IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

MYLAN INSTITUTIONAL LLC, APICORE US LLC, *Plaintiffs*, v. AUROBINDO PHARMA LTD, AUROBINDO PHARMA USA INC., AUROMEDICS PHARMA LLC, *Defendants*.	§ § § § § § § § § § § §	Case No. 2:16-CV-00491-RWS-RSP

REPORT AND RECOMMENDATION

Plaintiffs Apicore US LLC and Mylan Institutional LLC allege that Defendants Aurobindo Pharma Ltd., Aurobindo Pharma USA. Inc., and Auromedics Pharma LLC (collectively "Aurobindo") are importing and selling isosulfan blue formulations in violation of U.S. Patent Nos. 7,662,992, 8,969,616, and 9,353,050. Dkt. No. 12 (Amended Complaint) ¶¶ 13-14. Plaintiffs seek a preliminary injunction to prevent further infringement. Dkt. No. 20. The Court finds that Plaintiffs have established a likelihood of success on the merits with respect to at least one claim of each patent-in-suit, and that Apicore would be irreparably harmed without preliminary relief. Accordingly, Plaintiffs' motion for a preliminary injunction must be **GRANTED**.

I. BACKGROUND

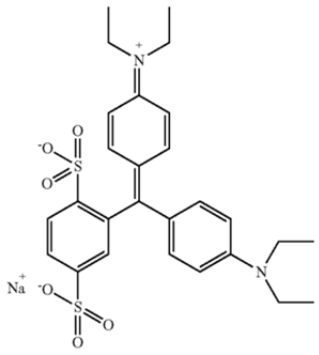
Sentinel lymph node biopsy is a procedure used to determine whether cancer cells have spread from an original tumor site to other parts of the body. *See* Dkt. No. 55-55 at 137. A sentinel lymph node is the lymph node (often nearest a tumor site) that is capable of "draining"

cancer cells from the tumor, allowing the cancer to spread to the rest of the lymphatic system. *Id.*; '050 patent at 1:54-56. To determine whether drainage has occurred, a surgeon biopsies the sentinel node and looks for cancer cells. Dkt. No. 55-55 at 137. The presence of cancer cells in the sentinel node is indicative of whether cancer has spread to the rest of the lymphatic system. *Id.*

It is difficult to perform a minimally-invasive sentinel lymph node biopsy without first mapping the lymphatic system surrounding the tumor site. *See, e.g.*, '050 patent at 1:53-54; Dkt. No. 80-9 at 1061. The lymphatic system is a network of interconnected vessels and nodes appearing to a surgeon's naked eye as clear fluid and is thus difficult to distinguish from surrounding tissue. *See* Dkt. No. 80-9 at 1061; Dkt. No. 55-52 ¶¶ 11-12. Since the early 1960s, surgeons mapped the lymphatic network surrounding a tumor site by making a subcutaneous or intradermal injection of a blue dye that is selectively absorbed by lymphatic cells. Dkt. No. 80-9 at 1061. The early medical literature acknowledged that surgeons used dyes that were not approved by the Food and Drug Administration (FDA), though no major problems were reported. *Id.*

A. Isosulfan Blue and Its FDA Approval

Isosulfan blue is the monosodium salt of a 2,5-disulfonated triarylmethane dye and is represented by the following structural formula:



See Dkt. No. 80-9 at 1061; '050 patent at 1:23-45. The chemical name for isosulfan blue is "N-[4-[[4-(diethyl amino) phenyl] (2,5-disulfophenyl) methylene]-2,5-cyclohexadien-1-ylidene]-N-ethylethanaminium, sodium salt." '050 patent at 1:23-45. The FDA approved the use of isosulfan blue for lymphatic vessel delineation in 1981. *See, e.g.*, Dkt. No. 20-2 ¶ 11.

After the FDA's approval, Dr. Jerry Hirsch and his colleagues from the Medical College of Virginia conducted clinical studies and found that an injectable 1% solution of isosulfan blue is safe and effective for identifying lymphatic cells during sentinel lymph node biopsy. *See* Dkt. No. 80-9 at 1064. Dr. Hirsch, through Hirsch Industries, Inc., commercially introduced the injectable 1% solution under the trade name Lymphazurin™. *See id.*; Dkt. No. 80-18. Hirsch Industries and successors-in-interest United States Surgical Corporation (U.S. Surgical), Tyco Healthcare, and later Covidien Ltd.[1] held the original New Drug Application (NDA) for the isosulfan blue solution and were the sole suppliers of Lymphazurin™ in the United States for 30 years. Dkt. No. 20-2 ¶ 11; Dkt. No. 79-33 ¶¶ 92, 105; Dkt. No. 81-3.

B. Problems with Isosulfan Blue Synthesis and Purity

From Lymphazurin™'s inception, Hirsch Industries reported problems associated with the synthesis and purification of isosulfan blue. Dr. Hirsch's original clinical trials publication described the use of an isosulfan blue mixture containing "94.5% dye content . . . as determined by high-pressure liquid chromatography." Dkt. No. 80-9 at 1061. The publication explained that "[t]he remaining 5.5% consists of closely related isomers produced during synthesis." *Id.* at 1061-62. Hirsch Industries later determined that the same lot of isosulfan blue contained only 83.4% isosulfan blue and 8.2% "other organics." Dkt. No. 80-18 at 1-2. Dr. Hirsch reported this finding to the FDA through a letter dated June 8, 1990, assuring the FDA that Hirsch Industries

[1] Covidien is now Medtronic Minimally Invasive Therapies, a division of Medtronic, Inc.

remained "committed to conduct studies designed to identify and/or remove the organic compound" found in the isosulfan blue product and welcomed the FDA's "advice as to the best approach to achieve this." *Id.* at 3.

The process used to prepare isosulfan blue was unknown to Hirsch Industries and later suppliers, but analytical testing suggested that manufacturers were using heavy-metal oxidants. *See, e.g.*, Dkt. No. 80-19; Dkt. No. 79-33 ¶ 96. For about 26 years following the FDA's approval of isosulfan blue, Sigma-Aldrich Corporation supplied Hirsch Industries and successors-in-interest with isosulfan blue manufactured by Allied Chemical Corporation. Dkt. No. 80-19; Dkt. No. 80-16; Dkt. No. 79-33 ¶¶ 96-97. Allied Chemical's manufacturing process was unknown, but records indicate the presence of lead, which is consistent with the use of a lead compound during synthesis. *See* Dkt. No. 80-19. Sigma-Aldrich "developed a recrystallization process that removed the lead and purified the [isosulfan blue]," but records do not specify the isosulfan blue percentage in the purified product. *See* Dkt. No. 80-16.

In early to mid-2000, after Hirsch Industries' original isosulfan blue NDA had been transferred to Covidien predecessors, Allied Chemical stopped supplying Sigma-Aldrich with isosulfan blue. *See* Dkt. No. 80-19; Dkt. No. 79-33 ¶ 101. Sigma-Aldrich and Covidien predecessors initiated efforts to identify a new supplier, an effort that took "more than five years of determination and focus," according to a Covidien press release. *See* Dkt. No. 81-3; Dkt. No. 80-16. Before a new supplier could be found, existing supplies of isosulfan blue became depleted, eventually prompting Covidien to send a letter to its customers notifying them that Covidien was "completely out" of Lymphazurin™, but that Covidien expected a "*potential* return to supply in February of 2008." Dkt. No. 81-2.

By June 2008, Covidien and Sigma-Aldrich had located a new supplier, Innovassynth Technologies, a chemical company located in Mumbai, India, and necessary process and manufacturing changes were approved by the FDA. Dkt. No. 81-3; Dkt. No. 80-19. Innovassynth's process involved the use of ammonium dichromate, resulting in chromium levels up to 100 parts per million (ppm). *See* Dkt. No. 80-19. Sigma-Aldrich developed a process to purify Innovassynth's crude isosulfan blue that reportedly reduced chromium levels to below 10 ppm, but the record does not indicate the percentage of isosulfan blue present in the purified Innovassynth product. *See id.* Sigma-Aldrich reported numerous problems with the purity of Innovassynth's product, *see* Dkt. No. 81-4, 81-5, 81-6, eventually prompting Sigma-Aldrich to develop its own manufacturing process sometime around 2010. *See* Dkt. No. 81-8.

C. The Patents-in-Suit and Apicore's Generic Isosulfan Blue Product

Apicore was founded in 2003 and, with six employees by 2004, began developing an improved process for synthesizing isosulfan blue. *See id.* In September 2004, Apicore partnered with Synerx Pharma, LLC, Mylan's predecessor and a manufacturer of finished drug products, to develop and market a generic version of Lymphazurin™. Dkt. No. 55-19. On May 11, 2007, Apicore filed Non-Provisional Patent Application No. 11/747,291 that ultimately led to the three patents-in-suit, all of which claim priority to the '291 application. *See* '992 patent at 1:5-10; '616 patent at 1:5-15; '050 patent at 1:5-15. Consistent with reports from isosulfan blue suppliers, the patents explain that existing methods of synthesizing isosulfan blue used hazardous oxidizing agents and crude methods of purification. *See, e.g.*, '050 patent at 1:63-2:14. The patents thus describe a need for preparing high-purity isosulfan blue that is suitable for use in pharmaceutical formulations. *Id.* at 2:20-23.

The patents claim both methods of preparing isosulfan blue and a high-purity form of isosulfan blue. The '992 and '616 patents claim processes in which an isoleuco acid is reacted in a polar solvent with silver oxide to form isosulfan blue acid, which is then treated with a sodium solution to form isosulfan blue. *See, e.g.,* '616 patent at 9:38-64. The '992 patent claims recite a more specific process in which the isoleuco acid is combined with "2.0 to 3.0 equivalents of silver oxide." '992 patent at 9:44-65. The claimed methods provide isosulfan blue "having purity greater than 99.5% by [High Performance Liquid Chromatography] HPLC." *See id.* at 7:29-34. The '050 patent claims isosulfan blue "having a purity of at least 99.0% by HPLC." '050 patent at 9:54-57. The '050 patent also claims solutions and compositions containing the high-purity isosulfan blue. *Id.* at 12:8-12.

Based on the process described in the patents-in-suit, Synerx[2] filed an Abbreviated New Drug Application (ANDA) seeking FDA approval to market a generic version of Lymphazurin™ in September 2008, and the FDA approved the ANDA in July 2010. Dkt. No. 55-20, 55-21. By 2011, isosulfan blue sales had become a significant portion of Apicore's revenue. *See* Dkt. No. 20-29 ¶¶ 11-15. At the same time, Covidien's Lymphazurin™ sales sharply declined, *see* Dkt. No. 20-14 ¶ 23, and Covidien withdrew Lymphazurin™ from the market by September 2012, *see* Dkt. No. 55-23 at 5561. The FDA determined that Covidien discontinued Lymphazurin™ for "reasons other than safety or effectiveness." Dkt. No. 55-23 at 5561. Since Covidien's exit from the market, Mylan became the sole supplier of isosulfan blue drug product until March 2016, when Aurobindo entered the market. *See* Dkt. No. 20-14 ¶ 23. Mylan sourced its supply of isosulfan blue exclusively through Apicore. *See* Dkt. No. 20-2 ¶ 14.

[2] By February 2012, Mylan Institutional LLC had acquired Synerx and became the ANDA holder and exclusive licensee of the patents-in-suit. *See* Dkt. No. 55-22; Dkt. No. 12 ¶¶ 4, 29.

D. Aurobindo's Entry into the Isosulfan Blue Market

Aurobindo Pharma, LTD is an Indian corporation headquartered in Andhra Pradesh, India. Dkt. No. 40 at 2; Dkt. No. 27-1 ¶ 5. Aurobindo Pharma USA Inc., and AuroMedics Pharma LLC are Delaware corporations and wholly-owned subsidiaries of Aurobindo India, both headquartered in Dayton, New Jersey. *Id.* at 3; Dkt. No. 27-1 ¶¶ 3-4.

Aurobindo sought FDA approval for a generic isosulfan blue product sometime after the application leading to Apicore's '992 patent was published. *See* Dkt. No. 80-14 at 3. Aurobindo informed the FDA that, after having studied a "number of patents" describing processes for manufacturing isosulfan blue, Aurobindo selected U.S. Patent No. 7,534,911, a patent filed after the priority date of the patents-in-suit, and Apicore's '992 patent. *See* Dkt. No. 80-14 at 3. Based on initial studies, Aurobindo "considered the process described in [the '992] patent for the initial sample preparation and further, the optimization of the process." *Id.*

Aurobindo acknowledged to the FDA that the '992 patent claims recite the use of silver oxide to convert the isoleuco acid to isosulfan blue acid, and thus Aurobindo was looking for a reagent "other than silver oxide." *Id.* at 6. Aurobindo reported results from a process involving manganese dioxide, but the process resulted in 5-10% impurity. *Id.* at 8. According to Aurobindo, the impurity could not be removed by recrystallization, column chromatography, or acid-base purification, and Aurobindo therefore decided to purify the material through preparatory HPLC to achieve a purity greater than 99.5%. *Id.*

The Food and Drug Administration approved Aurobindo's ANDA to market its isosulfan blue product on February 2, 2016, Dkt. No. 55-24, and Aurobindo publicly announced its intent to sell the product within the United States in March 2016, Dkt. No. 40 at 9. Aurobindo thereafter began importing and selling its isosulfan blue product, *id.* at 13-14, and as of October,

2016, Aurobindo had captured more than half of the isosulfan blue market, *see, e.g.*, Dkt. No. 97-1 at 5-6.

E. Procedural History

Plaintiffs filed this action on May 11, 2016, Dkt. No. 1, and later moved for a preliminary injunction on June 6, 2016, Dkt. No. 20. Aurobindo filed a declaratory judgment action against Apicore and Mylan in the District of New Jersey, seeking a judgment of noninfringement and invalidity. *See Aurobindo v. Apicore*, Case No. 1:16-cv-03358, Dkt. No. 1 (D.N.J. June 6, 2016). The New Jersey action was administratively stayed pending resolution of Aurobindo's motion to change venue in this case to New Jersey. Aurobindo's motion was denied on November 15, 2016, Dkt. No. 100, and Apicore and Mylan thereafter requested that the New Jersey action be consolidated with this case or dismissed. *See id.*, Dkt. No. 20 (D.N.J. Nov. 15, 2016). The parties dispute whether the New Jersey action will bar Aurobindo from petitioning the Patent Office for inter partes review of the patents-in-suit. *See id.*, Dkt. No. 16; *see also* 35 U.S.C. § 315(a)(1).

Plaintiffs seek a preliminary injunction because they allege that Defendants' product and method of manufacture will likely be found to infringe the patents-in-suit, and that irreparable harm will result if preliminary relief is not granted. Dkt. No. 20. Aurobindo contends that the patents are invalid and not infringed, and that Plaintiffs' harm is not irreparable. Dkt. No. 55.

II. DISCUSSION

"A plaintiff seeking a preliminary injunction must establish that he is likely to succeed on the merits, that he is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in his favor, and that an injunction is in the public interest." *Winter v. Natural Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008). These traditional four factors "apply with equal force to disputes arising under the Patent Act." *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006).

A. Likelihood of Success on the Merits

Assessing whether Plaintiffs are likely to prove that Aurobindo is infringing the patents-in-suit depends on the scope of the asserted claims and how those claims compare to the accused product. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). Accordingly, "[t]he first step is determining the meaning and scope of the patent claims asserted to be infringed." *Id.*

1. Claim Construction

"'[T]he claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (quoting *Innova/Pure Water Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)). To determine the meaning of the claims, a district court starts by considering the intrinsic evidence. *Id.* at 1313; *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 861 (Fed. Cir. 2004); *Bell Atl. Network Servs., Inc. v. Covad Commc'ns Group, Inc.*, 262 F.3d 1258, 1267 (Fed. Cir. 2001). The intrinsic evidence includes the claims themselves, the specification, and the prosecution history. *Phillips*, 415 F.3d at 1314; *C.R. Bard, Inc.*, 388 F.3d at 861. The general rule, subject to certain specific exceptions, is that each claim term is construed according to its ordinary and accustomed meaning as understood by one of ordinary skill in the art at the time of the invention. *Phillips*, 415 F.3d at 1312–13; *Alloc, Inc. v. Int'l Trade Comm'n*, 342 F.3d 1361, 1368 (Fed. Cir. 2003); *Azure Networks, LLC v. CSR PLC*, 771 F.3d 1336, 1347 (Fed. Cir. 2014) ("There is a heavy presumption that claim terms carry their accustomed meaning in the relevant community at the relevant time.").

"The claim construction inquiry . . . begins and ends in all cases with the actual words of the claim." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998). A term's context in the asserted claim can be instructive. *Phillips*, 415 F.3d at 1314. Other

asserted or unasserted claims can also aid in determining the claim's meaning. *Id.* Differences among the claim terms can also assist in understanding a term's meaning. *Id.* "[C]laims 'must be read in view of the specification, of which they are a part.'" *Id.* (quoting *Markman*, 52 F.3d at 979). "[T]he specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Id.* (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002).

a) Prosecution History Disclaimer

"The doctrine of prosecution disclaimer . . . preclud[es] patentees from recapturing through claim interpretation specific meanings disclaimed during prosecution." *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1323 (Fed. Cir. 2003). "[I]n order for prosecution disclaimer to attach, the disavowal must be both clear and unmistakable." *3M Innovative Props. Co. v. Tredegar Corp.*, 725 F.3d 1315, 1325 (Fed. Cir. 2013). "Where the alleged disavowal is ambiguous, or even 'amenable to multiple reasonable interpretations,'" the Federal Circuit has declined to find prosecution disclaimer. *Avid Tech., Inc. v. Harmonic, Inc.*, 812 F.3d 1040, 1045 (Fed. Cir. 2016) (quoting *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1359 (Fed. Cir. 2003)).

Although the parties do not yet dispute the meaning of the '992 and '616 patent claims, Aurobindo identifies a portion of the prosecution history that raises the issue of whether Apicore disclaimed "the use of an acid along with an oxidizing agent to oxidize isosulfan blue." *See* Dkt. No. 55 at 6. The examiner rejected Apicore's pending claims as unpatentable over the "Kulkarni" reference, which discloses the synthesis of isosulfan blue using ammonium dichromate and sulfuric acid. *See* Dkt. No. 55-6. Apicore distinguished Kulkarni by explaining that "[a]rtisans have typically used lead or chrome oxides with *an acid* to make isosulfan blue,"

and that "[t]he use by applicants of silver oxide *without acid* is significantly different than the use in Kulkarni of sulfuric acid and ammonium dichromate." *Id.* at 10 (emphasis added).

Apicore's discussion of the Kulkarni reference does not raise a question regarding disclaimer of a process involving a weak acid such as the acid used in the accused process. As explained by Plaintiffs' expert, Dr. Jonathan Sessler, Kulkarni's process involves a harsh oxidizing agent and concentrated sulfuric acid. Dkt. No. 79-33 ¶ 125-26, ¶ 43. Apicore distinguished this process by emphasizing that the use of heavy-metal oxidants with strong acids is different than the process claimed in the '992 and '616 patents, which simply uses silver oxide. *See* Dkt. No. 55-6 at 10. Apicore may have disclaimed a process involving strong acid, but because Kulkarni did not involve the use of a weak acid, Apicore's prosecution statement was not referring to a weak acid when describing the "acid" of Kulkarni. *See id.* As explained by Dr. Sessler at the hearing, there is no question that phosphoric acid is a weak acid.

b) Ensnarement

Plaintiffs' theory of infringement with respect to the '992 and '616 patents relies on the doctrine of equivalents. Aurobindo raises a defense based on ensnarement, which, like prosecution history disclaimer, is a "legal limitation on the application of the doctrine of equivalents." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1323 (Fed. Cir. 2009) (quoting *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1368 (Fed. Cir. 2003)). "Ensnarement bars a patentee from asserting a scope of equivalency that would encompass, or 'ensnare,' the prior art." *Id.* at 1322. To determine whether there would be ensnarement, a district court first constructs a hypothetical claim that literally covers the accused product or process. *Id.* at 1324. "Next, the district court must assess the prior art introduced by the accused infringer and determine whether the patentee has carried its burden of persuading the court that the hypothetical claim is patentable over the prior art." *Id.* at 1325. "Ultimately, '[i]f

such a claim would be unpatentable under 35 U.S.C. §§ 102 or 103, then the patentee has overreached, and the accused device is noninfringing as a matter of law." *Id.* (quoting *Interactive Pictures Corp. v. Infinite Pictures, Inc.*, 274 F.3d 1371, 1380 (Fed. Cir. 2001)).

Aurobindo contends that the hypothetical claim is one that literally covers manganese dioxide, the oxidant used in the accused process, and that such a claim is obvious in view of prior art disclosing the use of manganese dioxide to oxidize triarylmethane dyes. Dkt. No. 55 at 7. The numerous references relied on by Aurobindo describe the oxidation of various triarylmethane compounds with a number of different oxidizing agents, including manganese dioxide. *See* Dkt. No. 55-49 ¶ 43. Aurobindo's expert, Dr. Edward Brown, acknowledged that these references do not describe the use of manganese dioxide to synthesize isosulfan blue. Dkt. No. 79-2 at 152:1-6. Aurobindo appears to simply assume that a person of ordinary skill in the art would be motivated to combine the process described in one of the references with another reference that discloses isosulfan blue, such as Dr. Hirsch's original clinical trials publication, for example.

This unstated assumption leaves Aurobindo well short of raising a substantial question regarding ensnarement. An obvious analysis under the ensnarement doctrine is no different than an ordinary obvious analysis. *See Intendis GMBH v. Glenmark Pharm. Inc., USA*, 822 F.3d 1355, 1363-64 (Fed. Cir. 2016). It is not sufficient to identify numerous references that disclose various triarylmethane dyes and oxidizing agents without explaining through expert testimony or otherwise how a person of ordinary skill in the art would have arrived at the claimed invention. Dr. Brown opines that a person of ordinary skill in the art would be motivated to "try different oxidizing agents to see if any performed better," but this testimony—to the extent that it even establishes motivation—refers to motivation to try silver oxide, not manganese dioxide. *See* Dkt. No. 55-49 ¶ 80.

Other than the Apicore inventors' own disclosure, there is no evidence in the record suggesting that isosulfan blue purity was affected by the way in which the isoleuco acid is oxidized to form isosulfan blue acid. While isosulfan blue manufacturers such as Covidien and others reported problems meeting the market demand for isosulfan blue, *see, e.g.*, Dkt. No. 81-2, the prior art of record does not recognize the problem solved by the Apicore inventors. Aurobindo's unstated assumption reveals "hindsight of the worst kind, 'wherein that which only the invention taught is used against its teacher.'" *Sci. Plastic Prod., Inc. v. Biotage AB*, 766 F.3d 1355, 1362 (Fed. Cir. 2014), *cert. denied*, 135 S. Ct. 2380, 192 L. Ed. 2d 166 (2015) (Moore, J., dissenting) (quoting *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983); *see also Apple Inc. v. Samsung Elecs. Co.*, No. 2015-1171, 2016 WL 5864573, at *16-*17 (Fed. Cir. Oct. 7, 2016) (en banc); *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013).

Aurobindo is correct that the patents-in-suit generally acknowledge that prior art methods of preparing triarylmethane dyes involved strong oxidation reagents and crude purification processes. *See, e.g.*, '992 at 2:7-17. Yet there is no acknowledgement that triarylmethane dye purity was affected by the oxidation step. It may go without saying that if a heavy-metal oxidant is used, there would likely be traces of that metal in the final product. But there is no indication that existing oxidation methods would have created other impurities, such as the closely-related isomers recognized by Dr. Hirsch. The prior art described crude methods to prepare dyes for fabric, paper, and ink, and those same methods were used to prepare pharmaceutical dyes. *See id.* at 2:12-17. Such pharmaceutical dyes included isosulfan blue, as the Kulkarni reference

considered by the examiner during prosecution demonstrates. *See, e.g.*, Dkt. No. 55-49 ¶ 74.[3] Finally, even if the problem solved by Apicore was known in the prior art, the record does not reveal motivation to combine the manganese dioxide prior art with isosulfan blue publications, nor does it establish a reasonable expectation of success for the same reasons discussed below with respect to silver oxide.

The parties have not otherwise raised a dispute regarding the meaning of the '992 and '616 patents claims, and thus the Court will assess relevant terms according to their plain and ordinary meaning, informed by the parties' and experts' use of the terms.

c) "Purity"

Claim 1 of the '050 patent recites "[a] compound N-[4-[[4-(diethyl amino) phenyl] (2,5-disulfophenyl) methylene]-2,5-cyclohexadien-1-ylidene]-N-ethylethanaminium, sodium salt having a purity of at least 99.0% by HPLC." According to Aurobindo, a person having ordinary skill in the art would understand claim 1's purity limitation to mean "having not more than 1% extraneous material—i.e., material that is not isosulfan blue, sodium salt—as determined using HPLC with a reproducible set of conditions." Dkt. No. 55 at 8 (quoting Dr. Brown).

The Court does not agree. The term "purity," in the context of the '050 patent, does not simply refer to the absence of material that is not isosulfan blue. The claim requires the "compound" to have at least 99.0% purity. Claim 11 recites a "solution" containing the compound, and the compound is defined as having the same purity as recited in claim 1. '050 patent at 12:7-12. Aurobindo's proposed construction would exclude solutions covered by claim 11 because solvent would qualify as "more than 1% extraneous material." "[A] claim

[3] When describing the prosecution of the application leading to the '992 patent and Aurobindo's ensnarement defense, Dr. Brown refers to the Kulkarni reference as "Kulkarni." Dkt. No. 55-49 ¶ 60. Dr. Brown also opines that a combination of references—including Kulkarni—renders the '992 and '616 patent claims obvious. *See id.* ¶ 74. For the latter obviousness theory, Dr. Brown refers to Kulkarni as "the '003 application." *See id.*

construction that excludes a preferred embodiment . . . is rarely, if ever correct." *See Anchor Wall Sys., Inc. v. Rockwood Retaining Walls, Inc.*, 340 F.3d 1298, 1308 (Fed. Cir. 2003) (quoting *Vitronics*, 90 F.3d at 1583). Similarly, claim 15 recites "[a] composition consisting essentially of" the compound. '050 patent at 12:23-29. "'Consisting essentially of' is a transition phrase commonly used to signal a partially open claim in a patent." *PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998). "By using the term 'consisting essentially of,' the drafter signals that the invention necessarily includes the listed ingredients *and is open to unlisted ingredients* that do not materially affect the basic and novel properties of the invention." *Id.* (emphasis added).

The remainder of the specification is instructive. The patent's background describes prior art methods that "give rise to crude triarylmethane dyes." '050 patent at 2:8-11. As a result, the patent explains a "need in the art for an improved method in the process chemistry of isosulfan blue to be prepared in the purest form which is suitable for large scale . . . production." *Id.* at 2:20-23. The synthetic examples described in the specification involve steps resulting in "crude isosulfan blue acid." *Id.* at 7:29-31. The acid is then "purified by recrystallization from aqueous isopropyl alcohol/acetone to afford isosulfan blue acid of chromatographic purity NLT 99.5% performed by High Performance Liquid Chromatography." *Id.* at 7:31-37. These purification steps involve removing reaction by-products from a crude mixture to yield the claimed compound. "Purity" in the context of the '050 patent therefore refers to the absence of reaction by-products, rather than the absence of any extraneous material.

Testimony from Plaintiffs' expert, Dr. Jonathan Sessler, confirms that the '050 patent refers to "purity" according to the ordinary meaning as understood by those in the pharmaceutical industry. Dkt. No. 79-33 at 18-20. According to Dr. Sessler, the ordinary

meaning of the term refers to the absence of unwanted reaction products formed during synthesis. *Id.* ¶ 77. "This common understanding of purity is aptly demonstrated by numerous publications and regulatory guidelines." *Id.* ¶ 78. "[F]or pharmaceutical products, the [International Conference on Harmonisation] ICH defines impurities as 'substances in the product that are not the [active pharmaceutical ingredient] API itself or the excipients used to manufacture it, i.e., impurities are unwanted chemicals that remain within the formulation or API." *Id.* (quoting PHARMACEUTICAL IMPURITIES, AN OVERVIEW (2010) at 1). Dr. Brown's testimony to the contrary is not credible. Accordingly, the Court finds that the extrinsic evidence conclusively demonstrates that the term "purity" in the '050 patent refers to the absence of reaction by-products, not the absence of other extraneous material. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841-42 (2015) (describing the district court's fact-finding role in claim construction).

The Federal Circuit affirmed a nearly-identical construction in *Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339 (Fed. Cir. 2004). Apotex argued that the district court erred in construing the phrase "having a purity of at least 95%" to cover formulations with more than 5% of other ingredients. *Id.* at 1346. According to Apotex, the asserted claim covered only the pure compound and any other compounds added to the formulation rendered the compound impure for purposes of meeting the purity limitation. *Id.* The Federal Circuit held that Apotex's position was "both contrary to the ordinary meaning of such a phrase in the pharmaceutical arts and belied by the specification of the . . . patent." *Id.* at 1346-47. The same is true here.

d) Definiteness

A likelihood of success on the merits cannot be shown "if an alleged infringer raises a substantial question regarding either infringement or validity of the asserted patents." *Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 630 (Fed. Cir. 2015). A patent's

specification must "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as [the] invention." 35 U.S.C. § 112, ¶ 2. A patent is indefinite "if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014). "The definiteness requirement must take into account the inherent limitations of language." *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015). "Some modicum of uncertainty . . . is the 'price of ensuring the appropriate incentives for innovation.'" *Nautilus*, 134 S. Ct. at 2128 (quoting *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 732 (2002)). On the other hand, "a patent must be precise enough to afford clear notice of what is claimed, thereby appris[ing] the public of what is still open to them." *Id.* at 2129 (internal quotation marks and citations omitted). Indefiniteness is a question of law. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1365-66 (Fed. Cir. 2011).

Defendants argue that the claims of the '050 patent are indefinite because "having a purity of at least 99.0% by HPLC can be tested in many different ways." Dkt. No. 55 at 11. According to Defendants, the '050 patent "does not provide any conditions for HPLC analysis." *Id.* Dr. Brown explains that one set of conditions might indicate greater than 99% purity while the same sample run under different conditions might indicate less than 99% purity. *Id*.

The Court is not persuaded. Dr. Sessler testified that "[d]etermination of purity by HPLC is a common and well understood way of designating purity in publications and patents that are relied upon by the scientific and technical community." Dkt. No. 79-33 at 96-97. Numerous sources support Dr. Sessler's opinion. Patents filed before the application resulting in the '050 patent describe compounds by reference to HPLC purity without providing comprehensive

HPLC parameters. *See, e.g.*, U.S. Patent Nos. 9,403,770, 7,417,143, 7,960,545, and 8,633,241; Dkt. No. 79-33 at 98. Other scientific literature reflects the same convention. Dkt. No. 79-33 at 97-98.

Dr. Brown relies on a single patent application that does describe HPLC parameters for the contrary position that HPLC conditions must be specified to convey reasonable certainty. *See* Dkt. No. 55-49 at 53. Yet even Dr. Brown agrees that the phrase "purity by HPLC" is a term that is typically used in FDA submissions to describe purity levels allowed in an active pharmaceutical ingredient or a finished dosage form, and that "specific techniques and solvents and things" can be "*elucidated* . . . so that the practitioner knows how the material was purified." *See* Dkt. No. 80-2 at 53:23-54-7 (emphasis added).

Dr. Brown's opinion is based in part on the fact that a dye like isosulfan blue absorbs light at different wavelengths. *See* Dkt. No. 55-49 at 53 ¶ 146. A user could run HPLC at the peak absorption wavelength (approximately 640 nm), or the user could run HPLC at a lower ultraviolet wavelength, such as 220 nm. *Id.* Accordingly, Dr. Brown opines that "a person of ordinary skill could not tell whether performing HPLC analysis at these different wavelengths would lead to different determinations of purity by HPLC." *Id.* Dr. Brown admits, however, that he did not look at actual HPLC chromatograms of isosulfan blue to determine whether different purity results would be obtained if a user changed wavelengths. *See* Dkt. No. 80-2 (Brown Deposition) at 36:19-37:12. Dr. Brown also admitted that he had never performed HPLC on any triarylmethane dye, including isosulfan blue. *See id.* at 37:24-38:1.

Even if different wavelength HPLC detectors would yield different isosulfan blue purity levels, the scope of the claims would be reasonably certain. The term "purity" gives the claims reasonably certainty because one of ordinary skill in the art would understand that this term

means the absence of reaction by-products. Thus, even if some reaction by-products did not absorb radiation in the same way as isosulfan blue does, a person of ordinary skill in the art would know to use a different detector, if necessary, to determine by HPLC whether reaction by-products are present. Dr. Brown's testimony regarding HPLC supports this finding. *See* Dkt. No. 80-2 at 42:2-43:24.

Dr. Brown also suggests that because the patents do not indicate whether the HPLC "peak" for isosulfan blue is pure, the phrase "purity by HPLC" is not reasonably certain. Dkt. No. 44-49 at 53-54. According to Dr. Brown, a person of ordinary skill in the art needs to ensure that an unwanted compound is not co-eluting or co-migrating along with isosulfan blue and hiding within the isosulfan blue HPLC peak. *See id.* There is no evidence, however, of any reaction by-product or other compound co-eluting with isosulfan blue. Even if co-elution was a problem, Dr. Brown admits that techniques were available to distinguish between co-eluting compounds. *See id.* Such techniques could be used to determine the presence of reaction by-products and therefore determine whether the isosulfan blue contained more than 1% impurities.

Contrary to Aurobindo's assertion, the Federal Circuit's decision in *Teva* following remand from the Supreme Court does not compel a contrary conclusion. In *Teva*, the claims recited the term "molecular weight," and the parties agreed that this term could refer to weight-average molecular weight (M_w), number-average molecular weight (M_n), or peak-average molecular weight (M_p). *See* 789 F.3d at 1341. These measures of molecular weight are "calculated in a different way and would typically yield a different result for a given polymer sample." *Id.* Because the record did not establish which measure to use, the Federal Circuit held that the term "molecular weight" rendered the claims indefinite. *Id.* at 1345. Claims of the '050 patent would perhaps be analogous if the claims recited "purity by chromatography," without

any indication in the patent of which type of chromatography was intended. But the claims recite "purity by HPLC," which has a well-understood meaning in the pharmaceutical arts.

Accordingly, the Court finds that a person of ordinary skill in the art would readily understand the phrase "purity by HPLC" and would be able to elucidate HPLC conditions to determine whether an isosulfan blue sample satisfied the purity requirement. Although definiteness is an ultimate question of law, "in some instances, a factual finding may be close to dispositive of the ultimate legal question of the proper meaning of the term in the context of the patent." *Teva*, 135 S. Ct. at 841-42. Such is the case here. Plaintiffs will likely establish that the phrase "purity by HPLC" does not render claims of the '050 patent indefinite.

2. Infringement

At the preliminary injunction stage, a patentee must prove that infringement is "more likely than not." *Revision Military, Inc. v. Balboa Mfg. Co.*, 700 F.3d 524, 525–26 (Fed. Cir. 2012).

a) '992 and '616 Patents

The parties do not dispute that Aurobindo's isosulfan blue product is manufactured in India and formulated into the finished drug product before it is imported into the United States. *See* Dkt. No. 55 at 11-12. Section 271(g) of the Patent Act provides, however, that "[w]hoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer . . . ." 35 U.S.C. § 271(g). Plaintiffs contend that Aurobindo infringes claim 1 of the '992 and '616 patents by importing and selling isosulfan blue made by the claimed processes.

Dkt. No. 20 at 7.[4] It is undisputed that Aurobindo's process performs every step and includes every element recited in claim 1 of the '992 and '616 patents except silver oxide. *See* Dkt. No. 20, 20-3 ¶¶ 39-60; Dkt. No. 55 at 5-7. Because Aurobindo's process uses manganese dioxide, there is no dispute that Aurobindo does not literally infringe the claims. The only dispute is whether manganese dioxide is equivalent to silver oxide. *See* Dkt. No. 20 at 7-8; Dkt. No. 55 at 5-7.

Equivalence may be shown in one of two ways. *Pac. Coast Marine Windshields Ltd. v. Malibu Boats, LLC*, 739 F.3d 694, 700 (Fed. Cir. 2014). "[A] claim limitation not literally met may be satisfied by an element of the accused product if the differences between the two are 'insubstantial' to one of ordinary skill in the art." *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1351 (Fed. Cir. 2003) (quoting *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 40 (1997)). Equivalence can also be established "by showing on an element-by-element basis that 'the accused product performs substantially the same function in substantially the same way with substantially the same result as each claim limitation of the patented product,' often referred to as the function-way-result test." *Intendis*, 822 F.3d at 1360 (quoting *Crown Packaging Tech., Inc. v. Rexam Beverage Can Co.*, 559 F.3d 1308, 1312 (Fed. Cir. 2009)). "To succeed on a doctrine of equivalents theory, the patentee must demonstrate equivalence under one of these two tests." *Brilliant Instruments, Inc. v. GuideTech, LLC*, 707 F.3d 1342, 1347 (Fed. Cir. 2013).

Although Plaintiffs initially discuss the insubstantial difference test, *see* Dkt. No. 20 at 7-8, Aurobindo only addresses the function-way-result test and appears to concede that the

[4] Plaintiffs also contend that Aurobindo infringes the '992 and '616 patents under § 271(b), Dkt. No. 20 at 7, but the Court is unaware of authority suggesting that a party can infringe a *process* claim by inducing the domestic use of a product made overseas by a claimed process.

function-way-result test is the appropriate test to use in this case.[5] Although it is difficult to distinguish the two tests, they are not entirely coextensive. In *Intendis*, for example, the Federal Circuit considered a composition claim that included triglyceride and lecithin excipients that were not literally found in the accused composition. 822 F.3d at 1361-62. The district court found that an isopropyl myristate excipient in the accused composition was equivalent to the claimed excipients because the excipient in the accused product performed the same function as the claimed excipients. *Id.* at 1361. The Federal Circuit distinguished this issue on appeal from the insubstantial difference question, i.e., whether "the differences between the chemical structures of isopropyl myristate, triglyceride, and lecithin" are substantial. *Id.*

The distinction is relevant in this case. Aurobindo contends only that manganese dioxide does not perform the same function as silver oxide because manganese dioxide is a strong oxidant, whereas silver oxide is a weak oxidant. Dkt. No. 55 at 6. Yet claim 1 of the '992 and '616 patents does not specify how weak or strong the oxidation step must be. The silver oxide in the claims converts the isoleuco acid to the isosulfan blue acid. *See, e.g.*, '992 patent at 9:41-67, 6:42-7:43. Converting the isoleuco acid to isosulfan blue acid is the function of the silver oxide, and Aurobindo has not argued that the claims should be construed more narrowly.

Aurobindo highlights alleged chemical differences between silver oxide and manganese dioxide, but these differences are irrelevant under the function-way-results test as applied to the face of the claims. *See Intendis*, 822 F.3d at 1361-62. Aurobindo's factual equivalency theory does not match the legal test that it agrees is appropriate, illustrating why the Supreme Court in

[5] Dkt. No. 55 at 6 (Aurobindo stating that "manganese dioxide does not serve substantially the same function in substantially the same way to obtain substantially the same result."); Dkt. No. 55-49 ¶ 68 (Dr. Brown opining that "it is my opinion that manganese dioxide in the presence of phosphoric acid does not serve the same function (mild oxidation) as silver oxide without addition of an acid.").

Warner-Jenkinson acknowledged that the function-way-result test "may be suitable for analyzing mechanical devices, [but] it often provides a poor framework for analyzing other products or processes." 520 U.S. 17, 39-40 (emphasis added). There is no dispute that manganese dioxide converts the isoleuco acid to isosulfan blue acid in Aurobindo's accused process. Accordingly, the Court finds that Plaintiffs are likely to succeed in proving that Aurobindo's manganese dioxide is equivalent to silver oxide under the function-way-results test, given the scope of the claims on their face.[6]

Despite the Federal Circuit's acknowledgement of the differences between the two equivalency tests, the Court is mindful that "the particular linguistic framework used is less important than whether the test is probative of the essential inquiry: Does the accused product or process contain elements identical or equivalent to each claimed element of the patented invention?" *Warner-Jenkinson*, 520 U.S. at 40. The function-way-result test may inform whether insubstantial differences exist between a claim element and an accused element. *See, e.g.*, *Boehringer Ingelheim*, 320 F.3d at 1351-52. Because the '992 and '616 claims on their face simply require silver oxide and do not require that oxidation be carried out at any particular strength, the Court finds that the oxidation strength of manganese dioxide is irrelevant under the insubstantial difference test. *See id*.

The Court appreciates that infringement under the doctrine of equivalents is a "highly factual inquiry [that] rarely comes clear on a premature record." *Jeneric/Pentron, Inc. v. Dillon Co., Inc.*, 205 F.3d 1377, 1384 (Fed. Cir. 2000). Aurobindo's non-equivalency theory appears to be based on the unstated premise that the '992 and '616 patent claims are limited to "mildly

[6] Aurobindo does not argue that the term "silver oxide" implies that the claims are limited to "mildly oxidizing" the isoleuco acid. *Cf. Hill-Rom Co. v. Kinetic Concepts, Inc.*, 209 F.3d 1337 (Fed. Cir. 2000).

oxidizing" the isoleuco acid to isosulfan blue acid, perhaps because particular embodiments in the specification describe mild oxidation. *See, e.g.*, '992 patent at 6:61-67. Although Aurobindo has not given the Court a reason to limit the claims, a more fully-developed factual record and claim construction proceeding could change things.

Assuming for purposes of the Court's preliminary inquiry that the claims will be limited to a mild oxidation step, the Court finds manganese dioxide to be a mild oxidant equivalent to silver oxide in the context of the '992 and '661 patents. Dr. Sessler testified that manganese dioxide and silver dioxide are mild oxidizing agents that are both markedly different than stronger oxidizing agents such as lead oxide, chromium dioxide, ammonium dichromate, and others. Dkt. No. 20-3 ¶ 46. Dr. Brown testified, by contrast, that manganese dioxide is not equivalent to silver oxide because manganese dioxide is a strong oxidizing agent when used with phosphoric acid, as is done in the accused process. Dkt. No. 55-49 ¶ 67.

While there may be a generalized dispute as to whether manganese dioxide with an acid such as phosphoric acid is a strong or weak oxidizing agent, the Court agrees with Dr. Sessler's testimony in light of the evidence of record. According to an Indian patent application filed by Aurobindo, manganese dioxide provides a 66.93% yield of isosulfan blue acid. *See* Dkt. No. 20-3 ¶ 49. Embodiments described in the '992 and '616 patents describe similar yields ranging from 65 to 70%. *See, e.g.*, '992 patent at 9:22-24. Other than the oxidizing agent, other reaction conditions are the same, e.g., the molar equivalent of manganese dioxide (relative to the isoleuco acid) is within the range recited by claim 1 of the '992 patent. *See* Dkt. No. 20-3 ¶ 48. If it were true that manganese dioxide was acting as a substantially stronger oxidizing agent than silver oxide, then a person of ordinary skill in the art would expect different results. *See id.* ¶ 49.

b) ’050 Patent

Plaintiffs contend that Aurobindo infringes claim 1, 11, and 15 of the ’050 patent under § 271(a), Dkt. No. 20 at 6, which provides that “whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent.” 35 U.S.C. § 271(a). “To prove an accused product literally infringes the patent in suit, the product must contain each and every limitation of the asserted claim(s).” *Trebro Mfg., Inc. v. Firefly Equip., LLC*, 748 F.3d 1159, 1166 (Fed. Cir. 2014).

Aurobindo’s product has “HPLC Purity: [not less than] NLT 99.8%, Isoleuco acid not more than 0.15% and any other not more than 0.10%.” Dkt. No. 20-10 at 6, 7, 9; Dkt. No. 20-11 at 6, 7, 9. FDA submissions indicate that the product does not contain more than 0.15% of any reaction product used to synthesize the product, as determined by HPLC. Dkt. No. 80-12 at 18. On the basis of these materials, both Dr. Sessler and Dr. Brown agree that Defendants’ isosulfan blue product has a purity of greater than 99% as determined by HPLC. *See* Dkt. No. 80-2 at 222:14-18; Dkt. No. 79-33 at 21-22. Aurobindo admits that it has imported and sold the product within the United States. Dkt. No. 40 at 13-14.

Aurobindo contends that they do not infringe because their isosulfan blue product is “manufactured in India and is formulated into the finished product *before* it is imported to the U.S.” Dkt. No. 55 at 11-12. Thus, according to Defendants, the imported isosulfan blue product that is sold within the U.S. is a 1% solution of isosulfan blue, which does not meet the 99% purity limitation because 99% of the solution is not isosulfan blue. *Id.* at 11. This argument presumes that the term “purity” means the absence of any extraneous material, and the Court rejected such a construction above. Accordingly, it is more likely than not that Aurobindo is

infringing at least claim 1 of the ’050 patent by importing and selling their isosulfan blue product within the United States.

3. Validity

As the parties seeking preliminary relief, Plaintiffs carry the burden of establishing a likelihood of success on validity and must therefore show that Defendants will “not likely prove that the patent is invalid.” *Canon Computer Sys., Inc. v. Nu-Kote Int’l, Inc.*, 134 F.3d 1085, 1088 (Fed. Cir. 1998). Under § 282 of the Patent Act, however, “[a] patent shall be presumed valid” and “[t]he burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.” 35 U.S.C. § 282. Section 282 requires an invalidity defense to be proved by “clear and convincing evidence.” *Microsoft Corp. v. I4I Ltd. P’ship*, 564 U.S. 91, 95 (2011). A patent’s presumption of validity “exists at every stage of the litigation,” including the preliminary injunction stage. *Canon Computer*, 134 F.3d at 1088.

Accordingly, validity at the preliminary injunction stage “is determined in the context of the presumptions and burdens that would inhere at trial on the merits.” *Id.* (quoting *H.H. Robertson, Co. v. United Steel Deck, Inc.*, 820 F.2d 384, 388 (Fed. Cir. 1987)). At trial, a patent holder “need only submit sufficient evidence to rebut any proof of invalidity” offered by the challenger. *Id.* “[W]here the challenger fails to identify any persuasive evidence of invalidity, the very existence of the patent satisfies the patentee’s burden on the validity issue.” *Id.* Thus, whether a challenger has raised a “substantial question” regarding validity depends on “whether the challenger’s evidence of invalidity is sufficiently persuasive that it is likely to overcome the presumption of patent validity” at trial. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996).

a) Anticipation

The Patent Act defines several ways that an invention can be anticipated. As relevant here, a patent is invalid if the claimed invention (1) was known or used by others before invention by the patentee, § 102(a); (2) was patented or described in a printed publication in this or a foreign country, or in public use or on sale in this country more than a year before the filing date, § 102(b); or (3) was first made in this country by another inventor who did not abandon, suppress, or conceal the invention, § 102(g)(2). "[A]nticipation is a question of fact, including whether an element is inherent in the prior art." *In re Gleave*, 560 F.3d 1331, 1334-35 (Fed. Cir. 2009).

i. Sigma-Aldrich Documents

Aurobindo contends that Sigma-Aldrich made and sold isosulfan blue having a purity by HPLC of greater than 99% in March 2001, six years before the earliest priority date of the '050 patent, thus invalidating the patent under §§ 102(b) and 102(g)(2). Dkt. No. 71 at 2-3. To support this argument, Aurobindo cites to eleven documents produced by Sigma-Aldrich. *See* Dkt. No. 71-2 through Dkt. No. 71-12; Dkt. No. 72-1.

Aurobindo does not contend that any of the Sigma-Aldrich documents are printed publications or otherwise publicly-available, and Aurobindo filed the documents with the Court under seal. Aurobindo has attempted to authenticate the documents as business records under Fed. R. Evid. 902(11) through a declaration provided by a Sigma-Aldrich manager, who testified that the documents were "stored in Sigma's electronic record retention system." Dkt. No. 85-1 at 3. Regardless of any authenticity dispute, the Court will consider the documents at this stage even if the documents are not admissible. *See Sierra Club, Lone Star Chapter v. FDIC*, 992 F.2d 545, 551 (5th Cir. 1993) ("[A]t the preliminary injunction stage, the procedures in the district court are less formal, and the district court may rely on otherwise inadmissible evidence.").

Of the eleven Sigma-Aldrich documents, a Sigma-Aldrich Certificate of Analysis is most important. *See* Dkt. No. 72-1. The Certificate refers to a product named "Patent Blue Violet," having a product number "P4808," a Chemical Abstracts Service (CAS) number "68238-36-8," and Lot number "112F5011." *Id.* The Certificate includes an entry titled "Purity by HPLC," and the result is listed as "100%." *Id.* The HPLC purity amount is qualified by an asterisk: the value appears to have been "Corrected for Water Content," which is listed on the Certificate as "5%." *Id.* The Certificate includes an entry titled "QC Release Date" corresponding to "March 2001." *Id.* Aurobindo contends that the Certificate raises a substantial question that the claims are anticipated under § 102(g)(2) because the document indicates that the claimed isosulfan blue was made before the priority date, and the assigned product number and other catalog entries suggest that the product may have been sold before that date.

The Court does not agree. Even assuming, as Aurobindo asserts, that the Certificate sufficiently establishes or corroborates some sort of prior knowledge, use, or invention "within this country" under § 102, the Certificate suffers from two critical shortcomings. First, the record shows that the term "Patent Blue Violet," at least as that term was used by Sigma-Aldrich at the time, did not necessarily refer to isosulfan blue. A Sigma-Aldrich catalog entry states that "Patent Blue Violet" dyes differ structurally with "regard to the substituents on one of the aromatic rings." *See* Dkt. No. 71-3 at 15. This catalog entry is consistent with prior art distinguishing "Patent Blue Violet" dyes from "isosulfan blue." *See, e.g.*, Hirsch et al., *Use of Isosulfan Blue for Identification of Lymphatic Vessels: Experimental and Clinical Evaluation*, 139 American Journal of Roentgenology 1061, 1061 (1982) (Dkt. 80-9). Yet Sigma-Aldrich referred to these different dyes collectively as "Patent Blue Violet." *See* Dkt. No. 71-3 at 15. Other undated Sigma-Aldrich documents state that "Patent Violet Blue" and "isosulfan blue" are

synonyms, but these documents do not establish that the term "Patent Blue Violet," as it was used on the Certificate, refers to the claimed isosulfan blue. Dr. Sessler's extensive testimony on the issue supports the finding that there is simply no way to know which compound the Certificate is referring to. Dkt. No. 79-33 at 70-71.

Second, and more important, the record establishes that the Certificate's declaration of "100% purity by HPLC" is inaccurate. The Certificate contradicts numerous other Sigma-Aldrich documents. The Lot number identified in the Certificate, "Lot 112F5011," corresponds to a Sigma-Aldrich reference standard. *See* Dkt. No. 80-20. Sigma-Aldrich analyzed this standard annually to determine whether the Lot remained suitable for use as a reference. *Id.* The pages immediately following the Certificate in the produced document include other reports regarding the same "Lot 112F5011." In January 1998, the reference standard had a purity of "83.0%." Dkt. No. 72-1 at 4. Numerous other certificates for the same Lot reported purity levels no higher than 95%. Dkt. No. 79-33 at 77-82.

The balance of the Sigma-Aldrich documents are either catalog entries that contain no information regarding the purity of the Patent Blue Violet or are undated development documents detailing the synthesis of Patent Blue Violet or isosulfan blue. As Dr. Sessler's testimony explains, these documents do not disclose the claimed compound much less indicate that it had been made or sold. Dkt. No. 79-33 at 71-75. Accordingly, the Court finds that the Sigma-Aldrich documents do not raise a substantial question that the '050 patent claims are invalid under § 102.

ii. Publications Reporting Less Pure Forms of Patent Blue Violet or Isosulfan Blue

A claim is anticipated by a printed publication "if a single prior art reference discloses each and every limitation claimed." *See Trebro*, 748 F.3d at 1169. Defendants argue that "[e]ssentially pure forms of isosulfan blue for use in surgical applications were well known and

even commercially available well before the priority date of the Apicore patents." Dkt. No. 55 at 9. To support this proposition, Aurobindo cites to Newton et al., *Physicochemical Characterization of Patent Blue Violet Dye*, 70(2) JOURNAL OF PHARMACEUTICAL SCIENCES 122 (1981) ("Newton"). *Id.* at 55 n.5. Newton describes experiments to determine the physiochemical characteristics of "patent blue violet," a compound used to delineate the patency of lymph vessels. Dkt. No. 81-8 at 122. Newton explains that "[b]ased on the pKa for the equilibrium" between the patent blue violet compound and one of its isomers and "TLC [thin-layer chromatography] determinations," the patent blue violet compound "appears to be essentially pure with respect to its organic compound content." *Id.* at 126. Aurobindo argues that this disclosure anticipates the claims.

The Court does not agree. First, Newton indicates that the "patent blue violet" was purchased from Sigma-Adrich, *id.* at 122, and a Sigma-Aldrich catalog entry dated around the same time as Newton's publication date demonstrates that Sigma-Aldrich's "patent blue violet" products could have been dyes other than isosulfan blue. *See* Dkt. No. 71-3 at 15. Newton includes a reaction scheme that appears to include the structure of isosulfan blue, *see* Dkt. No. 81-18 at 124, but this does not mean the "patent blue violet" described Newton was in fact isosulfan blue. A person of ordinary skill in the art would have recognized the potential discrepancy based on a public catalog announcement in which Sigma-Aldrich disclosed that its "patent violet blue" refers to different dyes. *See* Dkt. No. 71-3 at 15. Indeed, Newton uses the generic "patent blue violet" phrase, and Dr. Sessler explains that a person of ordinary skill in the art would not understand this phrase to necessarily mean isosulfan blue. In light of the fact that Newton uses the term "patent blue violet," and Newton indicates that the patent blue violet was purchased from Sigma-Aldrich, there is ambiguity in what Newton teaches, and such ambiguity

would more likely than not preclude a finding that Newton anticipates the claims by clear and convincing evidence.

Second, even if Newton sufficiently discloses isosulfan blue, Newton does not describe isosulfan blue having a purity of 99% purity by HPLC. "Purity" and "99% purity" are very different phrases, as both experts appear to agree. Newton, for example, refers to "[p]urified patent blue violet" as a compound that is 85% pure. *See id.* at 122; *see also* Dkt. No. 79-33 at 55. Although Newton later discloses that this compound was purified by thin-layer chromatography, purity by thin-layer chromatography does not suggest 99% purity by HPLC. Dkt. No. 179-33 at 56. As Dr. Sessler explains, the "precision of [thin-layer chromatography] TLC is typically less than HPLC and, in fact, is not a quantitative measurement method." *Id.* This testimony is undisputed.

As contemporaneous prior art explains, isosulfan blue (or at least patent blue violet) could be prepared in "high purity of 94.5%," but [t]he remaining 5.5% consists of closely related isomers producing during synthesis." *See, e.g.*, Hirsch, Dkt. No. 80-9 (emphasis added). Less precise purification methods such as thin-layer chromatography would not have been expected to resolve closely-related isomers. *See* Dkt. No. 79-33 at 56. Accordingly, Newton and other analogous prior art disclosing patent blue violet or isosulfan blue having a purity of around 95% does not raise a substantial question that the '050 patent claims are invalid under § 102.

b) Obviousness

A claim is invalid as obvious if an alleged infringer proves that the differences between the claims and the prior art are such that "the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying facts. *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1356-57 (Fed. Cir. 2012). The Supreme Court set out the

framework for the obviousness inquiry in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), and *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007):

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

"A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four *Graham* factors." *Apple Inc. v. Samsung Elecs. Co.*, No. 2015-1171, 2016 WL 5864573, at *8 (Fed. Cir. Oct. 7, 2016) (en banc). "Objective indicia of nonobviousness must be considered in every case where present." *Id.*; *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012) ("The district court erred, however, by making its finding that the patents in suit were obvious before it considered the objective considerations and by shifting the burden of persuasion to Cephalon.").

"What a prior art reference teaches and whether a skilled artisan would have been motivated to combine references are questions of fact." *Apple*, 2016 WL 5864573, at *11. In addition to common knowledge or teachings in the prior art itself, a "design need or market pressure or other motivation" may provide a suggestion or motivation to combine prior art elements in the manner claimed. *Rolls Royce, PLC v. United Techs. Corp.*, 603 F.3d 1325, 1339 (Fed. Cir. 2010); *accord KSR*, 550 U.S. at 420. A party asserting that a patent is invalid as obvious must "show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention,

and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007).

i. Level of Ordinary Skill in the Art

Dr. Brown contends that a person of ordinary skill in the art would have an advanced degree such as a Ph.D. or foreign equivalent "in the field of chemistry or a closely related field, with additionally at least about 2 years of experience in synthetic, medicinal, and/or process chemistry, including analytical methodology relating to testing active pharmaceutical ingredients." Dkt No.. 55-49 at 8. Dr. Sessler contends that this characterization is too limiting in that it requires a Ph.D. Dr. Sessler explains that a person of ordinary skill could "hold a lower advanced degree in chemistry, biochemistry, chemical engineering, or complementary discipline along with laboratory experience." Dkt. No. 79-33 at 4. Dr. Brown appears to have agreed during a subsequent deposition that "[d]epending on the experience," a person of ordinary skill in the art could have a lesser advanced degree and still qualify as a person of ordinary skill in the art. Dkt. No. 80-2 at 99:1-8. Although the Court is inclined to agree that a Ph.D. may not necessarily be required, the Court's obviousness analysis at this stage will presume the higher level of skill articulated by Dr. Brown.

ii. Scope and Content of the Prior Art and Differences between the Claims and the Art

'992 and '616 Patents

Aurobindo argues that claim 1 of the '992 and '616 patents is obvious over the following combination of references (*see* Dkt. No. 55 at 7-8; Dkt. No. 55-49 ¶¶ 69-82, 97-110):

1. Hirsch et al., Use of Isosulfan Blue for Identification of Lymphatic Vessels: Experimental and Clinical Evaluation 139 AMERICAN JOURNAL OF ROENTGENOLOGY 1061 (1982) ("Hirsch")
2. Kondo, U.S. Patent No. 4,054,458 ("Kondo")
3. Gessner, U.S. Patent No. 5,659,053 ("Gessner")

4. Thoraval et al., Development Of Paper, Chemical Agent Detector, 3-Way Liquid Containing Non-Mutagenic Dyes. II-Replacement Of The Blue Indicator Dye Ethyl-bis-(2.4-DINITROPHENYL) Acetate (EDA), *available at* http://www.dtic.mil/dtic/tr/fulltext/u2/a193781.pdf ("Thoraval")
5. U.S. Patent Application Publication No. 2006/0224003 ("Kulkarni")

Specifically, Aurobindo contends that Hirsch describes isosulfan blue and its use as a pharmaceutical dye; Kulkarni discloses that isosulfan blue can be prepared by oxidizing the isoleuco acid to isosulfan blue acid; Thoravel teaches the use of silver oxide in a nonpolar solvent with triarylmethane dyes; Kulkarni discloses the use of polar solvents (such as an aqueous solution) during triarylmethane synthesis; Kondo teaches that isosulfan blue can be recovered by filtration and mixed with sodium; and Gessner teaches that triarylmethane dyes can be recovered from a reaction mixture in a conventional manner. *See, e.g.,* Dkt. No. 55-49 ¶¶ 75-78.

When all elements of a claim are found in the prior art, as they are here, there are additional factual questions: "whether a person of ordinary skill in the art would be motivated to combine those references, and whether in making that combination, a person of ordinary skill would have had a reasonable expectation of success." *Dome Patent L.P. v. Lee,* 799 F.3d 1372, 1380 (Fed. Cir. 2015). The critical gap in Aurobindo's prior art combination is between references such as Hirsch that disclose isosulfan blue for pharmaceutical use and Thoraval—the reference Aurobindo relies on for a disclosure of silver oxide as an oxidizing agent for triarylmethane dyes.

To bridge the gap, Dr. Brown seems to contend that the invention would have been obvious to try based on a disclosure in Thoraval. Dr. Brown highlights that Thoraval "found that the oxidation of a particular triphenylmethane intermediate performed best with silver oxide." Dkt. No. 55-49 ¶ 73. Dr. Brown then concludes that a personal of ordinary skill in the art would

be motivated to "*try* different oxidizing agents to see if any performed better." Dkt. No. 55-49 ¶ 80 (emphasis added). Aurobindo's Response Brief simply states the bare conclusion: "[a] skilled artisan would have had the motivation to combine these prior art references." Dkt. No. 55 at 8.

The Court cannot find the requisite motivation in the prior art or testimony of record. First, the prior art of record either does not recognize the problem with isosfulfan blue synthesis at all or does not attribute the problem to the oxidation step or the oxidizing agent, and thus the nature of the problem to be solved would not have provided motivation. *See* § II.A.1.b, *supra*. "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

Second, even if the problem was known, the problem would not have motivated a person of ordinary skill in the art to combine references such as Hirsch and Thoraval. Thoraval does not address the same problem. While Thoraval is not necessarily non-analogous art as Plaintiffs suggest, it is undisputed by both parties' experts that Thoraval discloses a particular class of triarylmethane dyes that are used as chemical weapons detectors. *See* Dkt. No. 79-33 ¶ 132; Dkt. No. 80-2 at 200:9-13. As Dr. Sessler explains, Thoraval's dyes are different in that none of them include diethylamine and sulfonate substituents on the aryl groups. *See* Dkt. No. 79-33 ¶ 132. Thoraval is not concerned with pharmaceutical purity.

Third, a person of ordinary skill in the art would not have expected silver oxide to work with a compound such as isosulfan blue on the basis of Thoraval. Although Thoraval discloses that silver oxide worked best for a particular triarylmethane compound, *see* Dkt. No. 55-49 ¶ 73, Thoraval also teaches that silver oxide was entirely incapable of oxidizing other triarylmethane dyes that were very similar in structure to the compound for which silver oxide was effective.

See Dkt. No. 79-33 ¶ 132; Thoraval at 31-34. Thoraval does not necessarily teach away from trying silver oxide as Plaintiffs assert, but Thoraval demonstrates that where silver oxide was unsuccessful, stronger oxidizing agents such as lead compounds were successful. *See* Dkt. No. 79-33 ¶ 133; Thoraval at 34. Thoraval establishes that modest structural changes to a triarylmethane dye can render silver oxide ineffective at oxidation. Accordingly, a person of ordinary skill in the art would not have had a reasonable expectation of success when using silver oxide with isosulfan blue because isosulfan blue is structurally different than the triarylmethane dyes disclosed in Thoraval. *See* Dkt. No. 79-33 ¶ 132.

'050 Patent

In addition to the Sigma-Aldrich documents discussed above, Aurobindo contends that various combinations of the following references raise a substantial question that the '050 claims are obvious:

1. Newton et al., *Physicochemical Characterization of Patent Blue Violet Dye*, 70(2) JOURNAL OF PHARMACEUTICAL SCIENCES 122 (1981) ("Newton")
2. Hirsch
3. Kulkarni
4. U.S. Patent Application Publication No. 2008/0008658
5. PCT Patent Application Publication No. WO 2004/092122 A2
6. Snyder et al., *Preparative HPLC Separation* in PRACTICAL HPLC METHOD DEVELOPMENT (John Wiley & Sons, Inc. 2d ed. 1997) ("Snyder")
7. Huber and Majors, *Principles in Preparative HPLC* (Agilent Pub. No. 5989-6639EN, April 2007) ("Huber")
8. Papenfuss, U.S. Patent No. 3,671,553
9. Canadian Patent Application No. CA 2 500 803 A1
10. Ranganathan, U.S. Patent No. 5,573,752
11. PCT Patent Application Publication No. WO2005/009423

Certain references such as Newton and Hirsch disclose patent blue violet or isosulfan blue having a purity of about 95%. *See* Dkt. No. 55 at 9. Aurobindo contends that purification of

such a mixture to achieve 99% purity would have been obvious because "[t]he law is well-settled that a claim to a purified form of a known compound is not patentable." *Id.* According to Aurobindo, the only exception to this rule is when a purified compound "results in 'properties and characteristics which were different in kind from those of the known product rather than in degree.'" *Id.* (quoting *In re Merz*, 97 F.2d 599 (CCPA 1938)). Thus, because Plaintiffs have not established that the 99% pure form of isosulfan blue is not "different in kind" than the 95% pure mixture known in the prior art, Aurobindo contends that the claims are obvious.

It is true that in the chemical arts, the Federal Circuit has long held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives a reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)).[7] "The analysis is similar where, as here, a claimed composition is a purified form of a mixture that existed in the prior art." *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007). As the Federal Circuit explained:

> [I]f it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with reason to believe that this is so, the purified compound is prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified.

Id. Ordinarily, a person of ordinary skill in the art "expects a concentrated or purified ingredient to retain the same properties it exhibited in a mixture, and for those properties to be amplified

[7] Whether "prima facie" obviousness of a chemical compound as described by cases like *Takeda* is a concept that survives later precedent such as *In re Cyclobenzaprine*, 676 F.3d 1063, and the Federal Circuit's recent en banc decision in *Apple*, 2016 WL 5864573, is a question that the Court need not answer because the Court addresses each *Graham* factor, including objective considerations, without engaging in burden-shifting.

when the ingredient is concentrated or purified." *Id.* at 1302. Indeed, "isolation of interesting compounds is a mainstay of the chemist's art." *Id.* "If it is known how to perform such an isolation, doing so 'is likely the product not of innovation but of ordinary skill and common sense.'" *Id.* (quoting *KSR*, 127 S.Ct. at 1742).

Critical to the analysis, however, is whether it was "known how to perform" the isolation or purification of the compound. As the Federal Circuit explained in *Aventis*,

> [A] purified compound is not always prima facie obvious over the mixture; for example, it may not be known that the purified compound is present in or an active ingredient of the mixture, ***or the state of the art may be such that discovering how to perform the purification is an invention of patentable weight in itself***.

Id. (emphasis added). Accordingly, a pure compound may be nonobvious over a prior art mixture when the purification method is inventive or, if the purification method is not inventive, when objective considerations suggest that the pure compound would not have been obvious. *See id.*

The prior art of record universally suggests that isosulfan blue had a purity of no more than 95%. The Court assumes without deciding, based on *Aventis* and other cases, that a person of ordinary skill in the art would have been motivated to purify existing isosulfan blue even further because, generally speaking, the purer the better. The Court also assumes without deciding that Aurobindo is correct that Plaintiffs have not demonstrated that 99% pure isosulfan blue is "different in kind" than the 95% mixture, as that phrase is defined by Federal Circuit precedent.[8]

The Court nevertheless finds that Plaintiffs have established that it is more likely than not that the state of the art was such that a person of ordinary skill in the art would not have been able to purify isosulfan blue to at least 99% purity before the priority date. Apicore's discovery

[8] The record is not clear whether the 99% pure isosulfan blue may be "different in kind" from the less pure mixture because of its ability to better withstand regulatory scrutiny by the FDA.

of a process to make highly-pure isosulfan blue is "an invention of patentable weight in itself." *Id.* The '050 patent describes the synthetic process used to obtain 99% pure isosulfan blue in detail. Starting with a commercially-available compound, the specification describes steps for obtaining a benzaldehyde intermediate. '050 patent at Scheme 1, 5:1-7:45. This intermediate is then reacted in a subsequent step, after which the isoleuco-acid "with chromatographic purity greater than 98.0% was obtained in the solid form out of the reaction mixture." *Id.* at 6:41-45. The isoleuco-acid is then reacted, in the critical step, under unique conditions to obtain isosulfan blue, which can then simply be filtered, precipitated, and recrystallized to obtain the isosulfan blue with greater than 99% HPLC purity. *Id.* at 7:25-45. Contrary to Aurobindo's suggestion, Apicore did not simply purify the known mixture of isosulfan blue using common methods and then claim the result. Accordingly, Apicore's process provides patentable weight to the resulting 99% pure isosulfan blue because the process is itself patentable.

Dr. Brown contends that the 95% pure isosulfan blue mixture known in the prior art could have been passed through a preparatory HPLC column to obtain highly-pure isosulfan blue. *See* Dkt. No. 55-49 at 45-50. Dr. Brown is correct that the prior art, including Snyder, Huber, the '658 application (to the extent this application is prior art), and other references teach that HPLC can generally be used to purify compounds. Dr. Brown is also correct that the prior art, including the '553 patent to Papenfuss, teaches that triarylamine dyes can be purified in a range from 96% to 98%. *Id.* at 48-49.

The '050 patent, however, indicates that prior art methods used for isosulfan blue synthesis resulted in particularly crude mixtures that made purification to highly-pure levels troublesome. *See* '050 patent at 2:8-19. This is consistent with the prior art of record, which explains that isosulfan blue contains "closely related isomers produced during synthesis." *See*,

e.g., Hirsch, Dkt. No. 80-9; Dkt. No. 79-33 at 69. Dr. Brown's explanation of HPLC confirms that a crude mixture of closely related isomers would be difficult to separate with HPLC alone because closely related isomers would have similar affinities for the stationary phase, s*ee* Dkt. No. 80-2 at 42:-43 (discussing HPLC generally), and could co-elute from an HPLC column at the same time as isosulfan blue, *see* Dkt. No. 44-49 at 53-54.

Dr. Sessler's testimony suggests that the success of HPLC and separation methods in general depends not only on the particular compound but also the mixture in which the compound is present. *See* Dkt. No. 79-33 at 66-69. For a "complex mixture, repeated chromatography will increase the overall purity, but only relative to the impurities for which there is good separation." *Id.* at 67. Repeated chromatography comes at the cost of decreased yield, which explains why a person of ordinary skill in the art would not have tried preparatory HPLC on a mixture of isosulfan blue and its isomers, and certainly not with an expectation of success. *See id.* at 67-69. Accordingly, the Court finds that Aurobindo has not raised a substantial question that the claims of the '050 patent are prima facie obvious.

iii. Objective Considerations

Various factors "serve to guard against slipping into use of hindsight, and to resist the temptation to read into the prior art the teachings of the invention in issue." *Apple*, 2016 WL 5864573, at *12 (quoting *Graham*, 383 U.S. at 36). The factors are known as "objective indicia of non-obviousness." *Id.* "These include: commercial success enjoyed by [products] 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." *Id.* As the Federal Circuit recently explained:

> Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light

> of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.

Id. (quoting *Stratoflex*, 713 F.2d at 1538-39). Plaintiffs contend that the following objective considerations support patentability: failure of others, long-felt need, commercial success, praise by others, copying, teaching away, and unexpected results. Dkt. No. 79 at 7-8. Relevant to these factors is the Court's view that objective considerations regarding the patentable process described in the '992 and '616 patents are relevant to the patentability of the '050 patent claims.

Long-Felt Need

"Evidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious." *Apple*, 2016 WL 5864573, at *15. Plaintiffs contend that isosulfan blue suppliers such as Covidien and others searched for years to find a reliable isosulfan blue manufacturer that could meet quantity and purity demands. Dkt. No. 79 at 7-8. The Court agrees. The evidence establishes that for over 30 years, isosulfan blue manufacturers had trouble maintaining supply and meeting purity demands, and it appears from the preliminary record that many of the purity problems may have been associated with the oxidation method used during synthesis. *See, e.g.*, Dkt. No. 80-18; Dkt. No. 80-19; Dkt. No. 81-3; Dkt. No. 80-16; *see also* Dkt. No. 79-33 ¶¶ 259-85.

Aurobindo argues that because Lymphazurin™ was on the market for 30 years "with only a few periods of shortages," Plaintiffs cannot establish long-felt need. Dkt. No. 92 at 4. It may be true as Aurobindo suggests that the market was capable of meeting isosulfan blue demand for extended periods of time during the Lymphazurin™ years, and that certain shortages were attributable to events unrelated to isosulfan blue synthesis, but there is no dispute that suppliers such as Sigma-Aldrich had a long-felt need for a reliable supply of high-purity

isosulfan blue. Sigma-Aldrich was itself forced to initiate efforts to purify isosulfan blue acquired from manufacturers, and Sigma-Aldrich eventually began developing its own manufacturing process sometime around 2010. *See* Dkt. No. 80-16; Dkt. No. 81-4, 81-5, 81-6, 81-8. It is undisputed that the claimed invention reliably provides high-purity isosulfan blue. Accordingly, the Court finds that evidence of long-felt need supports the likelihood that Apicore's invention claimed in the '616, '992, and '050 patents will not be found obvious.

Failure of Others

"Evidence that others tried but failed to develop a claimed invention may carry significant weight in an obviousness inquiry." *Cyclobenzaprine*, 676 F.3d at 1081. "While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure." *Boehringer Ingelheim*, 320 F.3d at 1354. "This is particularly true when the evidence indicates that others found development of the claimed invention difficult and failed to achieve any success." *Cyclobenzaprine*, 676 F.3d at 1081. "In such circumstances, 'evidence of failed attempts by others could be determinative on the issue of obviousness.'" *Id.* (quoting *Advanced Display Sys. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000).

The Court does not find that the record supports a finding that others had failed to develop the invention claimed by the patents-in-suit. Plaintiffs' argument regarding failure of others is too general. Plaintiffs contend that Covidien and others tried to develop a reliable method for synthesizing isosulfan blue, and they were unable to do so. Dkt. No. 79 at 7-8; Dkt. No. 79-33 ¶¶ 277-85. The claimed invention, however, is a method of preparing isosulfan blue using silver oxide and the resulting high-purity isosulfan blue compound. Plaintiffs have not suggested that others tried to use silver oxide to synthesize isosulfan blue but failed. *See, e.g.*,

Cyclobenzaprine, 676 F.3d at 1081 (referencing failure of others to develop the "claimed invention"); *Boehringer Ingelheim*, 320 F.3d at 1354. Failure of others therefore is not a factor the Court considers as weighing against a finding of obviousness at this stage.

Commercial Success

Plaintiffs argue that commercial success of their isosulfan blue product supports nonobviousness. Dkt. No. 79 at 7-8; Dkt. No. 79-33 ¶¶ 286-292. Though Aurobindo does not dispute this argument, *see* Dkt. Nos. 55, 92, Aurobindo raises arguments concerning nexus with respect to irreparable harm, *see, e.g.*, Dkt. No. 92-12 ¶ 6, and the Court is mindful that the primary concern with evidence of commercial success is establishing a nexus between the claimed invention and the success. *See Ransomes, Inc. v. Great Dane Power Equip., Inc.*, 232 F.3d 911 (Fed. Cir. 2000) ("When a patentee asserts that commercial success supports its contention of nonobviousness, there must be a sufficient relationship between the commercial success and the patented invention."). Nexus is an issue that Aurobindo raises with respect to irreparable harm, and the Court addresses the dispute below.

There is no question that Plaintiffs' commercial isosulfan blue product was commercially successful. Shortly after the FDA approved Synerx's ANDA for the isosulfan blue product, Apicore began generating significant revenue from isosulfan blue sales, despite Covidien's presence in the market. *See* Dkt. No. 20-29 ¶¶ 11-15. Covidien's Lymphazurin™ sales then sharply declined, *see* Dkt. No. 20-14 ¶ 23, and Covidien withdrew Lymphazurin™ from the market by September 2012, *see* Dkt. No. 55-23 at 5561. Sales figures coupled with market data provide strong evidence of commercial success. *See Tec Air, Inc. v. Denso Mfg. Mich., Inc.*, 192 F.3d 1353, 1360-61 (Fed. Cir. 1999). While the FDA determined that Covidien discontinued Lymphazurin™ for "reasons other than safety or effectiveness," Dkt. No. 55-23 at 5561, the

timing of Covidien's exit from the market provides circumstantial evidence that Covidien could not compete with Apicore.

Plaintiffs' commercial success is sufficiently tied to the invention claimed in at least the '919 and '616 patents. "A prima facie case of nexus is generally made out when the patentee shows both that there is commercial success, and that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent." *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988). If it were not for the process claimed in the '992 and '616 patents, it is likely that neither Apicore nor Aurobindo would be in the market. *See, e.g.*, Dkt. No. 55-19; *See also Akzo N.V. v. Int'l Trade Comm'n*, 808 F.2d 1471, 1481 (Fed. Cir. 1986) (finding commercial success where a product made by a patented method was commercially successful). The commercial success of the invention claimed in the '919 and '616 patents increases the likelihood that the claims would withstand an obviousness challenge. In addition, even if Aurobindo is correct that the market demand for isosulfan blue is not sufficiently tied to the 99% purity limitation of the '050 patent, the nonobviousness of the '919 and '616 patent claims supports the patentability of the '050 patent claims. *See Aventis*, 499 F.3d at 1301-02.

Copying and Praise by Others

"The copying of an invention may constitute evidence that the invention is not an obvious one. This would be particularly true where the copyist had itself attempted for a substantial length of time to design a similar device, and had failed." *Vandenberg v. Dairy Equip. Co., a Div. of DEC Int'l*, 740 F.2d 1560, 1567 (Fed. Cir. 1984) (citations omitted). Aurobindo admitted to the FDA that it searched the literature for a suitable process for preparing isosulfan blue and decided to use the invention disclosed in Apicore's '992 patent, though Aurobindo substituted

manganese dioxide for silver oxide. *See* Dkt. No. 80-14. Aurobindo's Indian patent application also reveals similarities to the invention claimed in Apicore's patents. *See* Dkt. No. 20-3 ¶¶ 49-53.

Copying may not always weigh against obviousness because copying may be explained by something other than the superiority of the patented invention, such as disrespect for patent rights, the inability of the patentee to enforce the patent, or "contempt for the specific patent in question." *See, e.g., Cable Elec. Prod., Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1028 (Fed. Cir. 1985), *overruled on other grounds by Midwest Indus., Inc. v. Karavan Trailers, Inc.*, 175 F.3d 1356 (Fed. Cir. 1999). In this case, however, Aurobindo told the FDA that isosulfan blue synthesis is described in a "number of patents," and after having "studied all these patents," Aurobindo selected the process described in the '992 patent. *See* Dkt. No. 80-14 at 3. Even if Aurobindo's likely insubstantial modification to the claimed process diminishes the significance of Aurobindo's copying, Aurobindo's statements to the FDA at least constitute praise of Apicore's invention.

Aurobindo contends that this alleged evidence of copying supports a finding of obviousness because Aurobindo resorted to preparatory HPLC to achieve greater than 99.5% purity. Dkt. No. 55 at 10. The Court does not agree. Aurobindo's process involving preparatory HPLC is not prior art. Neither are internal documents from Apicore discussing preparatory HPLC. *See, e.g.*, Dkt. No. 92 at 3 (Aurobindo arguing that Apicore lab notebook entries support obviousness); *See also* § 103 ("Patentability shall not be negated by the manner in which the invention was made.").

More importantly, Aurobindo's preparatory HPLC step was carried out on an isosulfan blue mixture prepared according to the process described and claimed by the '992 patent.

Aurobindo did not simply run a crude isosulfan blue mixture from the prior art through a preparatory HPLC column and achieve greater than 99% purity. Aurobindo started from something the '992 patent provided. Finally, the fact that Aurobindo made the effort to achieve greater than 99% purity for its FDA submission suggests that highly-pure isosulfan blue may be "different in kind" than less pure mixtures. *See Aventis*, 499 F.3d at 1301-02. Accordingly, the Court finds that evidence of copying and Aurobindo's praise of the invention to the FDA would weigh against a finding of obviousness.[9]

Unexpected Results and Teaching Away

Plaintiffs contend that the Apicore inventors unexpectedly found that high-purity isosulfan blue could be prepared by a process that used silver oxide, and the prior art taught away from this invention. Dkt. No. 79 at 7-8. Aurobindo appears not to dispute this point, arguing instead that objective considerations cannot "suffice to overcome a strong showing of obviousness in a case in which obviousness is clear from a comparison of the prior art references and the patent in suit." *See* Dkt. No. 92 at 4 (quoting *Kroy IP Holdings, LLC v. Safeway, Inc.*, 107 F. Supp. 3d 656, 675 (E.D. Tex. 2015)). As the Court has explained, Aurobindo has not established a substantial question concerning obviousness. Although the Court does not find that the record supports Plaintiffs' assertion of teaching away, there is significant evidence that the purity levels achieved by the claimed invention were unexpected. The Court therefore finds that unexpected results would weigh against a finding of obviousness.

iv. Obviousness Conclusion

Aurobindo does not raise a substantial question regarding motivation to combine prior art references to achieve the claimed invention with a reasonable expectation of success, and

[9] Plaintiffs present additional evidence of praise by others, *see* Dkt. No. 79-33 ¶¶ 293-300, but the Court finds this evidence insufficient.

objective considerations overwhelmingly weigh against a finding of obviousness. Accordingly, the Court finds that Plaintiffs have established that Aurobindo will not likely prove that the patents-in-suit are invalid as obvious. *See Canon Computer Sys., Inc. v. Nu-Kote Int'l, Inc.*, 134 F.3d 1085, 1088 (Fed. Cir. 1998).

B. Irreparable Harm

As the party seeking emergency relief, Plaintiffs "must make a clear showing that [they are] at risk of irreparable harm, which entails showing a likelihood of substantial and immediate irreparable injury." *See Apple, Inc. v. Samsung Electronics Co.*, 678 F.3d 1314, 1325 (Fed. Cir. 2012). The patentee must also establish that the harm is related to the infringement, a requirement referred to as the "causal nexus" requirement. *Id.* at 1324.

1. Substantial and Immediate Irreparable Injury

''Irreparable injury encompasses different types of losses that are often difficult to quantify.'' *Douglas Dynamics, LLC v. Buyers Products Co.*, 717 F.3d 1336, 1344 (Fed. Cir. 2013). ''Price erosion, loss of goodwill, damage to reputation, and loss of business opportunities are all valid grounds for finding irreparable harm.'' *Celsis In Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 930-31 (Fed. Cir. 2012). A showing of lost market share and sales can support a finding of irreparable harm. *See Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1154 (Fed. Cir. 2011); *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 861–62 (Fed. Cir. 2010), *aff'd*, 564 U.S. 91 (2011). A patentee can also demonstrate irreparable harm from a diminished ability to invest in research and development. *See Bio–Tech. Gen. Corp. v. Genentech, Inc.*, 80 F.3d 1553, 1566 (Fed. Cir. 1996). In addition, ''[w]here two companies are in competition against one another, the patentee suffers the harm—often irreparable—of being forced to compete against products that incorporate and infringe its own patented inventions.'' *Douglas Dynamics*, 717 F.3d at 1345; *see also Presidio Components, Inc. v. Am. Technical Ceramics Corp.*, 702 F.3d

1351, 1363 (Fed. Cir. 2012) (‘‘Direct competition in the same market is certainly one factor suggesting strongly the potential for irreparable harm without enforcement of the right to exclude.”).

With respect to lost sales, research and development, and price erosion, Apicore’s Chief Financial Officer, Mr. Rahul Devnani, testified that isosulfan blue sales constituted a significant portion of Apicore’s total revenue before Aurobindo entered the market, and profit from isosulfan blue sales fueled research and development. Dkt. No. 20-29 at 3-5. Mr. Devnani testified that if half or more of Apicore’s revenue from isosulfan blue is lost as Apicore projects, Apicore would need to eliminate or delay the research and development of new products currently in development. Dkt. No. 20-29 ¶ 16. Mr. Devnani testified further at the hearing that private financing would be unavailable to temporarily make up for lost isosulfan blue revenue through trial because of another significant loan obligation. In addition, Mr. Devnani testified that two of Apicore’s employees had already left the company since Apicore had ceased isosulfan blue manufacturing, and that employee morale was down because manufacturing activity at the Apicore facility was at a standstill. There is no question that Apicore will lose most if not all of its isosulfan blue sales to Aurobindo if infringement is allowed to continue. *See Automated Merch. Sys., Inc. v. Crane Co.,* 357 Fed.Appx. 297, 301 (Fed. Cir. 2009) (‘‘To the extent that failing to grant a preliminary injunction would permit Crane to drop its prices in order to drive AMS out of the market entirely, this might support a finding of irreparable harm sufficient to warrant a preliminary injunction.”). Finally, there is undisputed evidence that Aurobindo’s infringement has and is continuing to result in significant price erosion. *See, e.g.*, Dkt. No. 20-2 ¶¶ 41-61.

Aurobindo admits that it manufactures its own isosulfan blue product, and thus Apicore is directly competing with Aurobindo. Plaintiffs will likely establish that Aurobindo's competition is being fueled by its infringement of Apicore's valid patents. This supports a finding of irreparable injury. *Douglas Dynamics*, 717 F.3d at 1345; *Presidio Components*, 702 F.3d at 1363; *see also Trebro Mfg., Inc. v. Firefly Equip., LLC*, 748 F.3d 1159, 1171 (Fed. Cir. 2014) (''Trebro and FireFly are direct competitors selling competing products in this market. Thus, the record strongly shows a probability for irreparable harm.'').

Accordingly, the Court finds that Apicore has demonstrated that it has and will continue to suffer irreparable injury from Aurobindo's infringement in the form of lost sales, lost research and development ability, price erosion, and having to compete with an infringing competitor. Plaintiffs' expert testimony of record supports this finding.[10]

2. Causal Nexus

"[T]he causal nexus requirement is simply a way of distinguishing between irreparable harm caused by patent infringement and irreparable harm caused by otherwise lawful competition—e.g., sales [that] would be lost even if the offending feature were absent from the accused product." *Apple Inc. v. Samsung Elecs. Co.*, 735 F.3d 1352, 1361 (Fed. Cir. 2013) (internal quotation omitted). "The former type of harm may weigh in favor of an injunction, whereas the latter does not." *Id.*

Aurobindo argues at length that the causal nexus requirement has not been satisfied, and Aurobindo presents extensive expert testimony from a physician and economist on the subject. The Court is not persuaded. Plaintiffs have demonstrated that Apicore's irreparable injury is the direct result of Aurobindo's infringement. Without infringing the '992, '616, and '050 patents, Aurobindo would not be able to make the isosulfan blue product described in its ANDA. And

[10] The Court does not decide whether Mylan will suffer irreparable harm.

without a preliminary injunction, Aurobindo would continue using Apicore's patented process to produce a product that has already begun destroying Apicore's isosulfan blue business.

Aurobindo's arguments are for another product and another market that is not regulated by the FDA. In a nutshell, Aurobindo argues that Plaintiffs have not presented evidence that the patented features "actually drive consumer demand" for isosulfan blue. *See, e.g.*, Dkt. No. 55 at 14. The law on which Aurobindo bases this argument, however, is readily distinguishable. Unlike *Apple* and similar cases, this case does not involve a complex, multi-featured product. The finished drug product is isosulfan blue in an injectable solution, which is more like the "relatively simple products" the Federal Circuit contrasted with smart-phones and tablets in the *Apple* cases. *See, e.g.*, *Apple Inc. v. Samsung Elecs. Co.*, 735 F.3d 1352, 1362 (Fed. Cir. 2013). In addition, at least with respect to the '992 and '616 patents, the *Apple* cases dealt with features of a consumer good, not chemicals such as silver oxide that are used in a patented process. It is not possible to separate Apicore's patented process from the commercial isosulfan blue product for purposes of evaluating consumer demand and nexus. *See, e.g., Amgen Inc. v. F. Hoffman–La Roche Ltd.*, 580 F.3d 1340, 1386 (Fed. Cir. 2009) (affirming injunction in part based on finding of infringement of process patents under § 271(g)); *Kemin Foods, L.C. v. Pigmentos Vegetales Del Centro S.A. de C.V.*, 464 F.3d 1339, 1356 (Fed. Cir. 2006) (affirming injunction for infringement of patented process).

3. Balance of Equities

The balance of equities weighs in favor of Apicore. If an injunction is not granted, Apicore stands to lose its entire isosulfan blue business, a business which Apicore relies on to fund ongoing research and development. Aurobindo was aware of Apicore's process, and Aurobindo copied it. *See* Dkt. No. 80-14. "One who elects to build a business on a product found [likely] to infringe cannot be heard to complain if an injunction against continuing infringement

destroys the business so elected." *Windsurfing Int'l Inc. v. AMF, Inc.*, 782 F.2d 995, 1003 (Fed. Cir. 1986).

4. Public Interest

"[T]he public interest would not be disserved by a permanent injunction." *eBay*, 547 U.S. at 391. The Federal Circuit "has long acknowledged the importance of the patent system in encouraging innovation. Indeed, the 'encouragement of investment-based risk is the fundamental purpose of the patent grant, and is based directly on the right to exclude.'" *Sanofi Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1383 (Fed. Cir. 2006) (quoting *Patlex Corp. v. Mossinghoff*, 758 F.2d 594, 599 (Fed. Cir. 1985)). Disclosure of how to make and use an invention is the "quid pro quo" of the patent grant. *See JEM Ag Supply, Inc. v. Pioneer Hi–Bred Int'l, Inc.*, 534 U.S. 124 (2001). Apicore satisfied its end of the bargain by disclosing to the public its method for preparing isosulfan blue. Apicore would not likely have made such a disclosure if it had known that a competitor would use it to destroy Apicore's isosulfan blue business before Apicore could make it to trial.

Aurobindo argues that the public interest "favors competition and less expensive generic drugs." Dkt. No. 55 at 19. According to Aurobindo, denying an injunction would "restore the policy of the Hatch-Waxman Act" because Plaintiffs enjoyed the benefit of the statute by allegedly "piggy-backing" on Covidien's brand product and then creating a monopoly after Covidien exited the market, keeping isosulfan blue prices high. Dkt. No. 55 at 19. The Court disagrees. The policy of the Hatch-Waxman Act does not preclude or discourage district courts from promoting innovation in the generic drug market. "[W]hile the statutory framework . . . does seek to make low cost generic drugs available to the public, it does not do so by entirely eliminating the exclusionary rights conveyed by pharmaceutical patents. Nor does the statutory framework encourage or excuse infringement of valid pharmaceutical patents." *Pfizer,*

Inc. v. Teva Pharms., USA, Inc., 429 F.3d 1364, 1382 (Fed. Cir. 2005). Accordingly, the Court finds that the public interest will not be disserved by granting a preliminary injunction.

III. CONCLUSION

Plaintiffs have satisfied the burden required for preliminary relief. The Court therefore RECOMMENDS that Defendants be enjoined from manufacturing, selling or offering for sale, using, or importing the accused product within the United States until further order of the Court. Pursuant to Federal Rule of Civil Procedure 65(c), the Court RECOMMENDS that, following input from the parties, Plaintiffs be required to post bond "in an amount that the court considers proper to pay the costs and damages sustained by any party found to have been wrongfully enjoined." *See* Fed. R. Civ. P. 65(c).

A party's failure to file written objections to the findings, conclusions, and recommendations contained in this report by **December 4, 2016** shall bar that party from de novo review by the district judge of those findings, conclusions, and recommendations and, except on grounds of plain error, from appellate review of unobjected-to factual findings and legal conclusions accepted and adopted by the district court. Fed. R. Civ. P. 72(b)(2); *see Douglass v. United Servs. Auto. Ass'n*, 79 F.3d 1415, 1430 (5th Cir. 1996) (en banc).

SIGNED this 19th day of November, 2016.

ROY S. PAYNE
UNITED STATES MAGISTRATE JUDGE