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.	)	

MEMORANDUM AND ORDER

WOLF, D.J. July 30, 2018

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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.

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[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

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[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