lead compound analysis here would be inconsistent with the Supreme Court's admonition that obviousness is a "flexible" inquiry based on the facts of the case, not a framework of "rigid rule[s]." See KSR, 550 U.S. at 415, 419 ("Helpful insights, however, need not become rigid and

mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents. . . . [W]hen a court transforms the general principle into a rigid rule that limits the obviousness inquiry, as the Court of Appeals did here, it errs."); id. 421 ("Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it."). The Federal Circuit has also cautioned that "every case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts," and that "undue dependence on mechanical application of a few maxims of law . . . that have no bearing on the facts certainly invites error as decisions on obviousness must be narrowly tailored to the facts of each individual case." Pfizer, 480 F.3d at 1366 (quotations and citations omitted). Therefore, the court finds that it is not required to apply the lead compound analysis, and its requirement of motivation to select a particular prior art compound that was a preferable starting point compared with other compounds in the art, in this case, which involves mixtures of known ingredients, such as the claimed compositions.[4]

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[4] Even if the court applied the lead compound analysis, it would conclude that the GSK or Life Techs media would have been more suitable lead compositions than DMEM/F-12 as argued by Janssen. Choice of a lead compound, or in this case a lead composition, is "guided by evidence of the [composition]'s pertinent properties." Otsuka, 678 F.3d at 1292. As explained below, a POSA would have

Instead, it is most appropriate to analyze the obviousness of the hypothetical media under the principles applicable to combinations of known elements, which were applied in KSR. As KSR explained, "[w]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one

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had reason to select the GSK or Life Techs media compositions for further development, given that the GSK and Life Techs media already demonstrated the properties that the inventors sought to achieve with their invention: both were existing serum-free media capable of growing animal cells in culture with reduced contamination. See GSK application (Docket No. 227-18) at 3, 21; Life Techs application (Docket No. 227-17) at 2, 6-7. In contrast, DMEM/F-12 by itself would not work for the inventors' purposes - growing animal cells - unless and until additional ingredients, or serum, were added to it. See Dr. Butler Report (Docket No. 227-7) ¶¶13-14; Dr. Glacken Report (Docket No. 227-5) ¶88. Therefore, a POSA would have had a reason to select GSK or Life Techs media over DMEM/F-12 as the lead composition.

Even if the GSK and Life Techs media were not "basal" media, Dr. Glacken explained that "based on the cell line [he or she was] using," a POSA would be reasonable to choose a "combination" medium to start with that gives "a broader spectrum of ingredients Docket No. 262-6 (Janssen Ex. 4) (Glacken Dep.) at 79. If a POSA "[has] a particular cell line" and "see[s] a reference that . . . makes some advance," a POSA might start with that medium (as opposed to a basal medium) and then "mix and match based on that." Id. at 80-81. Dr. Butler's opinion that the GSK and Life Techs media had no "special significance," Dr. Butler Report (Docket No. 262-5), ¶¶95, 131, does not justify the conclusion that a POSA would have lacked a reason to start with them. Compare, e.g., Takeda, 492 F. 3d at 1359 (holding that that "rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation," and the proposed lead compound "exhibited negative properties," such as toxicity, "that would have directed [a POSA] away from that compound").

element for another known in the field, the combination must do more than yield a predictable result." 550 U.S. at 416. Accordingly, "[i]f a person of ordinary skill can implement a predictable variation [of a prior art reference], §103 likely bars its patentability." Id. As the Federal Circuit subsequently stated, when the "claimed elements are present in the prior art," the question becomes "(1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition . . . and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." PAR Pharm., Inc. v. TWI Pharm., Inc., 773 F.3d 1186, 1196-97 (Fed. Cir. 2014).[5] Applying these principles, "where all of the

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[5] In the MPEP §2143, titled "Examples of Basic Requirements of a Prima Facie Case of Obviousness," the PTO explains the findings necessary to conclude an invention would have been obvious based on this rationale (as well as other rationales):

> To reject a claim based on this rationale [that the claim substitutes one known element for another in a way that yields no more than predictable results], Office personnel must resolve the Graham factual inquiries. Then, Office personnel must articulate the following:
>
> (1) a finding that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with other components;

limitations of the patent were present in the [pertinent] prior art references, and the invention was addressed to a known problem, KSR compels the grant of summary judgment of obviousness." Wyers v. Master Lock Co., 616 F.3d 1231, 1240 (Fed. Cir. 2010) (quotations omitted).

IV. ANALYSIS

The court must determine whether any material facts are genuinely in dispute and, if not, whether Janssen has proven that the hypothetical claims would have patentable as nonobvious over the prior art proffered by defendants. See Jang, 872 F.3d at 1285. The Graham factors continue to control the obviousness inquiry. See KSR, 550 U.S. at 399. Accordingly, the court analyzes each of the Graham factors in turn below. Viewing the evidence in the light most favorable to Janssen, the court finds that there are no material facts in genuine dispute, and Janssen has not proven that the hypothetical claims would have been patentable over GSK and

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(2) a finding that the substituted components and their functions were known in the art;

(3) a finding that one of ordinary skill in the art could have substituted one known element for another, and the results of the substitution would have been predictable; and

(4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

Life Techs. Therefore, the defendants are entitled to summary judgment of noninfringement because the asserted scope of equivalents would have been obvious.

A. Level of Ordinary Skill in the Art

Obviousness must be analyzed from the perspective of the hypothetical "person having ordinary skill in the art to which the invention pertains" as of the patent's effective filing date. 35 U.S.C. §103; see In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998). The parties agree that the '083 patent's priority date is October 29, 2004. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶1, 33; '083 patent (Docket No. 227-13) at 1; Provisional application no. 60/623,718 (Docket No. 227-14). Therefore, the court must determine the level of ordinary skill in the art as of October 29, 2004. See Graham, 383 U.S. at 17.

It is undisputed that, as Janssen's and defendants' experts agree, "the relevant 'art' to which the '083 patent is directed is cell culture media compositions." Dr. Glacken Report (Docket No. 227-5) ¶65; see also Dr. Butler Report (Docket No. 262-5) ¶¶33-34. In addition, there is no dispute between the parties concerning the level of education and experience a POSA would have with respect to cell culture media compositions. A POSA in this field would have either (a) a doctorate in biochemistry, molecular biology, or a related field plus one to two years of direct experience with media formulation development, or (b) a bachelor's

or master's degree in one of those fields with two to three years of direct experience with media formulation development. See Dr. Glacken Report (Docket No. 227-5) ¶65; Dr. Butler Report (Docket No. 262-5) ¶¶33-34.

B. The Scope and Content of Prior Art

The second Graham factor the court must analyze is the scope and content of the prior art. As explained earlier, "the test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art" at the time of the invention. In re Young, 927 F.2d 588, 591 (Fed. Cir. 1991). The court must "take[] into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and . . . not . . . knowledge gleaned only from applicant's disclosure such as a prior patent application." Application of McLaughlin, 443 F.2d 1392, 1313-14 (Fed. Cir. 1971). Therefore, the court must "cast the mind back to the time the invention was made," in this case October 2004, "to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983). "Section 103 requires [the court] to presume full knowledge by the inventor of the prior art in the field of his endeavor." Application of Winslow, 365 F.2d 1017, 1020 (C.C.P.A. 1966). "The POSA is "picture[d] . . . as working in his

shop with the prior art references – which he is presumed to know – hanging on the walls around him." Id.

Here, the material facts concerning the scope and content of prior art are not genuinely disputed. The parties agree on the state of the art of cell culture media compositions and development in 2004, as well as the problems facing POSAs at the time.

Scientists began using cell culture media to grow cells in the 1950s, starting with the work of Harry Eagle. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶21-24; Dr. Glacken Report (Docket No. 227-5) ¶¶70-81, 99-103; Dr. Frohlich Report (Docket No. 232-3) ¶¶65-71; Dr. Butler Report (Docket No. 227-7) ¶¶12-17. In 1955, Eagle identified a mixture of specific nutrients that would support basic cell growth - 13 amino acids, 8 vitamins, 6 salts, and glucose - when supplemented with animal serum. See Celltrion SMF at ¶24. Based on his findings, Eagle published a classic cell culture medium known as "minimal essential medium" ("MEM") that is still sold today. Id. ¶24.

Early cells grown in liquid in a laboratory were grown in serum (blood extracts) from animals that provided those necessary nutrients identified by Eagle. However, due to the unknown contaminants in serum, there was the potential for transmission of dangerous diseases from the animals. As the use of cultured cells became more diverse with the advancement of science, demand for greater numbers of the cells grew, as did demand for more cost-

effective, reproducible, and safe methods for growing cells in culture. The Life Techs application stated that "serum and/or animal extracts are commonly used as relatively low-cost supplements to provide an optimal culture medium for the cultivation of animal cells," but "the use of serum or animal extracts in tissue culture applications has several drawbacks." Life Techs application (Docket No. 227-17) at 6-7. For example, "[t]he chemical composition of these supplements may vary between lots, even from a single manufacturer," and "[t]he supplements of animal or human origin may also be contaminated with infectious agents." Id.

In response to this demand, cell culture scientists began "mov[ing] away from animal-derived components, including serum, in cell culture media for biopharmaceutical production." Dr. Butler Report (Docket No. 227-7) ¶15. "To overcome these drawbacks of the use of serum or animal extracts," researchers developed "a number of serum-free media" formulations. Life Techs application (Docket No. 227-17) at 7. "Since the components (and concentrations thereof) in such culture media [were] precisely known, these media [were] generally referred to as 'defined culture media' and often as 'serum-free media' or 'SFM.' A number of SFM formulations [were] commercially available . . . ." Id. It is undisputed that by 2004, all of the ingredients in the claimed media, and by extension in the hypothetical media, were individually known in the art and

already used in cell culture media. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶30, 32.

As noted earlier, the defendants mainly rely on the GSK and Life Techs references, which are prior art to the '083 patent, to argue that Janssen's hypothetical media would have been obvious. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶33, 38. A POSA is presumed to know the teachings of those references, including the fact that the media they disclosed were serum-free formulations capable of growing animal cells in culture. See In re Rouffet, 149 F.3d at 1357. The GSK and Life Techs applications each contain all of the ingredients required by the hypothetical claims except for two to five ingredients that supply trace elements, such as iron and vanadium, to the cells in concentration ranges that overlap with the claimed ranges.

The GSK reference is an international patent application titled "Animal-Free Cell Culture Method." GSK application (Docket No. 227-18) at 3. The abstract describes GSK's invention as a serum-free medium with potential for growing different cell lines:

> In particular the invention concerns a cell culture medium which comprises at least one, more preferably several, exogenous animal-free growth factors. Such a medium is particularly adapted for culturing animal, such as mammalian, or preferably human diploid anchorage-dependent cells, e.g. with equivalent performance to that of a basal medium for the cell type supplemented with an appropriate serum.

Id. The invention was designed to culture "preferably eukaryotic cells." Id. at 21. This is the same "Field of the Invention" described in the '083 patent. See '083 patent (Docket No. 227-13) at col.1 ("The present invention relates to chemically defined media compositions for the culture of eukaryotic cells."); see also Resp. to Celltrion SMF (Docket No. 262-1) ¶3.

Table 3 of the GSK application is titled "Medium free from components of animal origin." GSK application (Docket No. 227-18) at 23. Table 3 discloses a cell culture medium composition in the form of a list of 96 ingredients for use in a cell culture medium ("the GSK medium"). It states that: "[a]n exemplary advantageous fresh culture medium comprises all or most of the common ingredients listed in Table 3." Id.; see Reply to Celltrion SMF (Docket No. 262-1) ¶35. The medium in Table 3 contains 50 of the 52 ingredients required by Janssen's hypothetical claims, as well other ingredients. See Ex. 1 (rows highlighted in blue are two required claimed ingredients not found in GSK); see also Resp. to Celltrion SMF (Docket No. 262-1) ¶35. In addition, the patent application states that Table 3 is only "an example of a basic composition" of "an animal-free medium" with "a source of trace elements, amino acids, vitamins" and other active ingredients that is "suitable for the cultivation of animal, such as mammalian...cells." GSK application (Docket No. 227-18) at 22 (emphasis added).

Table 3 also has columns that disclose different "Concentration ranges," "Preferred concentration ranges," and a "Preferred concentration" for each ingredient. See GSK application (Docket No. 227-18) at 23; Resp. to Janssen SMF (Docket No. 315) ¶24. In addition, for the 50 ingredients required by the hypothetical media that are disclosed in GSK, all of the concentration ranges of the hypothetical claims overlap at least partially with the "Concentration ranges" listed in GSK's Table 3. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶55-56.

The Life Techs reference is another international patent application titled "Animal Cell Culture Media Comprising Plant-Derived Nutrients." Life Techs application (Docket No. 227-17) at 2. The abstract explains that "[t]he present invention provides serum-free cell culture media formulations which are capable of supporting the in vitro cultivation of animal cells." Id. The specification discusses how "a number of serum-free media have been developed" to "overcome the[] drawbacks of the use of serum or animal extracts." Id. at 6-7; see Resp. to Celltrion SMF (Docket No. 262-1) ¶40.

Table 1 in Life Techs is titled "Animal cell culture basal medium component concentrations." Life Techs application (Docket No. 227-17) at 17. In Table 1, it provides an example of a "basal medium" to which other ingredients can be added. See id.; Reply to Janssen SMF (Docket No. 315) ¶15. Table 1 lists 88 ingredients for

use in a cell culture medium (the "Life Techs medium"). See Life Techs application (Docket No. 227-17) at 17; Reply to Janssen SMF (Docket No. 315) ¶29. Table 1 contains 47 of the 52 ingredients required by the hypothetical media, as well as other ingredients. See Reply to Janssen SMF (Docket No. 315) ¶30; see also Exhibit 2 attached to this Memorandum (comparing hypothetical claims to Life Techs Table 1; rows highlighted in blue are ingredients required by the claims that are not found in Life Techs). The application states that "trace elements which may be used in the media of the present invention include ions of . . . manganese . . . selenium . . . iron . . . [and] tin," among others, and that "ferric citrate chelate or ferrous sulfate can be used . . . as a substitute for transferrin," which is a source of chelated iron in serum-containing media. Life Techs application (Docket No. 227-17) at 12. Defendants' expert Dr. Glacken concludes, and Janssen's expert Dr. Michael Butler does not dispute, that "the specifically recited salts are [therefore] merely examples of the salt forms that can deliver these trace element ions to the cell culture medium." Glacken Report (Docket No. 227-5) ¶241; see also Dr. Butler Report (Docket No. 262-5) ¶107 (agreeing that the Life Techs application "sets forth only one example of 'trace element salts' that 'may be used in the media of the present invention,'" while noting that "it says nothing further about any other salt forms").

Table 1 of Life Techs also discloses concentration ranges for each ingredient ("Component Ranges (mg/L)"), and "A Preferred Embodiment" and a "Most Preferred Embodiment," which are precise concentrations as opposed to ranges. Reply to Janssen SMF (Docket No. 315) ¶29; Life Techs application (Docket No. 227-17) at 17. It is undisputed that for the 47 ingredients required by the hypothetical claims that are disclosed in Life Techs, Life Techs discloses concentration ranges that overlap at least partially with the claimed ranges for all but one required ingredient in Janssen's hypothetical claim, putrescine•2HCl. See Resp. to Celltrion SMF (Docket No. 262-1) ¶59; see also Ex. 2 at 4 (comparing hypothetical claims to Life Techs medium).

In summary, the GSK medium combined 50 of 52 ingredients required by the hypothetical claims, and for those 50 shared ingredients, the concentration ranges disclosed in GSK partially overlap with the concentration ranges in the hypothetical claims. Similarly, the Life Techs medium combined 47 of 52 ingredients required by the hypothetical claims, and for those 47 shared ingredients, 46 have partially overlapping concentration ranges. When asked what accounts for the large commonality of ingredients between Janssen's hypothetical and GSK (and Life Techs) media formulations (50 of 52 required ingredients are in GSK and 47 of 52 required ingredients are in Life Techs), Dr. Butler explained that there was a "convergence of opinion" in the field about "the

range of components" needed to grow cells. Resp. to Celltrion SMF (Docket No. 262-1) ¶36; Butler Dep. (Docket No. 227-16) at 273-75. Further, Dr. Butler testified that there were "plateau[s]" of "interchangeable" concentration ranges for each ingredient and that the claimed ranges were not "precise" or "critical." Jan. 30, 2018 Tr. at 44-45, 82-83; Resp. to Celltrion SMF (Docket No. 262-1) ¶¶12-13.

C. Differences Between the Hypothetical Claims and Prior Art

The third Graham factor the court must analyze is the differences between the hypothetical claims and the prior art. See Graham, 383 U.S. at 17. Janssen admits that GSK and Life Techs are the closest prior art to the claimed invention. See Opp. (Docket No. 262) at 7; June 12, 2018 Tr. at 24; Resp. to Celltrion SMF (Docket No. 262-1) ¶¶33, 38.

However, Janssen argues it is impermissible hindsight for the court to focus on the differences between GSK or Life Techs and the hypothetical media because there is no evidence a POSA would have started the development process with GSK or Life Techs, which in Dr. Butler's opinion had no "special significance." Dr. Butler Report (Docket No. 262-5) ¶¶95, 131. However, as explained earlier, unlike in the case of a chemical compound, "[t]here is no requirement . . . that the obviousness analysis for a composition or formulation claim must [] be based on a motivation to modify a particular reference composition." Ex Parte Abdul Gaffar, 2015 WL

7720188, at *3. In addition, §103 expressly focuses the court on "the differences between the claimed invention and the prior art." 35 U.S.C. §103. As the Supreme Court explained in KSR, "[t]he proper question" is not "whether a [POSA] writing on a blank slate" would necessarily have chosen GSK and Life Techs over another medium for further development, but whether he or she "would have seen a benefit" to modifying the teachings of GSK or Life Techs to achieve the claimed compositions. 550 U.S. at 424.

Consistent with the Supreme Court's analysis in KSR, it is not impermissible use of hindsight to analyze the differences between the claimed composition and a composition in the prior art that was directed to the same problem. To determine whether a patented combination is obvious, the court must consider "analogous" art, defined as art that is either (1) "from the same field of endeavor, regardless of the problem addressed," or (2) nevertheless "reasonably pertinent to the particular problem with which the inventor is involved." Sci. Plastic Prods., Inc. v. Biotage AB, 766 F.3d 1355, 1359 (Fed. Cir. 2014); see also In re Ethicon, 844 F.3d 1344, 1349 (Fed. Cir. 2017) (considering references that were "reasonably pertinent to the particular problem with which the inventor [was] involved" and affirming finding that a POSA "would have combined [their] teachings"). In this case, it is undisputed that the GSK and Life Techs references were "from the same field of endeavor" in which the inventors of

the '083 patent were working - the field of cell culture media development. See Sci. Plastic Prods., 766 F.3d at 1359. Therefore, the court may consider these analogous references, regardless of whether the inventors all sought to solve the same problem.

Moreover, the GSK and Life Techs references are "reasonably pertinent" to the problem the inventors set out to solve. See id. A reference is "reasonably pertinent" if it "logically would have commended itself to an inventor's attention in considering [the] problem." Id. (quotations omitted). "If a reference disclosure has the same purpose as the claimed invention, the reference relates to the same problem," and is "reasonable pertinent" to it, "and that fact supports use of that reference in an obviousness rejection." Id. (quotations omitted) (noting also that "the pertinence of the reference as a source of solution to the inventor's problem must be recognizable with the foresight of a [POSA]").

It is undisputed that the inventors of the '083 patent were attempting to solve the problem of "adventitious particle contamination" in "eukaryotic cell culture media." Resp. to Celltrion SMF (Docket No. 262-1 ¶¶3, 17. Therefore, they developed a "chemically defined" media, free of all proteins and animal components (such as serum), that could be used to grow different kinds of eukaryotic cells. Id.; Provisional patent application no. 60/623,718 (Docket No. 227-14) at 3. The patent claims cell culture

media compositions that are "animal component free," and can be used to grow eukaryotic cells. See '083 patent (Docket No. 227-13) at 1. As indicated earlier, it is undisputed that the need for media free of serum and other animal-derived components to culture cells without the associated risk of contamination was well-known in the field by 2004, and that GSK and Life Techs were directed to solving that problem as well by developing their own serum-free media. See GSK application (Docket No. 227-18) at 23; Life Techs application (Docket No. 227-17) at 2. Accordingly, a POSA would have considered GSK and Life Techs as providing solutions to the same known problem the inventors of the '083 media were trying to solve. See Sci. Plastic Prods., 766 F.3d at 1359. It is not "hindsight reconstruction" to "select[] and appl[y] . . . [such] pertinent art." Application of Winslow, 365 F.2d at 1020.

In addition, as explained below, a POSA would have had a motivation, based on these problems known in the field and the teachings of other references, to produce variations of GSK and Life Techs that supplied the same active ingredients in different salt forms and concentrations. See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1275-77 (Fed. Cir. 2004) (holding that "the district court did not use hindsight in its obviousness analysis, but properly found a motivation to combine because the two references address precisely the same problem of underpinning existing structural foundations").

Defendants produced a side-by-side comparison of the ingredients and concentrations of the medium disclosed in Table 3 of GSK and both of the hypothetical claims. See Ex. 1. As explained earlier, GSK discloses a medium that combines 50 of the 52 ingredients required by the hypothetical claims, as well other ingredients. See id. (rows highlighted in blue are two required claimed ingredients not found in GSK); see also Resp. to Celltrion SMF (Docket No. 262-1) ¶35.[6] The two claimed ingredients missing from GSK that are required by the hypothetical media are ferric ammonium citrate ("FAC") and ammonium metavanadate. See Resp. to Celltrion SMF (Docket No. 262-1) ¶37.

The defendants also provided a side-by-side comparison of the ingredients and concentrations of the Life Techs medium as compared to the hypothetically claimed media. See Ex. 2. As also explained earlier, Life Techs discloses a medium that combines 47 of the 52 ingredients required by the hypothetical media, as well as other

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[6] Despite Janssen's assertion that the nine optional ingredients are limitations of claim 1, both parties focused their arguments on the presence and amount of the 52 required claimed ingredients in the prior art. Janssen has not argued that the nine optional ingredients contribute in any particular way to the nonobviousness of the hypothetical media, other than its argument that the claimed composition "as a whole" is a unique, nonobvious formulation. Therefore, the parties have conceded the presence of nine optional ingredients is immaterial to assessing the differences between the prior art and claimed media. See United States v. Zannino, 895 F.2d 1, 17 (1st Cir. 1990).

ingredients. See id. (rows highlighted in blue are ingredients required by the claims that are not found in Life Techs); Reply to Janssen SMF (Docket No. 315) ¶30. The five claimed ingredients missing from Life Techs that are required by the hypothetical media are: FAC, ammonium metavanadate, manganese(II) sulfate monohydrate, sodium selenite, and tin(II) chloride dehydrate. See Docket No. 315 (Reply to Janssen SMF) ¶¶30-31; Ex. 2 (see rows highlighted in blue for ingredients missing from Life Techs).

With respect to the ingredients required by the hypothetical claims that are not disclosed in the GSK and Life Techs media, it is undisputed that the GSK and Life Techs media contain alternative, previously-known ingredients that were known to provide the same active components as the claimed ingredients, as explained below.

1. Ferric Ammonium Citrate

The hypothetical media require FAC to provide a sufficient amount of chelated iron to grow cells at acceptable levels. See Reply to Janssen SMF (Docket No. 315) ¶49; Resp. to Celltrion SMF (Docket No. 262-1) ¶50. GSK and Life Techs do not contain FAC; rather, they contain ferric fructose and ferric citrate,[7]

[7] It is disputed whether the Life Techs medium actually discloses the use of FAC. See Reply to Janssen SMF (Docket No. 315) ¶50; Resp. to Celltrion SMF (Docket No. 262-1) ¶41. Life Techs discloses "ferric citrate chelate" as the iron source. Life Techs application

respectively. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶37, 40-41, 52; GSK application (Docket No. 227-18) at 25-26; Life Techs application (Docket No. 227-17) at 21. However, all three of these ingredients - ferric fructose and ferric citrate, as well as FAC - were known in 2004 as ingredients that could replace transferrin for use in animal-component-free cell culture media because they would provide an acceptable amount of chelated iron to the cells. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶37, 46-52; Reply to Janssen SMF (Docket No. 315) ¶¶49-50; Dr. Glacken Report (Docket No. 227-5) ¶258. The only function identified for ferric fructose in GSK and for ferric citrate in Life Techs is to replace transferrin and supply chelated iron.

Despite arguing that the prior art taught away from using FAC, as discussed infra at 72, Janssen agrees that FAC does in fact supply chelated iron, and was not a "new" ingredient in cell culture media in 2004. See Resp. to Celltrion SMF (Docket No. 262-

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(Docket No. 227-17) at 21. Dr. Glacken opined that a POSA would have understood "ferric citrate chelate" as a reference to a class of ingredients that includes both ferric citrate and FAC, and not necessarily as reference to the ingredient commonly referred to as "ferric citrate." See Dr. Glacken Reply Report (Docket No. 221-6) ¶102; Life Techs application (Docket No. 227-17) at 16 ("Ferric citrate chelate or ferrous sulfate can be used in the present media as a substitute for transferrin."). However, this dispute is not material because even assuming that Life Techs did not disclose FAC, the hypothetical media's use of FAC in the place of ferric citrate would have been obvious for the reasons explained in this Memorandum.

1) ¶¶31-32, 51; Dr. Butler Dep. (Docket No. 227-16) at 55-58; Dr. Butler Dep. (Docket No. 314-1) at 155-56; Kitano 1991 chapter (Docket No. 227-24) at 83 (disclosing that "[t]wo highly water soluble iron salts, ferric ammonium citrate and ferric ammonium sulfate, can completely replace transferrin to support the growth of human leukemic cell lines (Titeux et al. 1984)."); International patent application no. WO 03/046132 (the "'162 application") (Docket No. 227-22) at 4 (stating in 2003 that "chelated salts such as ferric citrate and ferric ammonium citrate are preferred" sources of iron in an animal-component-free medium for culturing eukaryotic cells).

2. Ammonium Metavanadate

The hypothetical media also require ammonium metavanadate to supply vanadium. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶44-45. GSK and Life Techs do not contain ammonium metavanadate. Instead, they contain sodium metavanadate. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶37, 40-41; GSK application (Docket No. 227-18) at 23; Life Techs application (Docket No. 227-17) at 20. It is undisputed that both of these ingredients - ammonium metavanadate and sodium metavanadate - were known in 2004 as sources of vanadium in cell culture media. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶42, 44-45; Dr. Glacken Report (Docket No. 227-5) ¶258. Janssen has conceded that ammonium metavanadate and sodium metavanadate were known as interchangeable vanadium sources

in a medium. See June 12, 2018 Tr. at 127; Dr. Glacken Report (Docket No. 227-5) ¶258; Dr. Butler Dep. (Docket No. 314-1) at 139-40. Prior art from as early as 1993 demonstrates that sodium metavanadate could be substituted for ammonium metavanadate. See Cleveland 1983 article (Docket No. 227-19) at 223 tbl.1 (substituting "$NaVO_3$" (sodium metavanadate) "for NH_4VO_3" (ammonium metavanadate) "for reasons of convenience").

3. Other Trace Elements

The three other ingredients required by the hypothetical claims that are missing from Life Techs, but not GSK, are manganese(II) sulfate monohydrate (MnSO4.H2O), sodium selenite (Na_2SeO_3), and tin(II) chloride dehydrate ($SnCl_2.2H_2O$). See Resp. to Celltrion SMF (Docket No. 262-1) ¶41. These ingredients provide trace amounts of the active components manganese, selenium, and tin, respectively. See id. ¶¶40-41. Life Techs contains alternative ingredients that undisputedly supply the same required active components: $MnCl_4 \cdot H2O$ to provide manganese; H_2SeO_3 to provide selenium; and $SnCl_2$ to provide tin. See id.; see also Ex. 2 (see rows highlighted in blue); Life Techs application (Docket No. 227-17) at 20.

It is undisputed that by 2004, the ingredients providing manganese, selenium, and tin claimed in the hypothetical media were known sources of those active trace elements in cell culture media. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶30, 41, 54.

It was also known that various salt forms of these trace elements could be substituted for one another in a cell culture medium. For example, as indicated earlier, Life Techs disclosed that "[t]race elements which may be used in the media . . . include ions of . . . manganese . . . selenium, vanadium, . . . iron, . . . tin . . . . These ions may be provided, for example, in trace element salts . . . [listing examples of salts]." Life Techs application (Docket No. 227-17) at 15-16. Moreover, in 2003, the '162 patent application disclosed that in a serum free-medium, "[n]on-ferrous metal ions optionally of use in the medium include magnesium . . . and selenium. It is preferred to include in the medium selenite ions, such as in the form of sodium selenite," which is used in the hypothetical media. '162 application (Docket No. 227-22) at 5.

4. Overlapping Concentration Ranges

For those 50 ingredients required in the hypothetical media that were previously disclosed in the GSK medium, all of the concentration ranges of the hypothetical claims overlap at least partially with the "Concentration ranges" listed in the GSK application Table 3. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶55-56. In addition, it is undisputed that the alternative chelated iron sources used by GSK contribute to the medium a combined amount of chelated iron that overlaps with the amount of chelated iron required by the hypothetical media. See Resp. to Celltrion SMF (Docket No. 262-1) ¶60 (not disputing that amount of

active component overlaps); Dr. Glacken Report (Docket No. 227-5) ¶257; Ex. 1 at 1 & n.5 (see row labeled "ferric ammonium citrate [active component: chelated iron(III)]" and highlighted in blue). Further, the alternative vanadium source used by GSK delivers to the medium an amount of vanadium that overlaps with the amount of vanadium required by the hypothetical media. See Resp. to Celltrion SMF (Docket No. 262-1), ¶60; Dr. Glacken Report (Docket No. 227-5) ¶258; Ex. 1 at 2 & n.6 (see row labeled "NH_4VO_3 (ammonium metavanadate) [active component: vanadium]" and highlighted in blue). Therefore, for all 52 required ingredients in the hypothetical media, GSK discloses that same ingredient or an alternative that supplies the same active component, and discloses an amount of each that overlaps with the hypothetically claimed concentration ranges.[8]

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[8] Despite acknowledging the overlapping concentrations, Janssen points out that Table 3 of GSK actually discloses three different concentrations for each ingredient: a "Concentration range," a "Preferred concentration range," and a "Preferred concentration." GSK application (Docket No. 227-18) at 23. The "Preferred concentration" is a precise amount of the ingredient, as opposed to a range of concentrations. Janssen argues that if one looks at the "Preferred concentration ranges" - as opposed to the "Concentration ranges," which defendants use - fewer of the GSK ingredients fall within the hypothetically claimed ranges. This may be true, but the court is not required to look only at the "Preferred concentration ranges" listed in GSK. GSK "is prior art for all that it teaches." Geo. M. Martin Co. v. Alliance Machine Sys. Int'l LLC, 618 F.3d 1294, 1303 (Fed. Cir. 2010) (quoting Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1551 (Fed. Cir. 1989)). Even the "unpreferred embodiments" in GSK "must

Similarly, for the 47 ingredients required by the hypothetical media that are previously disclosed in the Life Techs medium, Life Techs discloses concentration ranges that overlap at least partially with the claimed ranges for all but one required ingredient: putrescine•2HCl. See Resp. to Celltrion SMF (Docket No. 262-1) ¶59; Ex. 2 at 4. In addition, for all five of the required claimed ingredients that are absent from Life Techs, Life Techs undisputedly discloses an amount of the same active component that overlaps with the concentration ranges disclosed in the hypothetical claims. See Resp. to Celltrion SMF (Docket No. 262-1) ¶41; Ex. 2 (see rows highlighted in blue). The fact that GSK and Life Techs disclose concentrations for the 52 required active ingredients that overlap (except for putrescine•2HCl in Life Techs) with the hypothetically claimed concentration ranges supports a finding of obviousness. See In re Peterson, 315 F.3d 1325, 1329 (Fed. Cir. 2003).

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be considered." Merck & Co. v. Biocraft Labs., Inc., 874 F.2d 804, 807 (Fed. Cir. 1989) ("[I]n a section 103 inquiry, the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.") (quotations omitted). Therefore, the court can properly compare the "Concentration ranges" in GSK to the hypothetically claimed ranges, even though GSK also discloses "Preferred concentration ranges and precise "Preferred concentration[s]."

Janssen argues that because the prior art discloses amounts of each ingredient that overlap only partially with the claimed concentration ranges, the non-overlapping portions constitute differences between the prior art and the hypothetical media that make the latter nonobvious. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶55, 60. However, the Federal Circuit has held in a series of cases that partially overlapping concentration ranges establish a prima facie case of obviousness. See In re Peterson, 315 F.3d at 1329 ("In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a prima facie case of obviousness."); see also Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311 (Fed. Cir. 2006) ("Where a claimed range overlaps with a range disclosed in the prior art, there is a presumption of obviousness."). Indeed, such a "prima facie case of obviousness" exists even "when the claimed range and prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." In re Peterson, 315 F.3d at 1329.

In such cases, "the existence of overlapping or encompassing ranges shifts the burden to the applicant to show that his invention would not have been obvious." Id. at 1330. The patentee can rebut the prima facie case by producing evidence "that the [claimed] range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range,"

or "by showing that the prior art teaches away from the claimed invention." Id.[9]

Janssen argues that the prima facie case of obviousness based on overlapping ranges is inapplicable here based on dicta in Peterson. In Peterson, the Federal Circuit stated in a footnote

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[9] Even though courts often speak of a "presumption" of obviousness and the patentee's "rebuttal," that language "should not be interpreted as establishing a formal burden-shifting framework." In re Cyclobenzaprine, 676 F.3d at 1076-77. The presumption of obviousness based on overlapping ranges merely shifts the burden of production to the patentee to come forward with rebuttal evidence; but the burden of proving invalidity always rests with the challenger. See id. at 1078; Allergan, Inc. v. Sandoz, Inc., 796 F.3d 1293, 1304-05 (Fed. Cir. 2015) ("[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range," "the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.").

However, the court need not decide whether the overlapping ranges have shifted any burden of production to Janssen. Even if it did, that shift would have no practical effect here because Janssen already bears the burden of proving that the hypothetical claims would not have been obvious. See Jang, 872 F.3d at 1287. Moreover, any presumption would not relieve the court of its obligation to consider all of the evidence put forth by both parties. See In re Cyclobenzaprine, 676 F.3d at 1076-77 (holding the "fact finder must consider all evidence of obviousness and nonobviousness before reaching a determination") (emphasis in original). Therefore, the court only considers here whether the overlapping ranges constitute evidence of obviousness. See Allergan, 796 F.3d at 1305 (stating that the disclosed ranges might be so broad that the burden of producing evidence did not shift to the patentee, but "we need not decide that issue" because the patentee "produced ample evidence of teaching away and unexpected results" to "support[] a conclusion of nonobviousness").

that when "the disclosed range is so broad as to encompass a very large number of possible distinct compositions," a POSA might not be motivated to conduct routine experiment to discover optimum ranges, and therefore a prima facie case of obviousness may not be warranted based on the overlapping ranges alone. In re Peterson, 315 F.3d at 1330 & n.1 (emphasis added); cf. Allergan, 796 F.3d at 1305 (noting that the disclosed ranges might be too broad but not deciding the issue because the patentee "produced ample evidence of teaching away and unexpected results" with the claimed ranges). In support of its argument Janssen cites one case, Genetics Institute, LLC v. Novartis Vaccines & Diagnostics, Inc., holding that overlapping ranges did not create a prima facie case of obviousness because the court found "the typical desire of scientists to find an optimum value within a narrow disclosed range" was not present. 655 F.3d 1291, 1306 (Fed. Cir. 2011) (quotations omitted).

However, Genetics Institute involved a physical structure consisting of a chain of 2,332 amino acids, not a concentration range. See id. 1294-95. The patent claimed numerous truncated segments of the chain, with various deletions and substitutions, and the court had to determine whether the overlapping segments disclosed in the prior art rendered the claims obvious. Id. at 1303, 1306; see also Gen. Hosp. Corp. v. Sienna Biopharms., Inc., 888 F.3d 1368, 1374 (Fed. Cir. 2018) (citing Genetics Inst., 655

F.3d at 1306, for the proposition that "when a reference discloses various structures rather than a range of values, optimization is not as likely to be routine"). The court found that a POSA would have been motivated to make "smaller, truncated proteins," but not to make "larger truncated proteins" as claimed in the patent. Genetics Inst., 655 F.3d at 1306. Therefore, a prima facie case of obviousness was not established by the overlap. See id. at 1307.

The '083 patent claims a composition of ingredients in concentration ranges, not segments of a physical structure, as in Genetics Institute. Janssen contends that "the disclosed range[s] [in the prior art] [were] so broad as to encompass" so many "possible distinct compositions" that a POSA would not have the typical motivation to optimize the concentrations, as suggested in In re Peterson, 315 F.3d at 1330 & n.1. However, Janssen provides no evidence to support that assertion. Dr. Butler's summary of the differences between the prior art and claimed ranges, and his conclusory statement that he is "aware of no reason that a POSA would have begun with the [GSK or Life Techs] application[s] and then modified [their] concentration ranges to arrive at those of the '083 patent," Dr. Butler Report (Docket No. 292-5) ¶140, do not address whether the ranges disclosed in the prior art would have been too broad to optimize. Therefore, these statements are insufficient to create a genuine dispute on the issue. See KSR, 550 U.S. at 427.

Dr. Glacken opined that, to the contrary, "a POSA in 2004 would have been motivated . . . to customize the concentrations of the ingredients [in Life Techs] . . . to achieve better results for a cell line of interest to the POSA." See Dr. Glacken Report (Docket No. 221-4) ¶78; Dr. Glacken Reply Report (Docket No. 262-17) ¶¶26, 38. He would testify that "a POSA would have used this concentration range [in Life Techs] as a guide in selecting concentrations to test in a cell culture experiment. [Life Techs] would have motivated a POSA to determine the optimum combination of concentrations for developing a cell culture media." Dr. Glacken Report (Docket No. 221-4) ¶86; see also id. ¶128 (same for the ranges in GSK). Janssen's experts do not contradict this testimony. Rather, Janssen's experts opined that for each active ingredient in a medium, there is a "plateau," or range, of "interchangeable" concentrations that will support growth, and that the hypothetically claimed ranges are not "precise" or "critical." See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶12-13; Jan. 30, 2018 Tr. at 44-45, 82-83. The references Dr. Butler cited for this proposition were all published before 2004. See Jan. 30, 2018 Hearing Ex. 1, Slides 23-31 to Direct Exam. of Dr. Butler (citing a references from 1977, 1979, and 1992). This evidence could not reasonably be found to establish that the concentration ranges in the prior art are so broad, or so critical to the medium's

properties, that a POSA would not have been motivated to optimize them through routine experimentation. See Pfizer, 480 F.3d at 1368.

As explained in General Hospital Corp. v. Sienna Biopharmaceuticals, Inc., "a showing [of overlapping ranges] may not ultimately be sufficient to establish obviousness where other facts cut against that conclusion," for example, when the patentee presents evidence of teaching away and/or secondary considerations. 888 F.3d at 1374. However, when the patentee does not "point[] to any such facts," the overlapping ranges may be sufficient to establish the claims would have been obvious. Id. Here, there is no evidence that the claimed range "achieve[d] unexpected results relative to the prior art range," or that "the prior art teaches away from the claimed invention." Peterson, 15 F.3d at 1330. Therefore, subject to considering objective indicia of non-obviousness, the concentration ranges in the hypothetical claim appear obvious over the ranges disclosed in GSK and Life Techs.

In summary, based on the foregoing undisputed facts, a reasonable factfinder could only conclude that the claimed ingredients that distinguish Janssen's hypothetical media from the GSK and Life Techs media were already known and used to provide specific active components to cell culture media in 2004. More specifically, with respect to GSK, the hypothetical media use 50 of the ingredients already combined and disclosed in GSK's Table

3, and replace two ingredients with alternative, known salt forms that provide the same active component. With respect to Life Techs, the hypothetical media use 47 of the ingredients already combined and disclosed in Life Tech's Table 1, and replace five ingredients with alternative, known salt forms that provide the same active component. Therefore, as in KSR, the inventors "claim[ed] a [medium] already known in the prior art that is altered by the mere substitution of one [ingredient] for another known in the field." KSR, 550 U.S. at 416. In addition, the concentration ranges in GSK and Life Techs overlap with those in the prior art and produce no unexpected results, such that "the experimentation needed" to determine the appropriate concentration ranges "was nothing more than routine application of a well-known problem-solving strategy" and, therefore, "the work of a skilled [artisan], not of an inventor." Pfizer, 480 F. 3d at 1368; In re Ethicon, 844 F.3d at 1351.

D. Motivation to Combine Prior Art Elements

As explained in KSR, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art," and that those known elements were being used "according to their established functions." 550 U.S. at 418. It would be an improper use of hindsight to "break an invention into its component parts (A + B + C), then find a prior art reference containing A, another

containing B, and another containing C, and on that basis alone declare the invention obvious." Ruiz, 357 F.3d at 1275 (emphasis added). This would "discount the value of" the combination. Id. Therefore, the court must "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does," KSR, 550 U.S. at 418 (emphasis added). In addition, the POSA must have had "a reasonable expectation" that the combination would be successful. In re Cyclobenzaprine, 676 F.3d at 1069. All that is required, however, is that there was "something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." In re Fulton, 391 F.3d at 1200; accord KSR, 550 U.S. at 424 ("The proper question to have asked was whether a pedal designer of ordinary skill, facing the wide range of needs created by developments in the field of endeavor, would have seen a benefit to upgrading Asano with a sensor.").

In the instant case, a POSA would have had several reasons to combine prior art teachings in the way that the hypothetical claim does. He or should also would have had reasonable expectation that the combination would be successful.

The motivation to combine teachings "may be found explicitly or implicitly in market forces; design incentives; the interrelated teachings of multiple patents; any need or problem known in the field of endeavor at the time of invention and

addressed by the patent; and the background knowledge, creativity, and common sense of the person of ordinary skill." Plantronics, Inc. v. Aliph, Inc., 724 F.3d 1343, 1354 (Fed. Cir. 2013) (quoting KSR, 550 U.S. at 418-21); see also Ruiz, 357 F.3d at 1276-77 ("[T]he motivation to combine the teachings in the prior art may come from the nature of a problem to be solved, leading inventors to look to references relating to possible solutions to that problem."). Accordingly, as explained in KSR, "design incentives and other market forces can prompt variations" of "works available in [the] field of endeavor." 550 U.S. at 417.

The evidence indicates that "design incentives" and "market forces" present in the field of cell culture media development prior to 2004 would have motivated a POSA to make a variation of GSK and Life Techs. See id. Before 2004, cell culture scientists were "mov[ing] away from animal-derived components, including serum, in cell culture media for biopharmaceutical production." Dr. Butler Report (Docket No. 227-7) ¶15; see GSK application (Docket No. 227-18) at 23; Life Techs application (Docket No. 227-17) at 2. As the GSK application explained:

> There are various disadvantages linked to the use of serum and of animal-derived components in these [cell culture] processes, mainly their cost, the batch to batch variability in their composition, their association with a higher contamination risk by adventitious agents, and the subsequent difficulties encountered in downstream processing (e.g. purification to get rid of the serum-proteins or of the introduced animal-derived proteins).

GSK application (Docket No. 227-18) at 4. The Life Techs application similarly described the "drawbacks" of the "use of serum or animal extracts in tissue culture," which included the variability of lots, contamination, and difficulty of studying specific growth factors. Life Techs application (Docket No. 227-17) at 5-6. Life Techs explained that "a number of serum-free media have been developed . . . [t]o overcome these drawbacks of the use of serum." Id.; see also Resp. to Celltrion SMF (Docket No. 262-1) ¶3 (noting that the claimed invention was intended to solve the problem of "adventitious particle contamination" in "eukaryotic cell culture media").

In view of the known problems with serum and the market demand for serum-free media, a POSA would have been motivated to continue developing GSK and Life Techs because they disclosed formulations of serum-free media that were capable of growing various types of eukaryotic cells. See KSR, 550 U.S. at 424 ("Technological developments made it clear that engines using computer-controlled throttles would become standard. As a result, designers might have decided to design new pedals from scratch; but they also would have had reason to make pre-existing pedals work with the new engines.").

The GSK and Life Techs references suggested that varying the sources of active trace elements in the media would also produce

effective, animal-free media compositions. As indicated earlier, they taught that the "trace element salts" listed were merely examples of compounds that could be used to deliver the active trace elements such as iron and vanadium to cells. See Life Techs application (Docket No. 227-17) at 15-16 ("Trace elements which may be used in the media . . . include ions of . . . manganese . . . selenium, vanadium . . . iron . . . [and] tin . . . These ions may be provided, for example, in trace element salts . . . [listing examples of salts]."). Dr. Glacken opined that "a POSA would understand that different salt forms of a trace element are interchangeable at least because these salts will dissociate into the desired ionic form of the trace element when placed in the aqueous cell culture media." Dr. Glacken Report (Docket No. 221-4) ¶¶241, 222-26; Dr. Glacken Dep. (Docket No. 262-6) at 172. Janssen's experts similarly opined that different ion or salt forms of an ingredient can be substituted for one another when they provide the same active component. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶25-27; Jan. 30, 2018 Tr. at 59-60; Dr. Butler Report (Docket No. 232-4) ¶¶73-74; Dr. Wurm Report (Docket No. 227-11) ¶¶51-53. GSK and Life Techs, therefore, would have suggested that a POSA should consult other references disclosing alternative sources of active trace elements, such as Kitano 1991, the '162 patent, and Cleveland 1983, which disclosed that FAC and

ammonium metavanadate were effective sources of iron and vanadium in animal-free cell culture media.

In an analogous case, In re Omeprazole Patent Litigation, the patent claimed an "alkaline reacting compound (ARC)," in which the ARC was "an alkaline salt of phosphoric acid, carbonic acid, or silicic acid." 483 F.3d 1364, 1367-68 (Fed. Cir. 2007). The prior art disclosed a different, generally well-known ARC, arginine, and the expert testified it was "easy to substitute" one ARC for another. Id. at 1374. The district court concluded that "it would have been obvious to one skilled in the art to substitute one ARC for another," and the Federal Circuit affirmed. Id. at 1373-74.

Similarly, in Galderma, a prior art acne drug formulation contained all of the same inactive ingredients as the claimed formulation, except for one ingredient called poloxamer 124. See 737 F.3d at 736-37. The prior art formulation instead contained poloxamer 182, which the district court found was "equivalent to" poloxamer 124. The district court then found that "the inactive ingredients in the claimed formulations [were] routine and obvious, and, therefore, non-inventive." Id. Finding that the concentration of the active ingredient fell within a range the prior art taught was "suitable" for treating acne, and that the invention did not produce unexpected results, the Federal Circuit affirmed. Id. at 737-41.

As in Galderma and In re Omeprazole, a POSA would have expected - based on the teachings of GSK, Life Techs, and references teaching that FAC would replace transferrin and produce chelated iron, and that ammonium metavanadate would produce vanadium - that using FAC instead of ferric fructose and ammonium metavanadate instead of sodium metavanadate in the GSK and Life Techs media would grow cells at acceptable levels without the risk of contamination associated with animal-derived components. See Dr. Glacken Report (Docket No. 221-4), ¶78. Dr. Glacken testified, without contradiction in the evidence, that a POSA would have "a reasonable expectation that . . . the outcomes would be similar to what is in the '083 patent" if he substituted different salt forms for various claimed ingredients. Dr. Glacken Dep. (Docket No. 262-6) at 172-73. There is no evidence that the media claimed in the '083 patent or the hypothetical claims would have performed better than expected as a cell culture medium.

This reasonable expectation of developing another successful solution to a known problem in the field would have given a POSA a reason to make the hypothetical claimed combinations. See In re Dillon, 919 F.2d 688, 693 (Fed. Cir. 1990) (where there was a "sufficiently close relationship" between two types of chemical additives, and the prior art "teaches their equivalence for a particular practical use," the court found "[t]he art provided the motivation to make the claimed compositions in the expectation

that they would have similar properties [to the prior art compositions]").[10] As the Supreme Court has stated, "reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening of a jigsaw puzzle. It is not invention." Sinclair, 325 U.S. at 335; see also Anderson's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62 (1969) (device combining a radiant-heat burner and paving machine was obvious because the two elements functioned just as expected; the combination "did not produce a new or different function" or "synergistic result"); Brunswick Corp. v. Champion Spark Plug Co., 689 F.2d 740, 750 (7th Cir. 1982) ("It is well established . . . that a mere change in material (here nickel-alloy to tungsten-alloy) cannot give rise to a patentable invention if the properties of the materials are already known and the result obtained was the one to be expected.").

In the instant case, the experts disagreed on whether FAC would have been equivalent to ferric fructose or ferric citrate. However, this dispute is not material to the issue of obviousness. Infringement under the doctrine of equivalents and obviousness are

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[10] Even under a lead compound analysis, which Janssen argues applies in this case, to prove obviousness, "it is sufficient to show . . . an expectation, in light of the totality of the prior art, that the new chemical compound will have similar properties to the old." Otsuka, 678 F.3d at 1293.

separate legal inquiries. See Siemens Med. Solutions USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc., 637 F.3d 1269, 1282 (Fed. Cir.), petition for reh'g en banc denied, 647 F.3d 1373 (Fed. Cir. 2011).[11] For obviousness, it is sufficient that the substitute ingredients were being used "according to their established functions" and yielded a predictable result. See KSR, 550 U.S. at 416-17; DePuy, 567 F.3d at 1326 ("[T]he 'predictable result' discussed in KSR refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose.").

A POSA would also have been motivated to make variations of GSK and Life Techs by "the normal desire of scientists or artisans

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[11] Although the requirements for equivalence and obviousness are distinct, the Federal Circuit has repeatedly noted in dicta that "[a] substitution in a patented invention cannot be both nonobvious and insubstantial [for infringement purposes]." Roton Barrier, Inc. v. Stanley Works, 79 F.3d 1112, 1128 (Fed. Cir. 1996) (Nies, J., concurring); see Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 493 F.3d 1368, 1380 (Fed. Cir. 2007) ("[T]here is a strong argument that an equivalent cannot be both non-obvious and insubstantial."); Siemens, 647 F.3d at 1379 (Dyk, J., dissenting) ("[J]ust as the doctrine of equivalents cannot extend a patent's scope to cover prior art, it should not permit patents to be extended to cover new and nonobvious inventions.") (citations omitted); cf. Zygo Corp. v. Wyko Corp., 79 F.3d 1563, 1570 (Fed. Cir. 1996) ("[F]or purposes of infringement under the doctrine of equivalents, the differences between the claimed device and the accused device must be insubstantial . . . . The nonobviousness of the accused device, evidenced by the grant of a United States patent, is relevant to the issue of whether the change therein is substantial.").

to improve upon what is already generally known." In re Peterson, 315 F.3d at 1330; see also KSR, 550 U.S. at 421 (noting that a POSA is presumed to be "a person of ordinary creativity, not an automaton"). This "desire of artisans to improve . . . can provide the motivation to optimize variables" in a prior art composition. In re Ethicon, Inc., 844 F.3d at 1349; see also PAR Pharm., 773 F.3d at 1197 (known "interpatient variability" with respect to bioavailability of a drug "would have been a valid motivation for a person of skill in the art to seek to improve the bioavailability of megestrol by using NanoCrystal technology"). Knowing that GSK and Life Techs disclosed media free of animal-derived components and capable of growing cells, a POSA would have been motivated to optimize these formulations to achieve better growth with his or her particular cell line of interest.

One obvious way to optimize the formulations would have been to use different salt forms of the ingredients which were known to provide the same active component. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶46, 50; Dr. Butler Dep. (Docket No. 314-1) at 154-55; Dr. Glacken Dep. (Docket No. 262-6) at 172 ("A person skilled in the art would consider various forms of an active component interchangeable . . . ."); Keenan 1996 article (Docket No. 262-9) at 453 ("[T]he effectiveness of any of these [iron chelators] will depend not only on the cell line but also the culture system being used . . . ."). Dr. Glacken opined that:

> [A] POSA in 2004 would have been motivated, with a reasonable expectation of success, as part of routine experimentation, to substitute alternative forms of ingredients that already provide the same active component (including manganese, selenium, tin, vanadium, and iron) to achieve certain advantages tangentially related to its cell culture performance (e.g., more readily available, already-in-hand, more soluble, more stable, and cheaper ingredients) and to customize the concentrations of the ingredients (including putrescine.2HCl) to achieve better results for a cell line of interest to the POSA.

Dr. Glacken Reply Report (Docket No. 221-6) ¶78. This provides evidence that a POSA would have been motivated to "improve upon" or "optimize" GSK and Life Techs by substituting different salt forms to achieve greater growth with their particular cell lines. See In re Ethicon, 844 F.3d at 1349. Janssen does not present contrary testimony to place this fact in dispute.

In addition, the court must consider the "routine steps" that a POSA would take when trying to optimize GSK or Life Techs, because a POSA would have been motivated to take those steps. Ball Aerosol & Specialty Container, Inc. v. Limited Brands, Inc., 555 F.3d 984, 993 (Fed. Cir. 2009) (district court "erred by failing to take account of the inferences and creative steps, or even routine steps, that an inventor would employ and by failing to find a motivation to combine related pieces from the prior art"). The evidence establishes beyond dispute that a POSA would have swapped out ingredients in GSK or Life Techs merely for cost or convenience. See Dr. Glacken Dep. (Docket No. 262-6) at 172 ("A

person skilled in the art would consider various forms of an active component interchangeable and would select a particular ingredient based on such considerations as availability, purity, stability and cost."); id. ("for the active component" of vanadium, "the salt form" chosen "would be what would be convenient or available to the [POSA]"); Dr. Glacken Report (Docket No. 221-4) ¶¶249, 260 (opining that "[i]t was well within the skill of a POSA to make small changes in the concentrations of the ingredients" in the GSK and Life Techs media); Dr. Glacken Reply Report (Docket No. 221-6) ¶78 (opining that a POSA would have "substitute[d] alternative forms of ingredients that already provide the same active component (including manganese, selenium, tin, vanadium, and iron) to achieve certain advantages tangentially related to its cell culture performance (e.g., more readily available, already-in-hand, more soluble, more stable, and cheaper ingredients)"); Resp. to Celltrion SMF (Docket No. 262-1) ¶42 (discussing Cleveland 1983 article which "substituted" different vanadium salts "for reasons of convenience"). Such routine and convenient substitutions are obvious, not inventive. See DyStar, 464 F.3d at 1370-71 (finding that a POSA would have been motivated to save "time, space, and money" by "exploitation of the well-known principle of vacuum packaging"; therefore, the asserted innovation was "the work of a skilled chemist, not of an inventor").

Janssen argues that defendants have not identified a particular reason a POSA would have chosen to change the chelated iron and vanadium sources in GSK and Life Techs, as well as the selenium, manganese, and tin sources in Life Techs, instead of one of the many other ingredients in the prior art media. Indeed, a POSA would have known there was a menu of multiple obvious choices for delivering each active ingredient and, therefore, permutations of the GSK and Life Techs media that would predictably work. However, obviousness does not require a particular motivation to choose one predictable variation over others. There is no requirement that an obvious solution have been the "best option, only that it [have] be[en] a suitable option from which the prior art did not teach away." PAR Pharm., 773 F.3d at 1197-98 (emphasis in original); In re Fulton, 391 F.3d at 1200 ("[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention.").

Therefore, a sufficient motivation to combine exists if "there is something in the prior art as a whole [that] suggest[s] the desirability, and thus the obviousness, of making the combination." In re Fulton, 391 F.3d at 1200 (quotations omitted) (emphasis in original). The prior art need not "suggest that the combination is the most desirable combination available." Id. (quotations omitted) (emphasis in original). Accordingly, in In re

Fulton, the Federal Circuit rejected the applicant's argument that the Board should have proven that the claimed shoe sole characteristics, hexagonal surfaces in a facing orientation, were "preferred over other alternatives disclosed in the prior art." Id.

Therefore, the fact that a POSA would have expected that any one of many combinations of ingredients would work – even if he or she did not know which one would produce the best growth - does not make each one of them nonobvious. "That the [prior art] discloses a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition is used for the identical purpose taught by the prior art." Merck, 874 F.2d at 807. For example, in In re Corkill, 771 F.2d 1496, 1498-500 (Fed. Cir. 1985), a claimed composition combined known laundry detergents with hydrated zeolites, minerals that soften water and aid in cleaning. The Federal Circuit affirmed composition would have been obvious even though there were "over 35 different types of zeolite framework structures and an infinite number of zeolites [were] possible" because prior art taught that all hydrated zeolites would work. Id. at 1500.

Similarly, in this case, the individual ingredients and the claimed media were used for the "identical purpose taught by" GSK and Life Techs - providing specific nutrients needed to grow animal

cells in a serum-free culture. Merck, 874 F.2d at 807. As indicated earlier, the GSK and Life Techs applications suggest that any workable source of the missing trace elements could be substituted and still yield a successful medium. Therefore, a POSA "would...have recognized that" FAC, ammonium metavanadate, and the other salt forms present in the hypothetical claim, but not Life Techs, "could have been combined with" the other ingredients in GSK and Life Techs "to predictably yield" successful, animal-free media. In re Mouttet, 686 F.3d at 1333. As the overlapping concentration ranges would have been optimized through only routine experimentation, the hypothetical claim would have "obviously withdraw[n] what already [was] known into the field of its monopoly and diminishe[d] the resources available to skillful men." KSR, 550 U.S. at 416.

E. The Prior Art Did Not Teach Away from Using Ferric Ammonium Citrate as a Chelated Iron Source

Janssen argues that, nevertheless, a POSA would not have been motivated to use FAC as a chelated iron source, as the hypothetical media does, because the prior art taught away from using FAC.

Janssen's argument that the prior art taught away from using FAC appears in a footnote in its brief. See Opp. at 22 n.2. The footnote simply cites Janssen's expert's conclusion as creating a factual dispute on the issue and does not provide a developed legal argument. See id. Undeveloped arguments, and arguments appearing

only in footnotes, are waived. See SmithKline Beecham Corp. v. Apotex Corp., 439 F.3d 1312, 1320 (Fed. Cir. 2006) (holding that "mere statements of disagreement with the district court as to the existence of factual disputes do not amount to a developed argument" and that "arguments raised in footnotes are not preserved"); see also Anderson v. City of Boston, 375 F.3d 71, 91 (1st Cir. 2004) ("When a party includes no developed argumentation on a point, as is the case here, we treat the argument as waived under our well established rule."); Zannino, 895 F.2d at 17 ("[I]ssues adverted to in a perfunctory manner, unaccompanied by some effort at developed argumentation, are deemed waived. . . . It is not enough merely to mention a possible argument in the most skeletal way, leaving the court to do counsel's work.").

Nevertheless, the court has carefully considered the issue and finds that the evidence does not create a genuine dispute concerning whether the prior art taught away from using FAC. "Whether the prior art teaches away from the claimed invention is a question of fact." Spectralytics, Inc. v. Cordis Corp., 649 F.3d 1336, 1344 (Fed. Cir. 2011). The answer depends on how a POSA would have read the prior art. See In re Kubin, 561 F.3d at 1357. "A reference teaches away when it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." Bayer Pharma AG v. Watson Labs., Inc., 874 F.3d 1316, 1327-28 (Fed. Cir. 2017);

see In re ICON Health & Fitness, Inc., 496 F.3d 1374, 1382 (Fed. Cir. 2007) ("[A] reference teaches away from a combination when using it in that combination would produce an inoperative result.").

In cell culture media containing serum, chelated iron is provided by a protein in the serum called transferrin. Therefore, when developing a serum-free medium, a POSA would need to include a substitute source of chelated iron to replace the transferrin. See Resp. to Celltrion SMF (Docket No. 262-1) ¶¶50-52; GSK application (Docket No. 227-18) at 3 ("Serum is a major source for . . . iron (transferrin) . . . "); Epstein Dep. (Docket No. 262-19) at 26 (inventors of '083 used FAC "to replace the need for transferrin," an "iron carrier" protein found in serum). The hypothetical media use FAC as a chelated iron source.

Janssen's expert, Dr. Butler, opined that the Keenan 1996 article in particular "teaches away from using FAC as a transferrin replacement." Dr. Butler Report (Docket No. 262-5) ¶82. Keenan tested seven potential transferrin replacements, including FAC, for their growth-promoting effects in one cell line. See Resp. to Celltrion SMF (Docket No. 262-1) ¶48; Keenan 1996 article (Docket No. 227-23) at 451. In support of his conclusion, Dr. Butler relied on statements in Keenan comparing the efficacy of the different potential transferrin replacements. See Dr. Butler Report (Docket No. 262-5) ¶¶83-84. Dr. Butler explained that "the authors of

Keenan 1996 discarded FAC" because it "only reache[d] about 70% of the transferrin performance"; whereas four other transferrin replacements performed better, were deemed "preferable" to FAC, and were "selected for further analysis." Id. ¶84. Dr. Butler opined that "the data in Keenan 1996 teaches that FAC is inferior to the four iron sources selected for further analysis." Id. He also opined that "given Keenan 1996, one would have been dissuaded from" adding FAC to a prior art medium "in favor of other iron-containing transferrin replacements." Id. ¶89.

However, Dr. Butler's statements that Keenan teaches FAC is merely "inferior" to other "preferable" transferrin replacements are insufficient to create a triable dispute concerning whether the prior art taught away from using FAC as a chelated iron source. The teaching away inquiry "does not focus on whether a person of ordinary skill in the art would have merely favored one disclosed option over another disclosed option." Bayer, 847 F.3d at 1327 (emphasis in original). "[T]hat better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes." Id. (quotations omitted). Accordingly, "the fact that there may be reasons a skilled artisan would prefer one over the other does not amount to a teaching away from the lesser preferred but still workable option." Id. (emphasis added).

For example, in Bayer, the Federal Circuit held that the district court erred in finding that the prior art taught away

from formulating an oral, immediate-release version of the drug vardenafil. See 847 F.3d at 1327. An expert opined that a POSA would have expected an immediate-release version to have two undesirable effects: it would leave a bitter taste in the mouth and increase bioavailability to a problematic level for some patients. However, the evidence did not show that the immediate-release formulation would be "unproductive." Id. The expert testimony supported a finding that "the taste and bioavailability of vardenafil raised concerns, and that a skilled artisan may have preferred a delayed-release formulation, but it [did] not support a finding of teaching away." Id. at 1328 (emphasis added); see id. at 1327 (noting the district court erred by "focus[ing] on whether a [POSA] would necessarily have made [the claimed] immediate release [formulation]" rather than whether the POSA would have believed it was "unlikely to be productive") (emphasis added). Similarly, in KSR, the Supreme Court held that the expert's declaration did not support a finding of teaching away because it did not indicate the prior art pedal system "was somehow so flawed that there was no reason to upgrade it." 550 U.S. at 425-26.

Therefore, Dr. Butler's opinions are insufficient to prove that Keenan taught away from using FAC as a chelated iron source. Although Dr. Butler stated that Keenan shows other transferrin replacements tested were "preferable" to FAC, and that FAC's performance was "inferior" to four others, he did not opine that

FAC would be "unproductive" as a chelated iron source, see Bayer, 847 F.3d at 1327, or that its performance was "so flawed" that no POSA would use it as a transferrin replacement, see KSR, 550 U.S. at 425-26.

Although Dr. Butler does not interpret Keenan as indicating that FAC would be "inoperative" as an iron source in media from of animal components, In re ICON, 496 F.3d at 1382, Janssen argues that the court could conclude based on its own reading of Keenan that it taught away from using FAC. However, in fact, Keenan teaches that FAC would be productive for delivering chelated iron to cells and growing them in cell culture media free of animal components. As explained earlier, Keenan tested seven potential transferrin replacements, including FAC, for their ability to grow MDCK cells. See Keenan 1996 article (Docket No. 227-23) at 451. Keenan noted that all the transferrin replacements tested, including FAC, "ha[d] been previously used as transferrin replacements with various degrees of success." Id. at 453. Keenan concluded that in the initial round of tests, all transferrin replacements, including FAC, were productive, stating that "[a]ll factors stimulated growth in a concentration-dependent manner." Id. at 452. FAC in particular "stimulated a maximum of 74-75% of the growth obtained by transferrin," meaning it was about 75% as effective as transferrin at producing MDCK cells. Id.

Keenan then conducted "subculture" studies on four transferrin replacements that seemed most promising, not including FAC, because they "stimulated growth almost equal to that of the bovine transferrin control." Id. Based on the results of the "subculture experiments," Keenan concluded that only three of the four transferrin replacements tested "appeared as suitable replacements for transferrin." Id. at 453.

In the summary of the results, however, Keenan wrote that "all the factors [meaning transferrin replacements] tested were able to exert a concentration-dependent, growth-promoting effect on MDCK cells in single-stage growth assays." Id. Keenan noted the "importance of assessing the stability of factors in media and their ability to support growth not only through single-stage growth assays but also over longer-term subcultures." Id. In addition, Keenan explained that "the effectiveness of any of these factors will depend not only on the cell line but also on the culture system being used." Id. (emphasis added). As an example, Keenan cited "Metcalf 1994," which "found that a combination of [sodium nitroprusside] and FAC could support high levels of growth in static culture, but not in suspension" for the cell line Metcalf tested. Id. Keenan expressed the hope that its results would "contribut[e] to the design of a safe, more reproducible [serum-free medium] devoid of animal proteins." Id.

Therefore, read as a whole, Keenan teaches that FAC had been used successfully before as a transferrin replacement, had a "growth-promoting effect" on MDCK cells, was about 75% as effective as transferrin in terms of its ability to produce chelated iron and grow a certain type of cell, and that its efficacy would vary based on the cell line being grown. See id.; Dr. Glacken Reply Report (Docket No. 221-6) ¶47 (opining that Keenan "suggest[s] that due to cell line to cell line differences, all of these iron chelators [used in Keenan] may be tested to determine which would work best for a given cell line"). Even though FAC was not the "best performing factor" in Keenan's test on MDCK cells, see Dr. Glacken Reply Report (Docket No. 221-6) ¶47, no reasonable factfinder could conclude that Keenan teaches that the use of FAC "would produce an inoperative result" for MDCK cells or other cell lines, or even that it would not grow cells at the same level as the GSK, Life Techs, or patented media. In re ICON, 496 F.3d at 1382.[12] Rather, Keenan would suggest to a POSA that FAC might be

[12] Keenan's brief reference to Metcalf 1994, which does not specify what experiments Metcalf performed and is only used as an example of why the level of growth, but not necessarily the potential for acceptable growth, depends on the cell line and culture system being used, does not alter this conclusion. In addition, Janssen presents no evidence that the performance of the hypothetical media would not also depend on the cell line and culture system being used; indeed, the evidence suggests the opposite. See Whitford Dep. (Docket No. 262-30) at 109-10 (stating that the HyClone media

superior to other iron chelators for certain cell lines and, therefore, encourage that POSA to try it with a variety of cell lines.

Furthermore, the court must consider that other references in the prior art taught that FAC was a workable option as a chelated iron source in an animal-component free medium. In re Young, 927 F.2d at 591 ("The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art.") (emphasis added); cf. Bayer, 874 F.3d at 1328 & n.6 (reversing finding of teaching away and noting district court failed to consider evidence that supported the development of an immediate-release formulation). For example, the '162 patent application, published June 5, 2003, states that "chelated salts such as ferric citrate and ferric ammonium citrate are preferred" sources of iron in an animal-component-free medium for culturing eukaryotic cells. '162 application (Docket No. 227-22) at 4; Resp. to Celltrion SMF (Docket No. 262-1) ¶47. Similarly, another prior art reference, the Kitano 1991 book chapter, disclosed that: "Two highly water soluble iron salts, ferric ammonium citrate and ferric ammonium sulfate, can completely replace transferrin." Resp. to Celltrion SMF (Docket No. 262-1) ¶49; Kitano 1991 chapter (Docket

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was not "universally effective," and was not effective even in the "majority of instances in which [HyClone] tried it").

No. 227-24) at 83. Considering these combined teachings, no reasonable factfinder could conclude that a POSA would have lacked a reason to use FAC in cell culture media.

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The foregoing analysis of the first three Graham factors establishes that an undisputed and strong prima facie case of obviousness exists. The claimed hypothetical media merely altered the serum-free media formulations disclosed in GSK and Life Techs by substituting several ingredients for known alternatives, and those alternatives performed according to their previously-established functions of delivering particular nutrients to cells. There is no evidence that the claimed formulations yielded anything other than the predictable result that GSK and Life Techs also achieved - namely, growth of animal cells in culture in volumes and conditions that were acceptable for producing biopharmaceuticals. Furthermore, the growing market demand for serum-free media, as well as the reasonable expectation that the GSK and Life Techs media formulations would work if one replaced certain salt forms of active nutrients with known substitutes, would have motivated a POSA to make the hypothetically claimed media formulations. In addition, the prior art did not teach away from using FAC in a cell culture medium. To the contrary, the prior art as a whole taught the desirability of the claimed combination of ingredients.

Therefore, the court must evaluate any evidence of secondary considerations proffered by Janssen to determine if it could be found to outweigh the strong, undisputed evidence of obviousness.

F. Secondary Considerations

The fourth Graham factor the court must consider is whether there are any objective indicia of nonobviousness, which are also called "secondary considerations." Graham, 383 U.S. at 17. Objective indicia of nonobviousness include "commercial success enjoyed by devices practicing the patented invention, industry praise for the patented invention, copying by others, and the existence of a long-felt but unsatisfied need for the invention." Apple Inc. v. Samsung Elecs. Co., 839 F.3d 1034, 1052 (Fed. Cir. 2016), cert. denied, 138 S. Ct. 420 (2017). Additional considerations may include the "failure of others" to achieve the invention, Graham, 383 U.S. at 17, and "evidence of unexpected results" obtained by the inventors, Pfizer, 480 F.3d at 1369. The Federal Circuit "requir[es] that a fact finder consider the objective evidence before reaching an obviousness determination" because these objective considerations, "when considered with the balance of the obviousness evidence in the record, guard as a check against hindsight bias." In re Cyclobenzaprine, 676 F.3d at 1079. Secondary considerations "focus attention on economic and motivational rather than technical issues and are, therefore, more

susceptible of judicial treatment than are the highly technical facts often present in patent litigation." Graham, 383 U.S. at 36.

The only secondary consideration raised by Janssen is copying. More specifically, as described in detail below, Janssen contends that HyClone copied Janssen's MET 1.5 medium in producing the medium that Celltrion allegedly uses to produce its products. "The response of the marketplace, and copying by competitors, may evidence the improved technology and beneficial properties of an invention." In re Ethicon, 844 F.3d at 1357. Copying the claimed invention, instead of something in the public domain, "may . . . be a[] form of flattering praise for inventive features, and thus evidence of copying tends to show nonobviousness." WBIP, 829 F.3d at 1336 (emphasis added) (quotations and citation omitted). However, "[n]ot every competing product that arguably falls within the scope of a patent is evidence of copying; otherwise, every infringement suit would automatically confirm the nonobviousness of the patent." Wyers, 616 F.3d at 1246. Therefore:

> copying requires evidence of efforts to replicate a specific product, which may be demonstrated through internal company documents, direct evidence such as disassembling a patented prototype, photographing its features, and using the photograph as a blueprint to build a replica, or access to the patented product combined with substantial similarity to the patented product.

Id.; see also Iron Grip Barbell Co. v. USA Sports, Inc., 392 F.3d 1317, 1325 (Fed. Cir. 2004).

In addition, "[a] nexus between the copying and the novel aspects of the claimed invention must exist for evidence of copying to be given significant weight in an obviousness analysis." Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC, 683 F.3d 1356, 1364 (Fed. Cir. 2012); see also Ohio Willow Wood v. Alps South, LLC, 735 F.3d 1333, 1344 (Fed. Cir. 2013)(affirming summary judgment of obviousness because patentee did not show "nexus" between secondary indicia, including copying, and the patented invention); Ormco, 463 F.3d at 1311-12 (reversing nonobviousness ruling because "the commercial success was [not] the result of claimed and novel features" and, therefore, "the evidence of secondary considerations is inadequate to raise any doubt as to the obviousness"). As the Federal Circuit has also stated, "more than the mere fact of copying by an accused infringer is needed to make that action significant to the determination of the obviousness issue." In re GPAC Inc., 57 F.3d 1573, 1580 (Fed. Cir. 1995). Therefore, Janssen must prove at trial that HyClone copied MET 1.5 because of its "inventive characteristics . . . as claimed in the patent," in order for the copying to carry significant weight in the balancing of the Graham factors. In re Cyclobenzaprine, 676 F.3d at 1079 n.6.

For example, in Wrigley, the patent claimed a new chewing gum formulation containing menthol, a known ingredient, and WS-23, a new cooling agent, as well as other ingredients. Internal documents

showed that Cadbury copied Wrigley's claimed formulation and added WS-23 to some of its products. See 683 F.3d at 1364. However, "Wrigley had not shown evidence suggesting that the novel combination of WS-23 and menthol is what led Cadbury to copy Wrigley's chewing gums, and in the absence of that evidence . . . Wrigley failed to establish the requisite nexus between Cadbury's copying and the merits of the claimed invention." Id. (emphasis added) (quotations omitted). The evidence, in fact, suggested that Cadbury was not led to copy by the allegedly novel combination of WS-23 and menthol; rather, Cadbury sought to copy other features of Wrigley's product, such as the sweeteners, not the added WS-23 cooling agent. See id. In addition, the court noted that chewing gum manufacturers "have a practice of marketing very similar products," and "typically copy any development by their competitors, whether patented or not," which suggested that the copying was not due to Wrigley's novel combination of WS-23 and menthol. Id. Because of "the absence of evidence of a nexus," and the "evidence suggesting the contrary," the Federal Circuit held that the "Wrigley's evidence of copying is therefore not a strong indicator of nonobviousness," and affirmed summary judgment of obviousness. Id.

Janssen asserts that HyClone, not Celltrion, copied the MET 1.5 medium because its novel features - the "unique never-before-seen combination" of 61 ingredients and concentrations - achieved

"remarkable success." Janssen Suppl. Br. (Docket No. 368) at 2. A unique combination of factors can indeed be the "novel" aspect of an invention where, as here, the claimed elements were all previously known in the art. See, e.g., Wrigley, 683 F.3d at 1364; WBIP, 829 F.3d at 1332.

The following evidence concerning copying is considered in the light most favorable to Janssen. In 2003, Janssen began working with HyClone to develop a new cell culture medium. See Reply to Janssen SMF (Docket No. 315) ¶57. Also in 2003, Janssen tried HyClone's off-the-shelf cell culture medium, ADCF-Mab, and found it produced "lousy growth" compared to other products tested. Id.; Centocor presentation (Docket No. 262-22) at 31.

Subsequently, in late 2003 or early 2004, Janssen, without HyClone, developed a different cell culture medium called MET 1.5, which became the preferred embodiment of the '083 patent. See Reply to Janssen SMF (Docket No. 315) ¶58. Janssen then hired HyClone to produce quantities of the MET 1.5 medium for testing purposes. Id. ¶59. HyClone employees who worked with Janssen in connection with the MET 1.5 project included R&D Manager William Whitford, Andra Kunzler, and Jonathan Foster. See id. ¶60. Foster wrote in an email to the lead inventor of the '083 patent, David Epstein: "It's good to hear MET 1.5 is performing well. Congratulations on your successful design!" Id. ¶61.

In about 2007, Whitford's R&D group at HyClone developed a new product, Cell Boost 5, intended to be used as a supplement to HyClone's off-the-shelf ADCF-Mab product. Id. ¶62. Standing alone, ADCF-Mab lacks nine of the ingredients in claim 1 of the '083 patent. See id. ¶63. Standing alone, Cell Boost 5 lacks 11 of the ingredients in claim 1 of the patent. See id. ¶64. However, when ADCF-Mab and Cell Boost 5 are combined, the resulting medium (the "combination product" or "HyClone medium") contains almost all of the ingredients in claim 1. See id. ¶65; List of ingredients (Docket No. 262-31) at 1-4. After combining ADCF-Mab and Cell Boost 5, HyClone recommended the combination product to its clients, including Celltrion. See Reply to Janssen SMF (Docket No. 315) ¶¶67-68. Whitford testified that the combination product might be superior to other media for producing certain cell lines, but would not have been considered universally more effective. See id. ¶66; Whitford Dep. (Docket No. 262-30) at 109-110. Celltrion purchased the combination media from HyClone. See Reply to Janssen SMF (Docket No. 315) ¶68. Janssen contends that Celltrion used it to develop the accused media. See Reply to Janssen SMF (Docket No. 315) ¶¶68-69. Based on this evidence, Janssen argues a reasonable factfinder would infer that Celltrion copied Janssen's MET 1.5 medium when it developed the accused media.

In summary, the evidence is sufficient to prove that HyClone had access to the MET 1.5 formula in about 2004, when Janssen hired

it to produce quantities of MET 1.5 for testing; and, in addition, when the formulation became public in 2006 when the '083 patent application was published, see '083 patent (Docket No. 227-13) at 1. Three years after it first gained access to the MET 1.5 formulation, in 2007, HyClone developed a composition that included the 61 components listed in claim 1 of the '083 patent. It is a close question whether this evidence is sufficient to permit a finding that HyClone copied MET 1.5. When they made the Cell Boost 5 supplement in 2007, HyClone's scientists already had experience using the claimed ingredients in combination. In addition, they had access to: the GSK and Life Techs formulations; advances in the art of cell culture media since 2004; and HyClone's own proprietary formulations, which had used FAC since 2001, before HyClone collaborated with Janssen. See Resp. to Celltrion SMF (Docket No. 262-1) ¶51; Douglass Dep. (Docket No. 232-6) at 235.

While the Federal Circuit in Wyers stated that copying may be proven by "access to, and substantial similarity to, the patented product (as opposed to the patent)," it also stated that "not every competing product that arguably falls within the scope of a patent," to which the public has access, "is evidence of copying." 616 F.3d at 1246. Janssen's expert, Dr. Butler, testified that in the field of cell culture media, there is a "convergence of opinion" about "the range of components" that are needed to grow cells, such that it was "not surprising" that GSK and Janssen

scientists "came up with a similar formulation." Resp. to Celltrion SMF (Docket No. 262-1) ¶¶32, 36; Dr. Butler Dep. (Docket No. 227-16) at 273-75. This testimony indicates that it would be equally unsurprising for HyClone's scientists - without copying the MET 1.5 - to come up with a formulation similar to the MET 1.5 composition, which is itself nearly identical to the preexisting combinations in GSK and Life Techs. Developing such a formulation would only have required HyClone's scientists to substitute ingredients, such as FAC, that HyClone and other public references already used in animal-component free cell culture media formulations.

In addition, when the accused product "is materially different from [the] patented invention," the evidence is insufficient to prove copying. Stone Strong, LLC v. Del Zotto Prod. of Fla., Inc., 455 F. App'x 964, 971 (Fed. Cir. 2011). A reasonable factfinder could find the accused hypothetical media satisfy all of the limitations of claim 1 of the '083 patent, which is a "comprising" claim that covers any composition that includes the 52 required ingredients in the required concentration ranges and allows additional ingredients to be added and still infringe. However, HyClone's ADCF-Mab/Cell Boost 5 combination may be materially different from Janssen's MET 1.5 - which is only one particular embodiment that falls within the patent's claims - for the purposes of copying analysis. ADCF-Mab/Cell Boost 5 contains

29 unclaimed ingredients, including chemically undefined ingredients like yeast extract and insulin growth factor, which are not in MET 1.5. These 29 ingredients arguably materially distinguish ADCF-Mab from MET 1.5, which the '083 patent describes as a desirable composition because it is "chemically defined." See Dr. Frohlich Report (Docket No. 252-3), ¶¶113-14, App'x C (listing ingredients in accused media); '083 patent (Docket No. 227-13) at col.6-7 (listing ingredients in MET 1.5); Dr. Glacken Rebuttal Report (Docket No. 260-11) ¶¶52, 58, 122, 139, 190; see also Reply to Janssen SMF (Docket No. 315) ¶65. As Whitford of HyClone testified without dispute, ADCF-Mab/Cell Boost 5 is "not a chemically-defined media and most everyone wants a chemically-defined media now." Whitford Dep. (Docket No. 262-30) at 112. In addition, there is no evidence that ADCF-Mab/Cell Boost 5 has the same or similar concentrations of ingredients as MET 1.5. See Reply to Janssen SMF (Docket No. 315) ¶65.

Nevertheless, it is undisputed that HyClone had access to the MET 1.5 formula and later developed ADCF-Mab/Cell Boost 5. In addition, although it is a close question, a reasonable factfinder could find that ACDF-Mab/Cell Boost 5 is substantially similar to MET 1.5. Therefore, a reasonable factfinder could conclude that HyClone copied the MET 1.5 formulation. See Wyers, 616 F.3d at 1246. In addition, because the MET 1.5 medium contains only claimed features, a reasonable factfinder could conclude that HyClone

copied MET 1.5 because of the novel combination of ingredients and concentrations, rather than for some other reason. See WBIP, 829 F.3d at 1329 ("[S]howing that the specific products [copied] are embodiments of the claimed invention" and are not only components of a product containing unclaimed features "is sufficient" to infer a nexus, absent rebuttal evidence showing another reason for the copying).

As indicated earlier, copying and nexus are not the end of the obviousness inquiry. Rather, "the strength of each of the Graham factors must be weighted" to determine whether the invention would have been obvious. WBIP, 829 F.3d at 1328 (emphasis in original). Therefore, "[w]hat remains for the objective indicia . . . is a weighing to produce a legal conclusion." Intercontinental Great Brands LLC v. Kellogg N. Am. Co., 869 F.3d 1336, 1347 (Fed. Cir. 2017). "[O]bviousness is not a factual inference." Newell Companies, Inc. v. Kenney Mfg. Co., 864 F.2d 757, 768 (Fed. Cir. 1988). "[T]he ultimate judgment of obviousness is a legal determination for the court." Intercontinental Great Brands LLC, 869 F.3d at 1343-44.

In the instant case, even if Janssen were to prove at trial that HyClone copied the MET 1.5 formulation because of its novel features, this fact would be insufficient to establish that the hypothetical claim was nonobvious. The court must weigh the copying against the other Graham factors - which are not genuinely disputed

and strongly favor a finding of obviousness - "to produce a legal conclusion" concerning whether the hypothetical claims "would have been obvious" to a POSA. Intercontinental Great Brands LLC, 869 F.3d at 1347. When the patentee proves that a competitor preferred to copy a patented product instead of using prior art, the copying "is only equivocal evidence of non-obviousness in the absence of more compelling objective indicia of other secondary considerations." Ecolochem, Inc. v. S. Calif. Edison Co., 227 F.3d 1361, 1380 (Fed. Cir. 2000). Here, the circumstances of the alleged copying do not deserve substantial weight in the court's legal determination of obviousness for at least two reasons.

First, HyClone is the only company that a factfinder could reasonably conclude copied MET 1.5. Compare Hughes Tool Co. v. Dresser Indus., Inc., 816 F.2d 1549, 1556 (Fed. Cir. 1987) (considering fact that multiple competitors copied the claimed features of the patentee's device, but not the unclaimed features). On December 22, 2016, the court found that a jury could reasonably find Celltrion knowingly induced HyClone to infringe the '083 patent based on evidence that Celltrion: bought the combination of ADCF-Mab/Cell Boost 5 from HyClone in 2008; directed HyClone to make certain adjustments to it to "improve the similarity" of its Inflectra to Janssen's Remicade; knew, by 2013, the formula for HyClone's media; and after 2013, continued to order shipments of the accused media despite knowing it infringed the patent. See

Dec. 22, 2016 Tr. at 19-21. However, unlike induced infringement, copying requires evidence that Celltrion made "efforts to replicate a specific product," such as MET 1.5. Wyers, 616 F.3d at 1246. Therefore, Janssen cannot prove that Celltrion attempted to copy MET 1.5 by proving only that it intended to induce HyClone to infringe the '083 patent.

Janssen does not argue Celltrion in particular attempted to produce a copy of MET 1.5. There is no evidence, in any event, that Celltrion directed or encouraged HyClone to design ADCF-Mab/Cell Boost 5 to copy MET 1.5. It is undisputed that Celltrion did not buy HyClone's ADCF-Mab/Cell Boost 5 combination product until 2008, after HyClone had designed it in 2007. See Janssen Mem. in Supp. of Motion for Summary Judgment on the Issue of Non-infringing Alternatives (Docket No. 250, under seal) at 9; Resp. to Celltrion SMF (Docket No. 262-1) ¶¶62, 67. Moreover, when Celltrion optimized HyClone's ADCF-Mab/Cell Boost 5 combination product, it directed only minor adjustments that made the accused media less similar to MET 1.5 than HyClone's standard product. "Nearly all of [Celltrion's] changes involve[d] ingredients that are not required by claim 1 of the '083 patent," and of the two that did, one moved the concentration of NaCl, a required ingredient, out of the claimed range. Frohlich Report (Docket No. 252-3) ¶109-10. Celltrion also removed two of the 61 claimed ingredients in MET 1.5, sodium hypoxanthine and thymidine. Compare

Ex. 1 (ingredients in claimed media) and '083 patent (Docket No. 227-13) col.6 (ingredients in MET 1.5) with Dr. Frohlich Rep. (Docket No. 252-3), App'x C-1, C-2 (ingredients in accused media); see Reply to Janssen SMF (Docket No. 315) ¶65.

In addition, Janssen concedes that when Celltrion directed those adjustments, Celltrion "did not even know the formula of the HyClone media"; therefore, Celltrion could not have known whether HyClone's combination product was substantially similar in composition to MET 1.5. Janssen Mem. in Supp. of Motion for Summary Judgment on the Issue of Non-infringing Alternatives (Docket No. 250, under seal) at 8; Janssen Statement of Material Facts (Docket No. 251, under seal) ¶¶49-50; Cho Decl. (Docket No. 251-29, under seal) ¶¶3-9 (stating that prior to this litigation, only three Celltrion employees had access to the confidential HyClone medium formulation, and that he learned the formulation in December 2013). Therefore, there is no evidence that Celltrion attempted to copy MET 1.5 or induced HyClone to try to copy it.

Moreover, if Celltrion had directed modifications to ADCF-Mab/Cell Boost 5 to make Inflectra more similar to Remicade, this would not affect the decision concerning obviousness. A biosimilar applicant's attempts to copy a patentee's reference composition are "not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc., 713 F.3d 1369, 1377 (Fed.

Cir. 2013); Purdue Pharma Prods. L.P. v. Par Pharm., Inc., 377 Fed. App'x 978, 983 (Fed. Cir. 2010). As Janssen explains in its complaint, in seeking fast-track FDA approval for Inflectra, Celltrion was required to show that it was "'highly similar to the reference product [Remicade] notwithstanding minor differences in clinically inactive components' and (2) ha[d] 'no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.'" Compl. ¶49 (quoting 42 U.S.C. §262(i)(2)(A)-(B)). Therefore, any attempts by Celltrion to increase the similarity of Inflectra to Remicade were likely a result of the biosimilar licensing process, not the merits of Janssen's invention. See Bayer, 713 F.3d at 1377; Purdue, 377 Fed. App'x at 983.

However, there is no evidence that the desire to make a biosimilar to Remicade would have motivated Celltrion to make the accused media more similar to MET 1.5. There is no evidence that MET 1.5 is necessary or even appropriate for producing a Remicade biosimilar. Although Janssen initially "hoped" MET 1.5 could someday be used to produce Remicade, it has never used MET 1.5 to produce Remicade or obtained FDA approval to do so. See Janssen Trial Br. (C.A. No. 15-10698, Docket No. 451 under seal) at 2. In addition, Janssen's expert, Dr. Butler, testified MET 1.5 would not have worked for producing a Remicade biosimilar without further

optimization. See Dr. Butler Dep. (Docket No. 314-1) at 47, 178-181.

Second, Janssen does not allege that the MET 1.5 medium produced unexpected results, achieved commercial success, or that there are other "more compelling objective indicia of . . . secondary considerations" in addition to copying. Ecolochem, 227 F.3d at 1380. In the only case Janssen cites for the proposition that copying in this case could overcome the fact, not genuinely disputed, that a POSA would have been motivated to combine the known elements in the prior art into the claimed media, the jury reasonably found that there was no motivation to combine, and that there was industry praise, commercial success, and a long-felt need for the invention, which supported the conclusion of nonobviousness. See Apple, 839 F.3d at 1052-57.

Janssen understandably does not argue that any such additional secondary considerations are present here. For example, Janssen does not contend, and there is no evidence to conclude, that HyClone copied the claimed combination of 61 ingredients because it produced results that would have surprised a POSA in 2004. The '083 patent reports that MET 1.5 "can sustain high cell growth and viability." '083 patent (Docket No. 227-13), col. 9; see Reply to Janssen SMF (Docket No. 315) ¶58. Jonathan Foster of HyClone stated in an email that MET 1.5 was a "successful design." Reply to Janssen SMF (Docket No. 315) ¶61. HyClone's R&D Manager,

Whitford, testified that the HyClone combination media - allegedly copied from MET 1.5 - "could" have performed exceptionally well for a given cell line. See Whitford Dep. (Docket No. 262-30) at 107-110. However, he also stated it was not "universally effective," and was not effective even in the "majority of instances in which [HyClone] tried it." Id. at 109-10. These undisputed statements would not permit the conclusion that the MET 1.5 composition, which was only part of the HyClone medium, produced higher or more consistent growth than prior art compositions, such as GSK or Life Techs. Nor would these statements permit the conclusion that the "high" growth MET 1.5 produced for the cell line the inventors tested, as reported in the patent, '083 patent, col. 4, was an unexpected result.

There is also no evidence that the allegedly inventive combination of 61 ingredients in MET 1.5, which also appear in HyClone's ADCF-Mab/Cell Boost combination, resulted in commercial success. Janssen presents no evidence that Celltrion or anyone else bought MET 1.5 because of that combination of 61 ingredients, or that anyone found them particularly useful or important to a cell culture medium. See In re Cyclobenzaprine, 676 F.3d at 1079 n.6; In re GPAC Inc., 57 F.3d at 1580. As explained earlier, there is no evidence Celltrion bought ADCF-Mab/Cell Boost 5 because of the 61 ingredients, rather than the 29 unclaimed ingredients. Dr. Butler testified that the 29 ingredients present in ADCF-Mab/Cell

Boost 5 but not in MET 1.5 "could contribute substantially to the ability of the[] two media [accused] to divide and grow cells." Case No. 15-10698, Docket No. 339, Ex. 1 (Butler Dep.) at 231.

As with copying, for the commercial success of a product containing patented components to be weighed in the obviousness inquiry, the patented components must drive the commercial success. For example, in In re Huang, the Federal Circuit found insufficient evidence of a nexus between the commercial success of patentee's tennis racquet grip and the novel aspects of the invention - namely the thicker polyurethane layer and alignment of the pores on the grip. 100 F.3d 135, 140 (Fed. Cir. 1996). The Federal Circuit held that commercial success, like copying, "is relevant in the obviousness context only if there is proof that the sales [or copying] were a direct result of the unique characteristics of the claimed invention - as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." Id. The court noted that customers may have bought the product due to lower manufacturing costs, the market position of patentee, or other attractive yet non-novel features of the product. See id. Because the patentee had not "provided sufficient proof to establish either that his grips were commercially successful or that the sales resulted from the merits of the claimed invention" in order to overcome the prima facie case of obviousness, the Federal Circuit affirmed the PTAB's

decision that the patented grip would have been obvious. Id. at 139. In this case, as in Huang, there is a lack of "factual evidence that demonstrates the nexus between the sales and the claimed invention - for example, an affidavit from a purchaser explaining that the product was purchased due to the claimed features." Id. at 140.

Therefore, although the evidence viewed most favorably to Janssen is barely sufficient to prove at trial the required nexus between any copying by HyClone and the "novel aspects" of the claimed hypothetical media, the copying is insufficient to overcome the strong case of obviousness based on the other Graham factors. In Ecolochem, the Federal Circuit held after a bench trial that the evidence established beyond dispute that the invention was copied and was commercially successful because of its patented features. See 227 F.3d at 1378, 1380. However, "weighing all the secondary considerations" in its "de novo obviousness review," the court held that the secondary considerations "taken as a whole, d[id] not overcome the other evidence of obviousness." Id. Similarly, in Wyers, the Federal Circuit, in holding that the patent claims were nonobvious, explained that even if the patentee established that the infringer copied the invention because of its novel features:

> [S]econdary considerations of nonobviousness . . . simply cannot overcome a strong prima facie case of obviousness. Here, where the inventions represented no

> more than 'the predictable use of prior art elements according to their established functions,' KSR, 550 U.S. at 417, the secondary considerations are inadequate to establish nonobviousness as a matter of law.

616 F.3d at 1246 (citations omitted); accord Ohio Willow Wood, 735 F.3d at 1344; Stone Strong, 455 F. App'x at 971; see also Pfizer, 480 F.3d at 1372 (reversing district court's conclusion of nonobviousness, holding that "even if [the patentee] showed that amlodipine besylate exhibits unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case").[13]

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[13] Wyers, Stone Strong, and Pfizer were not appeals from a grant of summary judgment. The Federal Circuit held that the district courts should have granted judgment of obviousness based on the evidence presented at trial. However, the standard for judgment as a matter of law after a trial is the same as the standard for summary judgment, except that the court must consider the evidence presented at trial rather than the evidence proffered at the close of discovery. A motion for judgment as a matter of law for the defendant at the close of evidence must be granted if "a reasonable jury would not have a legally sufficient evidentiary basis to find for the [plaintiff]." Fed. R. Civ. P. 50(a)(1). Similarly, on a motion for summary judgment, the court must grant judgment for the movant unless "the evidence is such that a reasonable jury could return a verdict for the nonmoving party." Anderson, 477 U.S. at 248; see also Fed. R. Civ. P. 56(a). The Supreme Court has held that the standard for summary judgment "mirrors the standard for a directed verdict under Federal Rule of Civil Procedure 50(a)." Anderson, 477 U.S. at 250. The Court explained: "The primary difference between the two motions is procedural . . . . In essence, though, the inquiry under each is the same: whether the evidence presents a sufficient disagreement to require submission to a jury or whether it is so one-sided that one party must prevail as a matter of law." Id. at 251-52.

As explained earlier, the undisputed evidence shows that the hypothetical media "represented no more than the predictable use of prior art elements according to their established functions" because it only modified the media disclosed in prior art - namely the GSK and Life Techs references - by substituting several ingredients for alternative salt forms known to provide the same active components. Wyers, 616 F.3d at 1246 (quotations omitted). There is no evidence that the hypothetical media achieved anything more than predictable results. Moreover, no reasonable factfinder could conclude that the prior art taught away from using FAC as it is used in the hypothetical claimed media. Furthermore, no reasonable factfinder could conclude a POSA would not have been motivated to make the hypothetically claimed media, based on the growing demand for serum-free media capable of growing animal cells; the knowledge that the GSK and Life Techs media were capable of achieving that result; the knowledge that replacing certain ingredients in GSK or Life Techs with their alternative salt forms would have been routine and would have worked for the '083 inventors' goals, which were shared by POSAs before 2004; and the motivation to optimize the concentrations of those ingredients in combination for cell lines of interest. Therefore, this case presents another situation where the secondary factors "do not . . . tip the scales of patentability" and do not overcome the strong case of obviousness. Graham, 383 U.S. at 36; see also Ecolochem,

227 F.3d at 1380; Ohio Willow Wood, 735 F.3d at 1344; Stone Strong, 455 F. App'x at 971; Pfizer, 480 F.3d at 1372.

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Based on a consideration of all four Graham factors, no reasonable factfinder could conclude that Janssen has satisfied its burden of proving that the hypothetical claims would have been patentable over the GSK and Life Techs media. Rather, the undisputed evidence requires a finding that it would have been obvious to a POSA in 2004 to combine the claimed ingredients at their claimed concentrations in order to create the hypothetical media, and a POSA would have been motivated to do so with a reasonable expectation of success. "Where . . . the content of the prior art, the scope of the patent claim, and the level of ordinary skill in the art are not in material dispute, and the obviousness of the claim is apparent in light of these factors, summary judgment is appropriate." KSR, 550 U.S. 426-27. Therefore, defendants are entitled to summary judgment of non-infringement of the '083 patent because Janssen has not produced sufficient evidence to prove that the scope of equivalents would not ensnare the prior art.

V. ORDER

For the foregoing reasons, it is hereby ORDERED that:

1. Defendants' Motion for Summary Judgment of Non-Infringement Based on Ensnarement (Docket No. 226) is ALLOWED.

2. Judgment shall enter for the defendants.

UNITED STATES DISTRICT JUDGE

Exhibit 1

Appendix A—Comparison of GSK to '083 Claim 1 And Hypothetical Claims

Green denotes an overlap. Blue denotes an overlap with respect to the active component.

'083 Patent Claim 1[1]		Hypothetical Range[2] (mg)		GSK Range[3] (mg)
Ingredient	**Range (mg)**	**CGM**	**CPM**	
anhydrous $CaCl_2$ (calcium chloride)	5-200	5-200	5-200	100-760
anhydrous $MgCl_2$ (magnesium chloride)	15-50	15-50	15-50	5-150
anhydrous $MgSO_4$ (magnesium sulfate)	20-80	20-80	20-80	20-150
$FeSO_4.7H_2O$ (iron(II) sulfate heptahydrate)	0.05-0.50	0.05-0.50	0.05-0.50	0.02-2
$Fe(NO_3)_3.9H_2O$ (iron(III) nitrate nonahydrate)	0.01-0.08	0.01-0.08	0.01-0.08	0.005-1
$ZnSO_4.7H_2O$ (zinc sulfate heptahydrate)	0.40-1.20	0.40-1.20	0.40-1.20	0.01-0.6
ferric ammonium citrate [active component: chelated iron(III)]	0.04-200 [1.53×10^{-1}-7.63×10^{2} µmol/L of chelated iron(III)][4]	0.04-200	0.04-200	[4.48×10^{-1}-8.95 µmol/L of chelated iron(III)][5]
KCl (potassium chloride)	280-500	280-500	280-500	180-600
NaCl (sodium chloride)	5000-7500	5000-7500	**4556.83**-7500	5000-8000
$NaH_2PO_4.H_2O$ (monosodium phosphate monohydrate)	30-100	30-**227.17**	30-**262.97**	60-280
Na_2HPO_4 (disodium phosphate monohydrate)	30-100	30-**374.15**	30-**432.64**	20-400
$CuSO_4.5H_2O$ (copper(II) sulfate pentahydrate)	0.001-0.005	**0.000536727**-0.005	**0.00062087**-0.005	0.00001-0.006

[1] Ex. 13 ('083 Patent) at Claim 1.

[2] The hypothetical range was formed by taking the '083 Patent Claim 1 range and extending it to match the concentrations in the accused products. The range extensions are denoted in bold/underline.

[3] Ex. 18 (GSK) at Table 3.

[4] Ex. 5 (Glacken Op.) at ¶ 257.

[5] *Id.*

'083 Patent Claim 1[1]		Hypothetical Range[2] (mg)		GSK Range[3] (mg)
Ingredient	**Range (mg)**	**CGM**	**CPM**	
$CoCl_2.6H_2O$ (cobalt(II) chloride hexahydrate)	0.001-0.10	**0.000369**-0.10	**0.00043**-0.10	0.000001-0.003
$(NH_4)_6Mo_7O_{24}$ $4H_2O$ (ammonium heptamolybdate tetrahydrate)	0.001-0.005	**0.000964**-0.005	0.001-0.005	0.00001-0.002
$MnSO_4.H_2O$ (manganese(II) sulfate monohydrate)	0.000070-0.0080	0.000070-0.0080	0.000070-0.0080	0.000001-0.005
$NiSO_4.6H_2O$ (nickel(II) sulfate hexahydrate)	0.000025-0.0005	0.000025-**0.00094471**	0.000025-**0.00109275**	0.000001-0.0002
Na_2SeO_3 (sodium selenite)	0.004-0.07	0.004-0.07	0.004-0.07	0.001-0.02
$Na_2SiO_3.9H_2O$ (disodium metasilicate nonahydrate)	0.02-0.4	0.02-0.4	0.02-0.4	0.001-0.2
$SnCl_2.2H_2O$ (tin(II) chloride dihydrate)	0.000025-0.0005	**0.000008**-0.0005	**0.00001**-0.0005	0.00001-0.0009
NH4VO3 (ammonium metavanadate) [active component: vanadium]	0.0001-0.0025 [8.55×10^{-4}-2.14×10^{-2} µmol/L of vanadium][6]	**0.000046**-0.0025	**0.00005**-0.0025	[8.20×10^{-5}-1.64 µmol/L of vanadium][7]
D-Glucose	500-8000	500-8000	500-8000	1000-4000
sodium pyruvate	0.0-1000	0.0-1000	0.0-1000	10-150
sodium hypoxanthine	0.0-20.0	0.0-20.0	0.0-20.0	0.01-6
glycine	0.0-150	0.0-150	0.0-150	7-60
L-alanine	0.0-150	0.0-150	0.0-150	5-50
L-arginine.HCl	200-5000	**63.34**-5000	**73.27**-5000	60-500
L-asparagine.H_2O	40-250	**3.22**-250	**3.72**-250	2-180
L-aspartic acid	20-1000	20-1000	20-1000	5-90
L-cysteine.HCl H_2O	25.0-250	25.0-250	25.0-250	0.1-30
L-cystine.2HCl	15-150	15-150	15-150	25-130
L-glutamic acid	0-1000	0-1000	0-1000	6-50
L-histidine.HCl.H_2O	100-500	**13.52**-500	**15.64**-500	15-70
L-isoleucine	50-1000	50-1000	50-1000	10-200
L-leucine	50-1000	50-1000	50-1000	30-200

[6] Ex. 5 (Glacken Op.) at ¶ 258.

[7] *Id.*

'083 Patent Claim 1[1]		Hypothetical Range[2] (mg)		GSK Range[3] (mg)
Ingredient	**Range (mg)**	**CGM**	**CPM**	
L-lysine.HCl	100-1000	100-1000	100-1000	30-240
L-methionine	50-500	**37.57**-500	**43.43**-500	2-60
L-ornithine.HCl,	0-100	0-100	0-100	0
L-phenylalanine	25-1000	25-1000	25-1000	2-45
L-proline	0-1000	0-1000	0-1000	2-45
L-serine	50-500	50-500	50-500	2-50
L-taurine,	0-1000	0-1000	0-1000	0
L-threonine	50-600	50-600	50-600	20-150
L-tryptophan	2-500	2-500	2-500	3-25
L-tyrosine.2Na.2H_2O	25-250	25-250	25-250	5-150
L-valine	100-1000	**90.56**-1000	100-1000	5-150
d-biotin	0.04-1.0	0.04-1.0	0.04-1.0	0.0001-0.5
D-calcium pantothenate	0.1-5.0	0.1-5.0	0.1-5.0	0.01-3
choline chloride	1-100	1-100	1-100	0.1-10
folic acid	1-10	1-10	1-10	0.01-20
i-Inositol	10-1000	10-1000	10-1000	0.6-20
nicotinamide	0.5-30	0.5-30	0.5-30	0.1-15
p-aminobenzoic acid	0.1-20	0.1-20	0.1-20	0.001-0.3
riboflavin	0.05-5.0	0.05-5.0	0.05-5.0	0.001-5
thiamine.HCl	0.5-20	0.5-20	0.5-20	0.001-20
thymidine	0-3.0	0-3.0	0-3.0	0.01-5
vitamin B_{12}	0.05-5.0	0.05-5.0	0.05-5.0	0.001-5
linoleic acid	0.01-2.0	0.01-2.0	0.01-2.0	0.001-0.3
DL-α-lipoic acid	0.03-1.0	0.03-1.0	0.03-1.0	0.001-0.7
pyridoxine.HCl	0.5-30	0.5-30	0.5-30	0.001-5
putrescine.2HCl	0.025-0.25	0.025-0.25	0.025-0.25	0.001-0.09
ethanolamine.HCl	2-100	2-100	2-100	0.1-6

Exhibit 2

Appendix B—Comparison of Life Techs to '083 Claim 1 And Hypothetical Claims

Green denotes an overlap. Blue denotes an overlap with respect to the active component.

'083 Patent Claim 1[1]		Hypothetical Range[2] (mg)		Life Techs Range[3] (mg)
Ingredient	**Range (mg)**	**CGM**	**CPM**	
anhydrous $CaCl_2$ (calcium chloride)	5-200	5-200	5-200	1-500
anhydrous $MgCl_2$ (magnesium chloride)	15-50	15-50	15-50	1-500
anhydrous $MgSO_4$ (magnesium sulfate)	20-80	20-80	20-80	10-500
$FeSO_4.7H_2O$ (iron(II) sulfate heptahydrate)	0.05-0.50	0.05-0.50	0.05-0.50	0.0001-0.5
$Fe(NO_3)_3.9H_2O$ (iron(III) nitrate nonahydrate)	0.01-0.08	0.01-0.08	0.01-0.08	0.05-5
$ZnSO_4.7H_2O$ (zinc sulfate heptahydrate)	0.40-1.20	0.40-1.20	0.40-1.20	0.0002-1.0
ferric ammonium citrate [active component: chelated iron(III)]	0.04-200 [1.53×10^{-1}-7.63×10^{2} µmol/L of chelated iron(III)][4]	0.04-200	0.04-200	[4.1×10^{-2} – 8.165×10^{1} µmol/L of chelated iron(III)][5]
KCl (potassium chloride)	280-500	280-500	280-500	1-500
NaCl (sodium chloride)	5000-7500	5000-7500	**4556.83**-7500	3000-9000
$NaH_2PO_4.H_2O$ (monosodium phosphate monohydrate)	30-100	30-**227.17**	30-**262.97**	10-750
Na_2HPO_4 (disodium phosphate monohydrate)	30-100	30-**374.15**	30-**432.64**	1-500
$CuSO_4.5H_2O$ (copper(II) sulfate pentahydrate)	0.001-0.005	**0.000536727**-0.005	**0.00062087**-0.005	0.00001-0.005

[1] Ex. 13 ('083 Patent) at Claim 1.

[2] The hypothetical range was formed by taking the '083 Patent Claim 1 range and extending it to match the concentrations in the accused products. The range extensions are denoted in bold/underline.

[3] Ex. 17 (Life Techs) at Table 1.

[4] Ex. 21 (Glacken Reb.) at ¶ 104.

[5] *Id.*

'083 Patent Claim 1[1]		Hypothetical Range[2] (mg)		Life Techs Range[3] (mg)
Ingredient	**Range (mg)**	**CGM**	**CPM**	
$CoCl_2.6H_2O$ (cobalt(II) chloride hexahydrate)	0.001-0.10	**0.000369**-0.10	**0.00043**-0.10	0.00001-0.005
$(NH_4)_6Mo_7O_{24}$ $4H_2O$ (ammonium heptamolybdate tetrahydrate)	0.001-0.005	**0.000964**-0.005	0.001-0.005	0.00001-0.01
$MnSO_4.H_2O$ (manganese(II) sulfate monohydrate) [active component: Mn(II)]	0.000070-0.0080 [4.14×10^{-4} – 4.73×10^{-2} µmol/L of Mn(II)][6]	0.000070-0.0080	0.000070-0.0080	[5.05×10^{-6} – 5.05×10^{-3} µmol/L of Mn(II)][7]
$NiSO_4.6H_2O$ (nickel(II) sulfate hexahydrate)	0.000025-0.0005	0.000025-**0.00094471**	0.000025-**0.00109275**	0.000001-0.0001
Na_2SeO_3 (sodium selenite) [active component: SeO_3(II)]	0.004-0.07 [2.31×10^{-2} – 4.05×10^{-1} µmol/L of SeO_3(II)][8]	0.004-0.07	0.004-0.07	[7.75×10^{-5} – 3.88×10^{-2} µmol/L of SeO_3(II)][9]
$Na_2SiO_3.9H_2O$ (disodium metasilicate nonahydrate)	0.02-0.4	0.02-0.4	0.02-0.4	0.001-0.2
$SnCl_2.2H_2O$ (tin(II) chloride dihydrate) [active component: Sn(II)]	0.000025-0.0005 [1.11×10^{-4} – 2.22×10^{-3} µmol/L of Sn(II)][10]	**0.000008**-0.0005	**0.00001**-0.0005	[5.27×10^{-6} – 5.27×10^{-4} µmol/L of

[6] Ex. 5 (Glacken Op.) at ¶ 244.

[7] *Id.*

[8] Ex. 5 (Glacken Op.) at ¶ 245.

[9] *Id.*

[10] Ex. 5 (Glacken Op.) at ¶ 246.

'083 Patent Claim 1[1]		Hypothetical Range[2] (mg)		Life Techs Range[3] (mg)
Ingredient	**Range (mg)**	**CGM**	**CPM**	
				Sn(II)][11]
NH4VO3 (ammonium metavanadate) [active component: vanadium]	0.0001-0.0025 [8.55×10^{-4}-2.14×10^{-2} µmol/L of vanadium] [12]	**0.000046**-0.0025	**0.00005**-0.0025	 [8.20×10^{-5} – 8.20×10^{-3} µmol/L of vanadium] [13]
D-Glucose	500-8000	500-8000	500-8000	1500-5000
sodium pyruvate	0.0-1000	0.0-1000	0.0-1000	10-300
sodium hypoxanthine	0.0-20.0	0.0-20.0	0.0-20.0	0.1-15
glycine	0.0-150	0.0-150	0.0-150	1-200
L-alanine	0.0-150	0.0-150	0.0-150	1-250
L-arginine.HCl	200-5000	**63.34**-5000	**73.27**-5000	10-500
L-asparagine.H_2O	40-250	**3.22**-250	**3.72**-250	5-150
L-aspartic acid	20-1000	20-1000	20-1000	5-125
L-cysteine.HCl H_2O	25.0-250	25.0-250	25.0-250	2-250
L-cystine.2HCl	15-150	15-150	15-150	0.1-250
L-glutamic acid	0-1000	0-1000	0-1000	5-250
L-histidine.HCl.H_2O	100-500	**13.52**-500	**15.64**-500	5-250
L-isoleucine	50-1000	50-1000	50-1000	5-500
L-leucine	50-1000	50-1000	50-1000	25-350
L-lysine.HCl	100-1000	100-1000	100-1000	25-500
L-methionine	50-500	**37.57**-500	**43.43**-500	5-200
L-ornithine.HCl,	0-100	0-100	0-100	0
L-phenylalanine	25-1000	25-1000	25-1000	5-250
L-proline	0-1000	0-1000	0-1000	1-250
L-serine	50-500	50-500	50-500	5-250
L-taurine,	0-1000	0-1000	0-1000	0
L-threonine	50-600	50-600	50-600	10-300
L-tryptophan	2-500	2-500	2-500	2-110
L-tyrosine.2Na.2H_2O	25-250	25-250	25-250	5-400
L-valine	100-1000	**90.56**-1000	100-1000	5-400
d-biotin	0.04-1.0	0.04-1.0	0.04-1.0	0.01-1
D-calcium pantothenate	0.1-5.0	0.1-5.0	0.1-5.0	0.05-10
choline chloride	1-100	1-100	1-100	1-150
folic acid	1-10	1-10	1-10	0.1-10

[11] *Id.*

[12] Ex. 5 (Glacken Op.) at ¶ 247.

[13] *Id.*

'083 Patent Claim 1[1]		Hypothetical Range[2] (mg)		Life Techs Range[3] (mg)
Ingredient	**Range (mg)**	**CGM**	**CPM**	
i-Inositol	10-1000	10-1000	10-1000	1-75
nicotinamide	0.5-30	0.5-30	0.5-30	0.1-5
p-aminobenzoic acid	0.1-20	0.1-20	0.1-20	0.001-0.1
riboflavin	0.05-5.0	0.05-5.0	0.05-5.0	0.01-5
thiamine.HCl	0.5-20	0.5-20	0.5-20	0.1-5
thymidine	0-3.0	0-3.0	0-3.0	0.05-25
vitamin B_{12}	0.05-5.0	0.05-5.0	0.05-5.0	0.01-5
linoleic acid	0.01-2.0	0.01-2.0	0.01-2.0	0.001-0.1
DL-α-lipoic acid	0.03-1.0	0.03-1.0	0.03-1.0	0.01-10
pyridoxine.HCl	0.5-30	0.5-30	0.5-30	0.005-10
putrescine.2HCl	0.025-0.25	0.025-0.25	0.025-0.25	0.0001-0.01
ethanolamine.HCl	2-100	2-100	2-100	0.1-10

US007598083B2

(12) **United States Patent**
Epstein et al.

(10) **Patent No.: US 7,598,083 B2**
(45) **Date of Patent: Oct. 6, 2009**

(54) **CHEMICALLY DEFINED MEDIA COMPOSITIONS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 468 days.

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(22) Filed: **Oct. 27, 2005**

(65) **Prior Publication Data**

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(51) **Int. Cl.**
C12N 5/00 (2006.01)
C12N 5/02 (2006.01)

(52) **U.S. Cl.** **435/404**; 435/325

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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Primary Examiner—Lora E Barnhart
(74) *Attorney, Agent, or Firm*—Kirk Baumeister

(57) **ABSTRACT**

Chemically defined media compositions for the culture of eukaryotic cells are disclosed. The compositions are useful for eukaryotic cell culture in perfusion bioreactors and other vessels.

11 Claims, 3 Drawing Sheets

Fig. 1

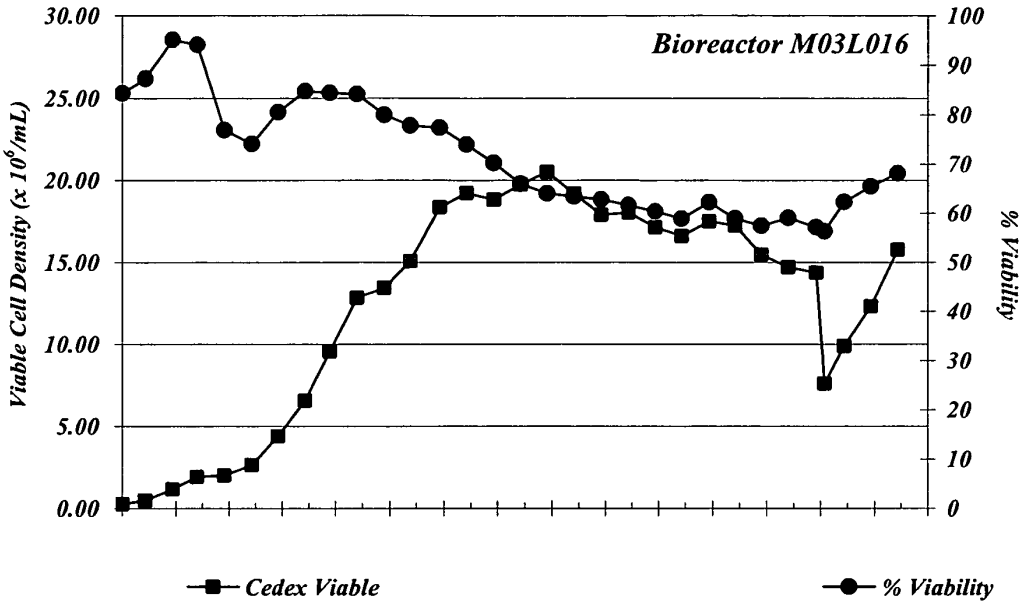

Bioreactor M03L016
Viable Cell Density (x 10^6/mL)
% Viability
30.00
25.00
20.00
15.00
10.00
5.00
0.00
100
90
80
70
60
50
40
30
20
10
0
Cedex Viable
% Viability

Fig. 2

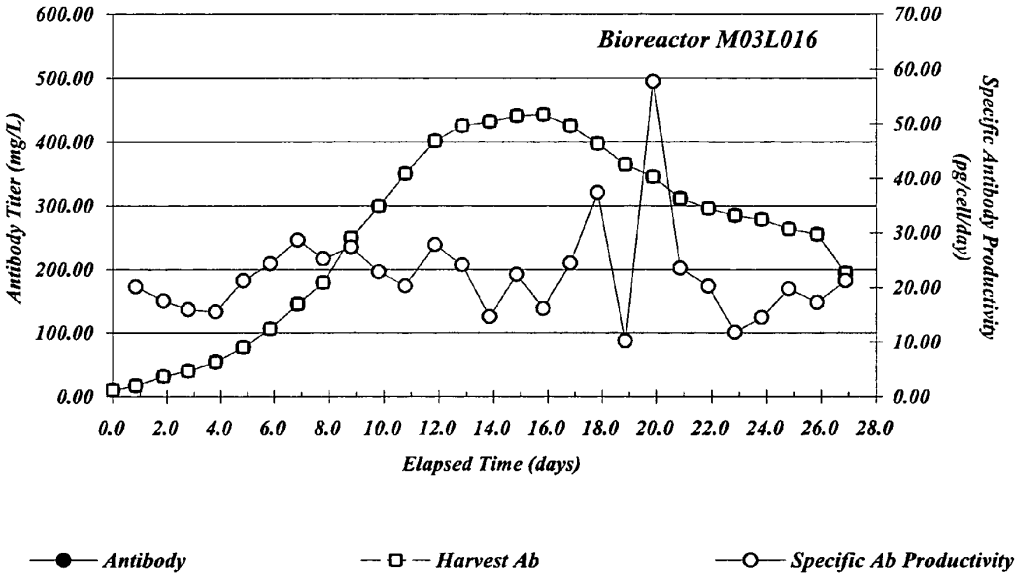
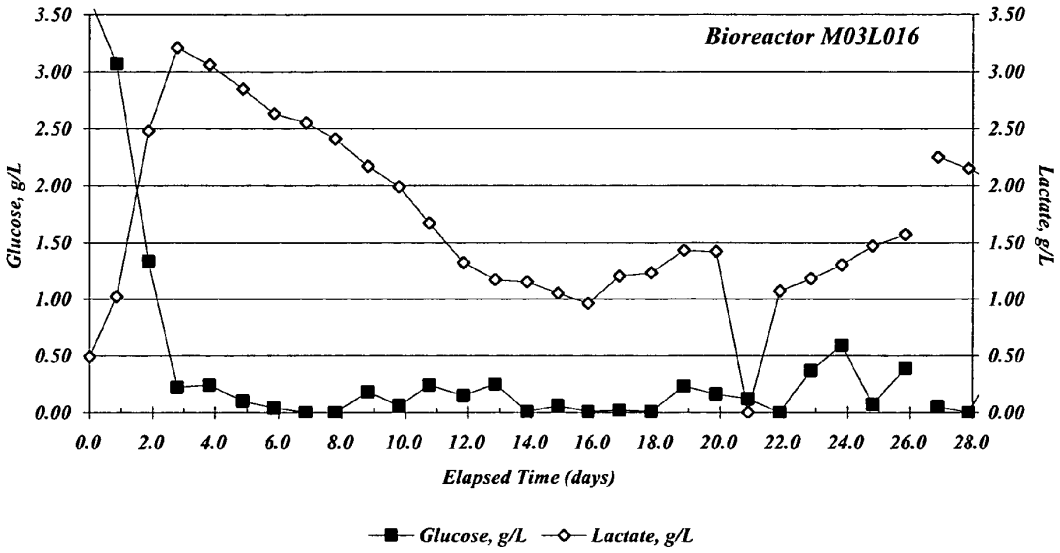

Bioreactor M03L016
Antibody Titer (mg/L)
600.00
500.00
400.00
300.00
200.00
100.00
0.00
Specific Antibody Productivity (pg/cell/day)
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
0.0 2.0 4.0 6.0 8.0 10.0 12.0 14.0 16.0 18.0 20.0 22.0 24.0 26.0 28.0
Elapsed Time (days)
Antibody
Harvest Ab
Specific Ab Productivity

Fig. 3


Bioreactor M03L016
Glucose, g/L
Lactate, g/L
Elapsed Time (days)
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
26.0
28.0
Glucose, g/L
Lactate, g/L

CHEMICALLY DEFINED MEDIA COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/623,718, filed 29 Oct. 2004, the entire contents of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to chemically defined media compositions for the culture of eukaryotic cells.

BACKGROUND OF THE INVENTION

Contamination of conventional eukaryotic cell culture media with "adventitious particles" such as bacterial, virus or prion particles is a serious potential problem in the industrial preparation of biopharmaceuticals such as antibodies or therapeutic proteins. Such contaminants in a biopharmaceutical are capable of causing patient infections and disease and may limit yields due to increased metabolic burdens on the host productioncell line.

Variant Creutzfeldt-Jakob disease (vCJD) is one example of a patient disease that could be caused by adventitious particle contamination. This disease is prion mediated in humans and is characterized by fatal neurodegeneration. vCJD has been strongly linked with exposure to the Bovine Spongiform Encephalopathy (BSE) prion which causes fatal, neurodegenerative "Mad Cow Disease" in cattle.

Adventitious particle contamination of conventional eukaryotic cell culture media can result from the incorporation of animal-derived components and protein growth factors into conventional media. Such contamination can occur when animal-derived media components are harvested from an animal harboring disease-causing bacteria, viruses, or prions. For example, bovine serum harvested from a cow with BSE may be contaminated with prions capable of causing human vCJD. The ultimate result of such adventitious particle contamination can be the contamination of eukaryotic cell cultures and the biopharmaceuticals prepared from such cultures.

Adventitious particle contamination can be avoided by culturing eukaryotic cells in animal component free cell culture media. Ideally, such media are "chemically defined" such that the media compositions contain only known chemical compounds, and are free of all proteins—even those not of animal origin such as recombinant proteins.

Chemically defined media compositions optimal for production of biopharmaceuticals, such as antibodies, must satisfy several different criteria. First, such compositions must limit eukaryotic cell damage resulting from shear forces and other cell-damaging processes that occur in the bioreactor vessels typically used for biopharmaceutical production. Second, such compositions must enable eukaryotic cell cultures to have high viable cell densities (i.e., number viable cells/ml media) and high percentages of viable cells. Third, such compositions must permit high titers of secreted biopharmaceutical products (i.e., antibody mg/L media) and high specific productivities (i.e., pg antibody/viable cell/day). Lastly, such compositions must limit the production of lactic acid by cultured eukaryotic cells to permit the most efficient cellular use of glucose.

Thus, a need exists for chemically defined media compositions which satisfy these criteria and are optimized for biopharmaceutical production.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**. Eukaryotic cell viability in MET 1.5 cell culture media.

FIG. **2**. Antibody titer and specific productivity in MET 1.5 cell culture media.

FIG. **3**. Decreased lactate production in MET 1.5 cell culture media.

SUMMARY OF THE INVENTION

One aspect of the invention is a soluble composition, suitable for producing a cell culture media, wherein the media comprises the following components in the following amounts per liter:

anhydrous $CaCl_2$, 5-200 mg;
anhydrous $MgCl_2$, 15-50 mg;
anhydrous $MgSO_4$, 20-80 mg;
$FeSO_4.7H_2O$, 0.05-0.50 mg;
$Fe(NO_3)_3.9H_2O$, 0.01-0.08 mg;
$ZnSO_4.7H_2O$, 0.40-1.20 mg;
ferric ammonium citrate, 0.04-200 mg;
KCl, 280-500 mg;
NaCl, 5000-7500 mg;
NaH_2PO_4—H_2O, 30-100 mg;
Na_2HPO_4, 30-100 mg;
$CuSO_4.5H_2O$, 0.001-0.005 mg;
$CoCl_2.6H_2O$, 0.001-0.10 mg;
$(NH_4)_6Mo_7O_{24}$ $4H_2O$, 0.001-0.005 mg;
$MnSO_4$—H_2O, 0.000070-0.0080 mg;
$NiSO_4.6H_2O$, 0.000025-0.0005 mg;
Na_2SeO_3, 0.004-0.07 mg;
$Na_2SiO_3.9H_2O$, 0.02-0.4 mg;
$SnCl_2.2H_2O$, 0.000025-0.0005 mg;
NH_4VO_3, 0.0001-0.0025 mg;
D-Glucose, 500-8000 mg;
sodium pyruvate, 0.0-1000 mg;
sodium hypoxanthine, 0.0-20.0 mg;
glycine, 0.0-150 mg;
L-alanine, 0.0-150 mg;
L-arginine.HCl, 200-5000 mg;
L-asparagine.H_2O, 40-250 mg;
L-aspartic acid, 20-1000 mg;
L-cysteine.HCl H_2O, 25.0-250 mg;
L-cystine.2HCl, 15-150 mg;
L-glutamic acid, 0-1000 mg;
L-histidine.HCl.H_2O, 100-500 mg;
L-isoleucine, 50-1000 mg;
L-leucine, 50-1000 mg;
L-lysine.HCl, 100-1000 mg;
L-methionine, 50-500 mg;
L-ornithine.HCl, 0-100 mg;
L-phenylalanine, 25-1000 mg;
L-proline, 0-1000 mg;
L-serine, 50-500 mg;
L-taurine, 0-1000 mg;
L-threonine, 50-600 mg;
L-tryptophan, 2-500 mg;
L-tyrosine.2Na.$2H_2O$, 25-250 mg;
L-valine, 100-1000 mg;
d-biotin, 0.04-1.0 mg;
D-calcium pantothenate, 0.1-5.0 mg;
choline chloride, 1-100 mg;
folic acid, 1-10 mg;
i-Inositol, 10-1000 mg;
nicotinamide, 0.5-30 mg;
p-aminobenzoic acid, 0.1-20 mg;

riboflavin, 0.05-5.0 mg;
thiamine.HCl, 0.5-20 mg;
thymidine, 0-3.0 mg;
vitamin B_{12}, 0.05-5.0 mg;
linoleic acid, 0.01-2.0 mg;
DL-α-lipoic acid, 0.03-1.0 mg;
pyridoxine.HCl, 0.5-30 mg;
putrescine.2HCl, 0.025-0.25 mg; and
ethanolamine.HCl, 2-100 mg.

Another aspect of the invention is a soluble composition, suitable for producing a cell culture media, wherein the media comprises the following components in the following amounts per liter:
$CaCl_2$, 100.95 mg;
$MgCl_2$, 24.77 mg;
$MgSO_4$, 42.24 mg;
$FeSO_4.7H_2O$, 0.3607 mg;
$Fe(NO_3)_3.9H_2O$, 0.0432 mg;
$ZnSO_4.7H_2O$, 0.6225 mg;
ferric ammonium citrate, 43.25 mg;
KCl, 386.9 mg;
NaCl, 5866.0 mg;
NaH_2PO_4—H_2O, 54.07 mg;
Na_2HPO_4, 61.44 mg;
$CuSO_4.5H_2O$, 0.003287 mg;
$CoCl_2.6H_2O$, 0.0020606 mg;
$(NH_4)_6Mo_7O_{24}.4H_2O$, 0.000535 mg;
$MnSO_4.H_2O$, 0.00008571 mg;
$NiSO_4.6H_2O$, 0.0000514 mg;
Na_2SeO_3, 0.007489 mg;
$Na_2SiO_3.9H_2O$, 0.03671 mg;
$SnCl_2.2H_2O$, 0.0000488 mg;
NH_4VO_3, 0.0002530 mg;
D-Glucose, 3680.52 mg;
sodium pyruvate, 100 mg;
sodium hypoxanthine, 2.069 mg;
glycine, 16.23 mg;
L-alanine, 79.31 mg;
L-arginine.HCl, 674.89 mg;
L-asparagine.H_2O, 182.25 mg;
L-aspartic acid, 67.23 mg;
L-cysteine.HCl.H_2O, 57.63 mg;
L-cystine.2HCl, 106.70 mg;
L-glutamic acid, 6.36 mg;
L-histidine.HCl.H_2O, 250.55 mg;
L-isoleucine, 245.43 mg;
L-leucine, 263.42 mg;
L-lysine.HCl, 276.41 mg;
L-methionine, 85.40 mg;
L-ornithine.HCl, 2.44 mg;
L-phenylalanine, 104.23 mg;
L-proline, 14.94 mg;
L-serine, 146.36 mg;
L-taurine, 3.64 mg;
L-threonine, 199.09 mg;
L-tryptophan, 70.71 mg;
L-tyrosine.2Na.2H_2O, 195.58 mg;
L-valine, 174.34 mg;
d-biotin, 0.4359 mg;
D-calcium pantothenate, 1.9394 mg;
choline chloride, 10.8009 mg;
folic acid, 3.4329 mg;
i-inositol, 81.7965 mg;
nicotinamide, 3.1342 mg;
p-aminobenzoic acid, 2.1645 mg;
riboflavin, 0.5359 mg;
thiamine.HCl, 2.3377 mg;
thymidine, 0.316 mg;
vitamin B_{12}, 0.5887 mg;
linoleic acid, 0.0364 mg;
DL-α-lipoic acid, 0.0909 mg;
pyridoxine.HCl, 3.0442 mg;
putrescine.2HCl, 0.0701 mg; and
ethanolamine.HCl, 14.37 mg.

The invention also provides compositions comprising cell culture media which can be made from the soluble compositions of the invention.

DETAILED DESCRIPTION OF THE INVENTION

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

The term "buffering molecule" as used herein and in the claims means a molecule that has a buffering range suitable for maintaining a pH between 5.9 and 7.8.

The term "pK_a" as used herein and in the claims means the negative logarithm of the acid dissociation constant (K_a) of a buffering molecule in an aqueous solution. pK_a is, in part, a function of the temperature of the aqueous solution in which a buffering molecule is solubilized.

The term "cell protectant" as used herein and in the claims means a substance that protects eukaryotic cells from damage. Such damage may be caused, for example, by shear forces or the effects of gas bubble sparging in a bioreactor vessel.

The present invention provides chemically defined compositions useful in the culture of eukaryotic cells. Such eukaryotic cells may have insect, avian, mammalian, or other origins. These cells may secrete a protein, such as an antibody, or produce other useful products or results. These proteins, products, or results may be constituatively produced by a cell or produced as the result of transfection with a nucleic acid sequence. The cells may be cultured in liquid media as suspension cultures or as adherent cultures. Cells may also be cultured by suspension in semi-solid media comprising the compositions of the invention.

Cells may be cultured in a variety of vessels including, for example, perfusion bioreactors, cell bags, culture plates, flasks and other vessels well known to those of ordinary skill in the art. Ambient conditions suitable for cell culture, such as temperature and atmospheric composition, are also well known to those skilled in the art. Methods for the culture of cells are also well known to those skilled in the art.

The compositions of the invention are particularly useful in the culture of mammalian cells. Examples of mammalian cells include myeloma derived cells, non-immortalized cells of the B cell lineage, and immortalized cells of the B cell lineage such as hybridomas. Examples of myeloma derived cell lines include the SP2/0 (American Type Culture Collection (ATCC), Manasas, Va., CRL-1581), NSO (European Collection of Cell Cultures (ECACC), Salisbury, Wiltshire, UK, ECACC No. 85110503), FO (ATCC CRL-1646), and Ag653 (ATCC CRL-1580) cell lines which were obtained from mice. The C743B cell line is an example of a SP2/0 derived cell line that produces a fully human, anti-IL-12 mAb as the result of stable transfection. The YB2/0 cell line (ATCC CRL-1662) is an example of a myeloma derived cell line obtained from rats (*Rattus norvegicus*). An example of a myeloma derived cell line obtained from humans is the U266 cell line (ATTC CRL-TIB-196). Some myeloma derived cell lines, such as NSO, YB2/0, and Ag653 cells and related cell lines may require chemically defined lipid concentrates or other supplements for successful culture. Those skilled in the

art will recognize other myeloma cell lines and myeloma derived cell lines as well as any supplements required for the successful culture of such cells.

In one aspect the invention provides a soluble composition, suitable for producing a cell culture media, wherein the media comprises the following components in the following amounts per liter:

anhydrous $CaCl_2$, 5-200 mg;
anhydrous $MgCl_2$, 15-50 mg;
anhydrous $MgSO_4$, 20-80 mg;
$FeSO_4.7H_2O$, 0.05-0.50 mg;
$Fe(NO_3)_3.9H_2O$, 0.01-0.08 mg;
$ZnSO_4.7H_2O$, 0.40-1.20 mg;
ferric ammonium citrate, 0.04-200 mg;
KCl, 280-500 mg;
NaCl, 5000-7500 mg;
$NaH_2PO_4.H_2O$, 30-100 mg;
Na_2HPO_4, 30-100 mg;
$CuSO_4.5H_2O$, 0.001-0.005 mg;
$CoCl_2.6H_2O$, 0.001-0.10 mg;
$(NH_4)_6Mo_7O_{24}$ $4H_2O$, 0.001-0.005 mg;
$MnSO_4.H_2O$, 0.000070-0.0080 mg;
$NiSO_4.6H_2O$, 0.000025-0.0005 mg;
Na_2SeO_3, 0.004-0.07 mg;
$Na_2SiO_3.9H_2O$, 0.02-0.4 mg;
$SnCl_2.2H_2O$, 0.000025-0.0005 mg;
NH_4VO_3, 0.0001-0.0025 mg;
D-Glucose, 500-8000 mg;
sodium pyruvate, 0.0-1000 mg;
sodium hypoxanthine, 0.0-20.0 mg;
glycine, 0.0-150 mg;
L-alanine, 0.0-150 mg;
L-arginine.HCl, 200-5000 mg;
L-asparagine.H_2O, 40-250 mg;
L-aspartic acid, 20-1000 mg;
L-cysteine.HCl H_2O, 25.0-250 mg;
L-cystine.2HCl, 15-150 mg;
L-glutamic acid, 0-1000 mg;
L-histidine.HCl.H_2O, 100-500 mg;
L-isoleucine, 50-1000 mg;
L-leucine, 50-1000 mg;
L-lysine.HCl, 100-1000 mg;
L-methionine, 50-500 mg;
L-ornithine.HCl, 0-100 mg;
L-phenylalanine, 25-1000 mg;
L-proline, 0-1000 mg;
L-serine, 50-500 mg;
L-taurine, 0-1000 mg;
L-threonine, 50-600 mg;
L-tryptophan, 2-500 mg;
L-tyrosine-2Na-$2H_2O$, 25-250 mg;
L-valine, 100-1000 mg;
d-biotin, 0.04-1.0 mg;
D-calcium pantothenate, 0.1-5.0 mg; choline chloride, 1-100 mg;
folic acid, 1-10 mg;
i-Inositol, 10-1000 mg;
nicotinamide, 0.5-30 mg;
p-aminobenzoic acid, 0.1-20 mg;
riboflavin, 0.05-5.0 mg;
thiamine.HCl, 0.5-20 mg;
thymidine, 0-3.0 mg;
vitamin B_{12}, 0.05-5.0 mg;
linoleic acid, 0.01-2.0 mg;
DL-α-lipoic acid, 0.03-1.0 mg;
pyridoxine.HCl, 0.5-30 mg;
putrescine.2HCl, 0.025-0.25 mg; and
ethanolamine.HCl, 2-100 mg.

This type of soluble composition has been named "MET" and typically is a powder.

In another aspect the invention provides a soluble composition, suitable for producing a cell culture media, wherein the media comprises the following components in the following amounts per liter:

$CaCl_2$, 100.95 mg;
$MgCl_2$, 24.77 mg;
$MgSO_4$, 42.24 mg;
$FeSO_4.7H_2O$, 0.3607 mg;
$Fe(NO_3)_3.9H_2O$, 0.0432 mg;
$ZnSO_4.7H_2O$, 0.6225 mg;
ferric ammonium citrate, 43.25 mg;
KCl, 386.9 mg;
NaCl, 5866.0 mg;
$NaH_2PO_4.H_2O$, 54.07 mg;
Na_2HPO_4, 61.44 mg;
$CuSO_4.5H_2O$, 0.003287 mg;
$CoCl_2.6H_2O$, 0.0020606 mg;
$(NH_4)_6Mo_7O_{24}.4H_2O$, 0.000535 mg;
$MnSO_4.H_2O$, 0.00008571 mg;
$NiSO_4.6H_2O$, 0.0000514 mg;
Na_2SeO_3, 0.007489 mg;
$Na_2SiO_3.9H_2O$, 0.03671 mg;
$SnCl_2.2H_2O$, 0.0000488 mg;
NH_4VO_3, 0.0002530 mg;
D-Glucose, 3680.52 mg;
sodium pyruvate, 100 mg;
sodium hypoxanthine, 2.069 mg;
glycine, 16.23 mg;
L-alanine, 79.31 mg;
L-arginine.HCl, 674.89 mg;
L-asparagine.H_2O, 182.25 mg;
L-aspartic acid, 67.23 mg;
L-cysteine.HCl.H_2O, 57.63 mg;
L-cystine.2HCl, 106.70 mg;
L-glutamic acid, 6.36 mg;
L-histidine.HCl.H_2O, 250.55 mg;
L-isoleucine, 245.43 mg;
L-leucine, 263.42 mg;
L-lysine-HCl, 276.41 mg;
L-methionine, 85.40 mg;
L-ornithine-HCl, 2.44 mg;
L-phenylalanine, 104.23 mg;
L-proline, 14.94 mg;
L-serine, 146.36 mg;
L-taurine, 3.64 mg;
L-threonine, 199.09 mg;
L-tryptophan, 70.71 mg;
L-tyrosine.2Na.$2H_2O$, 195.58 mg;
L-valine, 174.34 mg;
d-biotin, 0.4359 mg;
D-calcium pantothenate, 1.9394 mg;
choline chloride, 10.8009 mg;
folic acid, 3.4329 mg;
i-inositol, 81.7965 mg;
nicotinamide, 3.1342 mg;
p-aminobenzoic acid, 2.1645 mg;
riboflavin, 0.5359 mg;
thiamine.HCl, 2.3377 mg;
thymidine, 0.316 mg;
vitamin B_{12}, 0.5887 mg;
linoleic acid, 0.0364 mg;
DL-α-lipoic acid, 0.0909 mg;

pyridoxine.HCl, 3.0442 mg;
putrescine.2HCl, 0.0701 mg; and
ethanolamine.HCl, 14.37 mg.

This soluble composition has been named "MET 1.5" and typically is a powder.

In one embodiment the soluble MET and MET 1.5 compositions of the invention comprise a buffering molecule with a pK_a of between 5.9 and 7.8; and a cell protectant. Examples of buffering molecules with a pK_a of between 5.9 and 7.8 include MOPS (pK_a 7.20 at 25° C.; pK_a 7.02 at 37° C.), TES (2-[tris (hydroxymothyl) methyl]amino ethanesulphonic acid; pK_a 7.40 at 25° C.; pK_a 7.16 at 37° C.), and imidazole (pK_a 6.95 at 25° C.). Examples of cell protectants are non-ionic surfactants such as Pluronic-F68, polyvinyl alcohol (PVA), polyethylene glycol (PEG), and dextran sulfate. Those skilled in the art will recognize other buffering molecules with a pK_a of between 5.9 and 7.8 and cell protectants.

In another embodiment of the soluble MET compositions of the invention the buffering molecule consists of MOPS in the amount of 1047-5230 mg per liter of media volume, and the cell protectant consists of Pluronic-F68 in the amount of 250-1500 mg per liter of media volume.

In another embodiment of the soluble MET1.5 compositions of the invention the buffering molecule consists of MOPS in the amount of 2709.66 mg per liter of media volume, and the cell protectant consists of Pluronic-F68 in the amount of 865.80 mg per liter of media volume.

The soluble compositions of the invention may be prepared in a variety of forms. It is preferred that the soluble compositions of the invention are prepared in the form of a powder. The powdered forms of the soluble compositions of the invention are suitable for cell culture for at least 3 years from the date the soluble composition is prepared. The soluble compositions of the invention may also be prepared, for example, in the form of one or more pellets or tablets.

The soluble compositions of the invention can be solubilized in water. Typically, the water used to solubilize the soluble compositions of the invention has a resistivity of 18.2 MΩ·cm at 25° C., a total organic content of less than 20 ppb, a total microorganism content of less than 10 colony forming units per ml, a total heavy metal content of less than 0.01 ppm, a total silicates content of less than 0.01 ppb, and a total dissolved solids content of less than 0.03 ppm. Water with these properties can be prepared using a Super-Q™ Plus Water Purification System (Millipore Corp., Billerica, Mass., USA). The water used to solubilize the soluble compositions of the invention may also be filtered through a filter suitable for the removal of microorganisms. A filter with a 0.22 μM pore size is an example of such a filter. Microorganisms and other adventitious particles may also be removed or inactivated by other means well known in the art.

In one embodiment the invention provides a composition comprising a cell culture media made by the steps comprising selecting a final media volume, providing a soluble MET composition, solubilizing the soluble composition in a volume of water less than the final media volume, adding 1.022 g of L-glutamine per liter of final media volume, adding a bicarbonate ion providing substance sufficient to a produce a bicarbonate ion concentration of between 0.020 M and 0.030 M in the final media volume, optionally adding at least one substance selected from the group consisting of mycophenolic acid, hypoxanthine, xanthine, or soy hydrosylate, adding a quantity of base sufficient to adjust the pH of the solution to between pH 5.9 and pH 7.8, and adding water sufficient to bring the volume of the composition to the selected final media volume. In this embodiment of the invention the media composition that is the product of this process has been named "MET media." Typically MET media is a liquid media.

In another embodiment the invention provides a composition comprising a cell culture media made by the steps comprising selecting a final media volume; providing a soluble MET1.5 composition, solubilizing the soluble composition in a volume of water less than the final media volume, adding 1.022 g of L-glutamine per liter of final media volume, adding a bicarbonate ion providing substance sufficient to a produce a bicarbonate ion concentration of between 0.020 M and 0.030 M in the final media volume, optionally adding at least one substance selected from the group consisting of mycophenolic acid, hypoxanthine, xanthine or soy hydrosylate, adding a quantity of base sufficient to adjust the pH of the solution to between pH 5.9 and pH 7.8, and adding water sufficient to bring the volume of the composition to the selected final media volume. In this embodiment of the invention the media composition that is the product of this process has been named "MET 1.5 media." Typically MET 1.5 media is a liquid media.

In one embodiment of the invention the bicarbonate ion providing substance sufficient to a produce a bicarbonate ion concentration of between 0.020 M and 0.030 M in the final media volume is 2.1 g of $NaHCO_3$ per liter of final media volume. Adding this amount of $NaHCO_3$ per liter of final media volume produces a bicarbonate ion concentration of 0.025 M in the final media volume.

In one embodiment of the invention MET 1.5 media comprises the following components added in the following amounts per liter:
0.5 mg mycophenolic acid;
2.5 mg hypoxanthine; and
50 mg xanthine.

The MET media and MET 1.5 media compositions of the invention are typically provided to cells as a liquid media. The pH of the MET media and MET 1.5 media compositions of the invention is between pH 5.9 and pH 7.8. The pH of a liquid is a function of the temperature of the liquid. It is preferred that the pH of each media composition be between 7.1 and 7.25 at the temperature at which eukaryotic cell culture is being performed. Eukaryotic cell culture may be performed at temperatures higher or lower than 37° C., but is typically performed at 37° C.

In some applications liquid MET media and liquid MET 1.5 media may be used in the preparation of semi-solid cell culture media. For example, methylcellulose may be used to generate a semi-solid media incorporating the liquid MET media and liquid MET 1.5 media compositions of the invention. Such semi-solid media may be prepared by methods well known to those skilled in the art. Eukaryotic cells may be suspended in such semi-solid media and cultured by methods well known to those skilled in the art.

Other substances that can enhance cell growth or productivity may also be added to the soluble MET, MET media, soluble MET 1.5 and MET 1.5 media compositions of the invention. These substances may be lipids, nucleosides, peptide chains, corticosteroids, steroids, and the like. Such substance may be, for example:
adenosine preferably 0-20 μM;
guanosine preferably 0-20 μM;
cytidine preferably 0-20 μM;
uridine preferably 0-20 μM;
deoxyadenosine preferably 0-20 μM;
deoxyguanosine preferably 0-20 μM;
deoxycytidine preferably 0-20 μM;
thymidine preferably 0-20 μM;

dexamethasone preferably 10-150 nM;
hydrocortisone preferably 0-150 μM;
L-glycine-L-Lysine-L-glycine (GKG) peptide chain preferably 0-200 μm;
N-acetyl cysteine preferably 0-500 mg/L;
betaine preferably 0-500 mg/L;
L-malic acid preferably 0-500 mg/L;
oxaloacetic acid preferably 0-500 mg/L;
glycyrrhizic acid preferably 0-500 mg/L;
glycyrrhizic acid ammonium salt preferably 0-500 mg/L;
α-ketoglutarate preferably 0-500 mg/L;
L-leucine preferably 245-490 mg/L;
L-isoleucine preferably 220-440 mg/L;
L-lysine-HCl preferably 187-360 mg/L;
L-valine preferably 155-310 mg/L;
L-methionine preferably 57-114 mg/L;
L-phenylalanine preferably 76-152 mg/L;
L-serine preferably 37-74 mg/L;
L-threonine preferably 107-214 mg/L;
L-arginine.HCl preferably 200-300 mg/L;
L-asparagine preferably 114-170 mg/L;
L-aspartic acid (10-25 mg/L);
L-cysteine.HCl.H_2O preferably 46-75 mg/L;
Histidine.HCl.H_2O preferably 75-150 mg/L;
L-tyrosine preferably 40-80 mg/L;
L-tryptophan preferably 41-82 mg/L;
nicotinamide preferably 0.9-1.8 mg/L; and
ethanolamine HCl preferably 14-20 mg/L.

The quantities of each substance added to the compositions of the invention are those necessary to achieve the preferred molar concentration or mass per unit media volume prepared shown above.

The present invention is further described with reference to the following examples. These examples are merely to illustrate various aspects of the present invention and are not intended as limitations of this invention.

EXAMPLE 1

Eukaryotic Cell Viability in MET 1.5 Cell Culture Media

Chemically defined MET 1.5 cell culture media can sustain high cell growth and viability (FIG. **1**). To examine viable cell numbers, MET 1.5 media was supplied to 3 L perfusion bioreactors. Bioreactors were then inoculated with C743B cells such that the initial cell density was 3×10^6 cells/ml of MET 1.5 media. The C743B cell line produces a fully human, anti-IL-12 mAb and is a chemically adapted cell line derived from SP2/0 myeloma cells. C743B cells were grown for 29 days in the bioreactor and viable cell densities were monitored. Cell culture media was neutralized with a 0.2 M Na_2CO_3 (aq) solution for the first 9 days of culture and with 0.2 M Na_2CO_3, 0.0054 M K_2CO_3 (aq). Excessive cell density in the bioreactor was prevented by the removed of biomass from the bioreactor; cell removal began on day 15 and was gradually increased until day 26. The bioreactor was perfused with one volume of MET 1.5 media per day. Viable cell numbers were determined via a standard trypan blue dye exclusion assay using a CEDEX cell counter (Innovatis AG, Bielefeld, Del.). Total cell numbers for calculation of the percentage of viable cells were determined with the CEDEX instrument. For each determination the CEDEX instrument was used according to the manufacturer's instructions. O_2 and CO_2 were supplied to the bioreactor as a gas stream sparged into the bioreactor vessel. Data presented in Example 1, 2, and 3 are all from the same bioreactor run.

EXAMPLE 2

Antibody Titer and Specific Productivity in MET 1.5 Cell Culture Media

Chemically defined MET 1.5 cell culture media can sustain high monoclonal antibody titers and specific productivity (FIG. **2**). Cell culture and bioreactor operation was as described above. Fully human, anti-IL-12 mAb titers (mg/L) were determined by standard nephelometry techniques using a Beckman Array Analyzer. A purified fully human, anti-IL-12 mAb of known concentration was used to generate a standard curve for the determination of mAb titers by nephelometry. Viable cell numbers for calculation of specific productivity were determined as described above. Data presented in Example 1, 2, and 3 are all from the same bioreactor run.

EXAMPLE 3

Decreased Lactate Production in MET 1.5 Cell Culture Media

Lactate concentrations in MET 1.5 media decrease (FIG. **3**) as viable cell density increases (FIG. **1**). Cell culture and bioreactor operation was as described above. Lactate concentrations and glucose concentrations in the bioreactor culture media were determined using standard assays. Data presented in Example 1, 2, and 3 are all from the same bioreactor run.

As FIG. **3** indicates, lactate concentrations in MET 1.5 media gradually decreased until day 16 when biomass removal to decrease total cell density in the bioreactor began. During the same period glucose concentrations remained comparatively constant (FIG. **3**). Comparison of FIG. **3** to FIG. **1** reveals that viable C743B cell numbers in the same bioreactor were increasing until day 16. Together this data indicates a decrease in lactate production by C743B cells cultured in MET 1.5 media and more efficient metabolism of D-glucose by cells cultured in MET 1.5 media.

The present invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

The invention claimed is:

1. A soluble composition, suitable for producing a final volume of cell culture media, wherein the composition comprises the following components in the following amounts per liter of the final volume of cell culture media:
anhydrous $CaCl_2$, 5-200 mg;
anhydrous $MgCl_2$, 15-50 mg;
anhydrous $MgSO_4$, 20-80 mg;
$FeSO_4.7H_2O$, 0.05-0.50 mg;
$Fe(NO_3)_3.9H_2O$, 0.01-0.08 mg;
$ZnSO_4.7H_2O$, 0.40-1.20 mg;
ferric ammonium citrate, 0.04-200 mg;
KCl, 280-500 mg;
NaCl, 5000-7500 mg;
$NaH_2PO_4.H_2O$, 30-100 mg;
Na_2HPO_4, 30-100 mg;
$CuSO_4.5H_2O$, 0.001-0.005 mg;
$CoCl_2.6H_2O$, 0.001-0.10 mg;
$(NH_4)_6Mo_7O_{24}$ $4H_2O$, 0.001-0.005 mg;
$MnSO_4.H_2O$, 0.000070-0.0080 mg;

$NiSO_4.6H_2O$, 0.000025-0.0005 mg;
Na_2SeO_3, 0.004-0.07 mg;
$Na_2SiO_3.9H_2O$, 0.02-0.4 mg;
$SnCl_2.2H_2O$, 0.000025-0.0005 mg;
NH_4VO_3, 0.0001-0.0025 mg;
D-Glucose, 500-8000 mg;
sodium pyruvate, 0.0-1000 mg;
sodium hypoxanthine, 0.0-20.0 mg;
glycine, 0.0-150 mg;
L-alanine, 0.0-150 mg;
L-arginine.HCl, 200-5000 mg;
L-asparagine.H_2O, 40-250 mg;
L-aspartic acid, 20-1000 mg;
L-cysteine.HCl H_2O, 25.0-250 mg;
L-cystine.2HCl, 15-150 mg;
L-glutamic acid, 0-1000 mg;
L-histidine.HCl.H_2O, 100-500 mg;
L-isoleucine, 50-1000 mg;
L-leucine, 50-1000 mg;
L-lysine.HCl, 100-1000 mg;
L-methionine, 50-500 mg;
L-ornithine.HCl, 0-100 mg;
L-phenylalanine, 25-1000 mg;
L-proline, 0-1000 mg;
L-serine, 50-500 mg;
L-taurine, 0-1000 mg;
L-threonine, 50-600 mg;
L-tryptophan, 2-500 mg;
L-tyrosine.2Na.2H_2O, 25-250 mg;
L-valine, 100-1000 mg;
d-biotin, 0.04-1.0 mg;
D-calcium pantothenate, 0.1-5.0 mg;
choline chloride, 1-100 mg;
folic acid, 1-10 mg;
i-Inositol, 10-1000 mg;
nicotinamide, 0.5-30 mg;
p-aminobenzoic acid, 0.1-20 mg;
riboflavin, 0.05-5.0 mg;
thiamine.HCl, 0.5-20 mg;
thymidine, 0-3.0 mg;
vitamin B_{12}, 0.05-5.0 mg;
linoleic acid, 0.01-2.0 mg;
DL-α-lipoic acid, 0.03-1.0 mg;
pyridoxine.HCl, 0.5-30 mg;
putrescine.2HCl, 0.025-0.25 mg; and
ethanolamine.HCl, 2-100 mg.

2. The soluble composition of claim **1** further comprising a buffering molecule with a pK_a between 5.9 and 7.8 and a cell protectant.

3. The soluble composition of claim **2** wherein the buffering molecule consists of MOPS in the amount of 1047-5230 mg per liter of final media volume and the cell protectant consists of Pluronic-F68 in the amount of 250-1500 mg per liter of final media volume.

4. A composition comprising a cell culture media made by the steps comprising:

a) selecting a final media volume;
b) providing the soluble composition of claim **2** or claim **3**;
c) solubilizing the soluble composition in a volume of water less than the final media volume;
d) adding 1.022 g of L-glutamine per liter of final media volume;
e) adding a bicarbonate ion providing substance sufficient to produce a bicarbonate ion concentration of between 0.020 M and 0.030 M in the final media volume;
f) optionally adding at least one substance selected from the group consisting of mycophenolic acid, hypoxanthine, xanthine, and soy hydrolysate;
g) adding a quantity of base sufficient to adjust the pH of the solution to between pH 5.9 and pH 7.8; and
h) adding water sufficient to bring the volume of the composition to the selected final media volume.

5. The composition of claim **4** where the bicarbonate ion providing substance sufficient to a produce a bicarbonate ion concentration of between 0.020 M and 0.030 M in the final media volume is 2.1 g of $NaHCO_3$ per liter of final media volume.

6. A soluble composition, suitable for producing a final volume of cell culture media, wherein the composition comprises the following components in the following amounts per liter of the final volume of cell culture media:

$CaCl_2$, 100.95 mg;
$MgCl_2$, 24.77 mg;
$MgSO_4$, 42.24 mg;
$FeSO_4.7H_2O$, 0.3607 mg;
$Fe(NO_3)_3.9H_2O$, 0.0432 mg;
$ZnSO_4.7H_2O$, 0.6225 mg;
ferric ammonium citrate, 43.25 mg;
KCl, 386.9 mg;
NaCl, 5866.0 mg;
$NaH_2PO_4.H_2O$, 54.07 mg;
Na_2HPO_4, 61.44 mg;
$CuSO_4.5H_2O$, 0.003287 mg;
$CoCl_2.6H_2O$, 0.0020606 mg;
$(NH_4)_6Mo_7O_{24}.4H_2O$, 0.000535 mg;
$MnSO_4.H_2O$, 0.00008571 mg;
$NiSO_4.6H_2O$, 0.0000514 mg;
Na_2SeO_3, 0.007489 mg;
$Na_2SiO_3.9H_2O$, 0.03671 mg;
$SnCl_2.2H_2O$, 0.0000488 mg;
NH_4VO_3, 0.0002530 mg;
D-Glucose, 3680.52 mg;
sodium pyruvate, 100 mg;
sodium hypoxanthine, 2.069 mg;
glycine, 16.23 mg;
L-alanine, 79.31 mg;
L-arginine.HCl, 674.89 mg;
L-asparagine.H_2O, 182.25 mg;
L-aspartic acid, 67.23 mg;
L-cysteine.HCl.H_2O, 57.63 mg;
L-cystine.2HCl, 106.70 mg;
L-glutamic acid, 6.36 mg;
L-histidine.HCl.H_2O, 250.55 mg;
L-isoleucine, 245.43 mg;
L-leucine, 263.42 mg;
L-lysine.HCl, 276.41 mg;
L-methionine, 85.40 mg;
L-ornithine.HCl, 2.44 mg;
L-phenylalanine, 104.23 mg;
L-proline, 14.94 mg;
L-serine, 146.36 mg;
L-taurine, 3.64 mg;
L-threonine, 199.09 mg;
L-tryptophan, 70.71 mg;
L-tyrosine.2Na.2H_2O, 195.58 mg;
L-valine, 174.34 mg;
d-biotin, 0.4359 mg;
D-calcium pantothenate, 1.9394 mg;
choline chloride, 10.8009 mg;
folic acid, 3.4329 mg;
i-inositol, 81.7965 mg;
nicotinamide, 3.1342 mg;

p-aminobenzoic acid, 2.1645 mg;
riboflavin, 0.5359 mg;
thiamine.HCl, 2.3377 mg;
thymidine, 0.316 mg;
vitamin B_{12}, 0.5887 mg;
linoleic acid, 0.0364 mg;
DL-α-lipoic acid, 0.0909 mg;
pyridoxine.HCl, 3.0442 mg;
putrescine.2HCl, 0.0701 mg; and
ethanolamine.HCl, 14.37 mg.

7. The soluble composition of claim **6** further comprising a buffering molecule with a pK_a of between 5.9 and 7.8 and a cell protectant.

8. The soluble composition of claim **7** wherein the buffering molecule consists of MOPS in the amount of 2709.66 mg per liter of final media volume, and the cell protectant consists of Pluronic-F68 in the amount of 865.80 mg per liter of final media volume.

9. The soluble composition of claim **7** further comprising the following components in the following amounts per liter of final media volume:

0.5 mg mycophenolic acid;
2.5 mg hypoxanthine; and
50 mg xanthine.

10. A composition comprising a cell culture media made by the steps comprising:

a) selecting a final media volume;
b) providing the soluble composition of claim **7** or claim **8**;
c) solubilizing the soluble composition in a volume of water less than the final media volume;
d) adding 1.022 g of L-glutamine per liter of final media volume;
e) adding a bicarbonate ion providing substance sufficient to produce a bicarbonate ion concentration of between 0.020 M and 0.030 M in the final media volume;
f) optionally adding at least one substance selected from the group consisting of mycophenolic acid, hypoxanthine, xanthine and soy hydrolysate;
g) adding a quantity of base sufficient to adjust the pH of the solution to between pH 5.9 and pH 7.8; and
h) adding water sufficient to bring the volume of the composition to the selected final media volume.

11. The composition of claim **10** where the bicarbonate ion providing substance sufficient to a produce a bicarbonate ion concentration of between 0.020 M and 0.030 M in the final media volume is 2.1 g of $NaHCO_3$ per liter of final media volume.

* * * * *

United States Court of Appeals for the Federal Circuit

CERTIFICATE OF SERVICE

I, Robyn Cocho, being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

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1. This brief complies with the type-volume limitation of Fed. Cir. R. 32(a). This brief contains 13,987 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f) and Fed. Cir. R. 32(b).

2. This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6). This brief has been prepared in a proportionally spaced typeface using MS Word in a 14 point Times New Roman font.

Dated: December 10, 2018

/s/ Gregory L. Diskant
Gregory L. Diskant