UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LUITPOLD PHARMACEUTICALS, INC.
Petitioner,

v.

APICORE US LLC,
Patent Owner.

Case No.: IPR2018-01640
Patent No. 9,353,050

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,353,050

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I. Introduction

Luitpold Pharmaceuticals, Inc. ("Luitpold") petitions for *inter partes* review of claims 1–18 ("challenged claims") of U.S. Patent No. 9,353,050 (Ex. 1001, "the '050 patent"). Luitpold demonstrates in this Petition that the challenged claims of the '050 patent are unpatentable. An isosulfan blue sodium salt ("ISB") product was FDA-approved and in pharmaceutical use since the early 1980s, long before the priority date of the '050 patent. The claims of the '050 patent are directed to an ISB product, but require a higher level of purity (specifically, at least 99.0%) than the ISB previously known and sold in the prior art. The only allegedly novel aspect of the challenged claims is the purity level. Patent Owner likely will rely heavily on secondary considerations of non-obviousness, but a prior district court did not attribute any such considerations to the '050 patent alone, and no secondary considerations outweigh the strong *prima facie* showing of obviousness here.

Patent Owner and its expert have admitted that a person skilled in the art would have been able to perform analytical high-performance liquid chromatography ("HPLC") for ISB as of the critical date. Armed with a strong motivation to make a more pure pharmaceutical product—supported by the declarations of two experts in the fields of chromatography and pharmaceutical development—the person of ordinary skill in the art ("POSITA") in 2007 could scale up this admittedly-known analytical HPLC method to a preparative HPLC

method to obtain ISB with a purity of at least 99.0% as assessed by HPLC.

The prior art and the Expert Declarations of Geoff Cox, Ph.D. and R. Christian ("Chris") Moreton, Ph.D., whose expertise in the fields of chromatography and pharmaceutical development, respectively, each spans more than five decades, demonstrate that it would have been obvious to a POSITA in 2007 to purify ISB by well-known methods to at least 99.0% purity as assessed by HPLC.

II. Grounds for Standing (37 C.F.R. § 42.104(a)):

The undersigned and Luitpold certify that the '050 patent is available for *inter partes* review. Luitpold certifies that it is not barred or estopped from requesting this *inter partes* review on the grounds identified herein.

III. Identification of Challenge (37 C.F.R. § 42.104(b)):

A. Citation of Prior Art

The '050 patent was filed on December 2, 2011 and claims priority through a series of continuation applications to U.S. Patent Application No. 11/747,291 filed on May 11, 2007. In support of the grounds of unpatentability below, Luitpold cites the following prior art references:

U.S. Patent Application Publication No. 2006/0224003 to Kulkarni ("Kulkarni"), provided as Exhibit 1007, is prior art under at least 35 U.S.C. § 102(a) as of its October 5, 2006 publication date, and 35 U.S.C. § 102(e) as of its April 4, 2006 U.S. filing date.

Lloyd R. Snyder *et al.*, "Preparative HPLC Separation" in *Practical HPLC Method Development* (John Wiley & Sons, Inc. 2nd Ed. 1997) ("Snyder"), provided as Exhibit 1008, is prior art under at least 35 U.S.C. § 102(b) because it published in 1997.

J.P. Brown *et al.,* "*Synthesis of ^{14}C-Labeled FD & C Blue No. 1 (Brilliant Blue FCF) and its Intestinal Absorption and Metabolic Fate in Rats*," Fd. Cosmet. Toxicol., 18:1–5 (1980) ("Brown"), provided as Exhibit 1009, is prior art under at least 35 U.S.C. § 102(b) because it published in 1980.

Jerry I. Hirsch *et al.,* "*Use of Isosulfan Blue for Identification of Lymphatic Vessels: Experimental and Clinical Evaluation*," Am. J. of Roentgenology 139: 1061–64 (1982) ("Hirsch"), provided as Exhibit 1010, is prior art under at least 35 U.S.C. § 102(b) because it published in 1982.

B. Statutory Grounds for the Challenge

Luitpold requests review on the following four grounds:

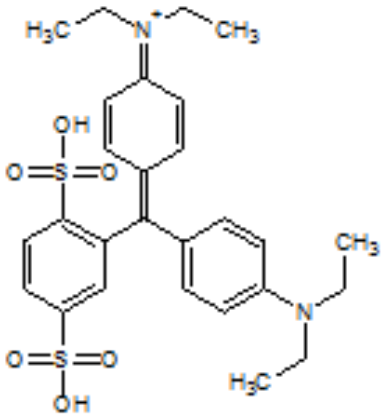
- Ground 1: Kulkarni in view of Snyder renders claims 1–18 obvious under 35 U.S.C. § 103.
- Ground 2: Kulkarni in view of Snyder, or further in view of Brown, renders claims 1–18 obvious under 35 U.S.C. § 103.
- Ground 3: Hirsch in view of Snyder renders claims 1–18 obvious under 35 U.S.C. § 103.
- Ground 4: Hirsch in view of Snyder, or further in view of Brown,

renders claims 1–18 obvious under 35 U.S.C. § 103.

None of the cited prior art or the proposed grounds was applied by the Examiner in a rejection during prosecution of the ’050 patent. (*See* Ex. 1002, ’050 File History.)

IV. The State of the Art in 2007

ISB (CAS 68238-36-8), shown below, is a member of a family of triarylmethane dyes that share a common three-ring base structure:



Isosulfan Blue

(Ex. 1003, Cox Decl., ¶49.) Synthesis of these dyes often results in both the desired dye compound and isomers that are structurally closely related to the dye. (*Id.*) An “isomer” is “one of two or more compounds, radicals, or ions that contain the same number of atoms of the same elements but differ in structural arrangement and properties.” (*Id.*) All triarylmethane dyes are easily detectable using chromatography because, as dyes, they are easily visualized. (*Id.*, ¶50.) This

includes the separation of isomers of these dyes from the dye itself and other isomers, because even the isomers have strong UV-absorbing functionality, so they are easy to detect. (*Id.*)

There is more than one way to further purify a compound like ISB from a pharmaceutical grade composition and arrive at the claimed higher purity levels. The available methods take into account the separation of the compound from these isomers and include, for example, direct chemical synthesis, crystallization and re-crystallization techniques, or chromatography. The ’050 patentees chose the first option—employing silver dioxide as a catalyst—to claim an ISB product having a purity of at least 99.0% by HPLC. Yet chromatography can purify ISB to the same levels. The science of chromatography is more than a hundred years old. (*Id.*, ¶¶40–41.) It has been used for decades to purify compounds, even those that have closely-related isomers. (*Id.*, ¶¶43–45.)

HPLC is a technique to separate, identify, and quantify components in a mixture. It is the most widely used of all the chromatography techniques. There are two primary ways to use HPLC—analytical and preparative. (*Id.*, ¶37.) Analytical HPLC is a quantitative analysis of the amount of product(s) in the sample. (*Id.*, ¶38.) It is used to completely separate one or more (including all) compounds of interest in a sample from each other. (*Id.*) This process is carried out on a chromatography column and the results are visually displayed using a

chromatograph. (Cox Decl., ¶36.) The chromatograph (the machine) displays a chromatogram (a plot of detector response against time), which shows a peak for each compound in the sample that was separated by the chromatography and detected by the chromatograph. (*Id.*) Using an internal or external standard, a POSITA can identify and quantify each compound, usually by comparing the area under each of the peaks with the standard. (*Id.*) Preparative chromatography involves the same process, but on a larger scale and with a different goal in mind: to separate the product(s) of interest from the remainder of the sample, which then is used for another purpose. (*Id.*, ¶39.)

The difference between analytical and preparative chromatography procedures is that, in analytical chromatography, the retention time of the peak is measured (for qualitative identification), as is its area (for quantitation), whereas in preparative chromatography, the peak itself is collected. (*Id.*, ¶39.) That said, there are no fundamental technical differences between carrying out analytical and preparative chromatography. (*Id.*) A POSITA would understand how to scale up an analytical separation to a preparative one. (*Id*.) By 2007, preparative chromatography was a mature and well-developed purification procedure. (*Id.*, ¶¶43–44.)

Before the critical date, chromatography (both analytical and preparative) was used to analyze and purify triarylmethane dyes from less pure preparations,

including from structurally-related synthetic precursors and isomers. (*Id.*, ¶50.) In 1980, Brown purified a dye known as FD&C Blue No. 1 to "more than 99%" purity using preparative HPLC under conventional conditions. (Ex. 1009, Brown, 3; *id.* at Fig. 2) In 1999, Kusaka successfully resolved the closely-related isomers of the same compound as Brown, and purified another triarylmethane related impurity to a single peak by preparative HPLC. (Ex. 1025, Kusaka, 503; *see also* Cox Decl., ¶53.) In 2001, Ngang separated the closely related isomers of a green food dye, FD&C Green No. 3 or Food Green No. 3, using preparative HPLC until the isomers indicated a single peak on the chromatogram. (Ex. 1026, Ngang, 299–30; *see also* Cox Decl., ¶54.) A commercial publication by Lee in 2005 showed the chromatographic separation of six triarylmethane dyes that are closely related to ISB, including Patent Blue VF and Patent Blue V. (Ex. 1024, Lee; *see also* Cox Decl., ¶51.)

These pre-critical date references demonstrate—using a variety of conventional chromatography conditions—that HPLC could separate and purify closely-related structural isomers and other impurities with ease. (Cox Decl., ¶55.) Because of the close structural relationship between the compounds separated in Lee, Brown, Kusaka, and Ngang, on the one hand, and ISB, on the other, the POSITA would have reasonably understood that she could have separated highly

pure ISB from related compounds, including isomers, under similar conditions. (*Id.*)

V. The ’050 Patent

The ’050 patent is entitled “Process for Preparation of Isosulfan Blue” and is assigned on its face to Apicore US LLC. The listed inventors of the ’050 patent are Ravishanker Kovi, Satyam Nampalli, and Peter Xavier Tharial. The ’050 patent issued on May 31, 2016 from U.S. Application No. 13/310,019, filed on December 2, 2011. The ’050 patent claims its earliest priority to May 11, 2007. (Cox Decl., ¶31.) Despite the title, the ’050 patent claims are directed to a substantially pure form of ISB, sodium salt (*i.e.*, at least 99.0% pure) as measured by HPLC, including certain product-by-process claims covering silver oxide as the catalyst. (’050 patent, 2:26–67.)

The ’050 patent is largely directed to a purportedly novel process for making ISB. The Abstract of the ’050 patent provides for “[a] process for the preparation of ISB (Active Pharmaceutical Ingredient)[,]” “[a] process…for preparation of the intermediate, 2-chlorobenzaldehyde-5-sufonic acid, sodium salt of formula (2), used in the preparation thereof and a procedure for the isolation of benzaldehyde-2,5-disulfonic acid, di-sodium salt of formula (3)[,]” and a “process for the preparation of an isoleuco acid of formula (4), which upon mild oxidation gives rise to isosulfan blue of pharmaceutical grade which can be used for preparation of

pharmaceutical formulations." The Abstract concludes that "[t]he isolation and purification procedures provided in the process provide substantially pure isosulfan blue with HPLC purity of 99.5% or greater."

Patent Owner admitted that there only is one allegedly new element in the claims—the purity level. In the Background, Patent Owner recognizes that much of the claimed invention is not new, including that: (1) the compound, ISB, is known ('050 patent, 1:3–44); (2) it is "useful as a contrast agent for the delineation of lymphatic vessels and is particularly useful as a cancer diagnostic agent" (*id.*, 1:47–49); (3) FDA approved ISB for use in human patients under the trade name Lymphazurin® (*id.*, 1:50–53); (4) "the literature is replete with methods of preparing triarylmethane dyes" (*id.*, 1:63–2:8); and (5) "[o]ne skilled in the art would recognize the type of column, mobile phase, and other conditions necessary to obtain a purity value using HPLC for the compound of the claims." (Cox Decl., ¶59.)

Patent Owner, however, recognized a "need in the art for an improved method in the process chemistry of ISB to be prepared in the purest form which is suitable for large scale cGMP production for its pharmaceutical formulation manufacturing." ('050 patent, 2:20–23.) Despite this description, each of the challenged claims are directed to ISB itself, having a certain level of purity greater than or equal to 99.0% as assessed by HPLC. (Cox Decl., ¶63.) Notably, the claims

are *product* claims directed to ISB and solutions containing ISB; there are no *method* claims, and the claims do not require any particular scale of production. (*Id*.)

A. Claim Construction

Claim terms are given their ordinary and accustomed meaning as understood by a POSITA. *Phillips v. AWH Corp*., 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). In accordance with 37 C.F.R. § 42.100(b), the challenged claims in an unexpired patent must be given their broadest reasonable interpretation in light of the specification ("BRI"). *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131 (2016). This Petition analyzes the claims under the BRI; those constructions would not change even if the *Phillips* standard were applied. 415 F.3d at 1314-17 (claim terms are given their ordinary and customary meaning as would be understood by a POSITA in view of the specification).

Claim 1 includes the phrase "having a purity of at least 99.0% by HPLC." [1] In response to an indefiniteness rejection from the Examiner for claims directed to

[1] As explained below with respect to dependent claims of the '050 patent, the same construction covers the more narrow limitations of "between 99.0% to 99.5% by HPLC" and "greater than 99.5% by HPLC."

ISB, sodium salt containing "1.0% or less impurities," Applicants amended the claims as follows:

> 1. (currently amended) A compound N-[4-[[4-(diethyl amino) phenyl] (2, 5-disulfophenyl) methylene]-2, 5-cyclohexadien-1-ylidene]-N-ethylethanaminium, sodium salt ~~containing 1.0% or less impurities~~having a purity of at least 99.0% by HPLC.

('050 File History, 116.) Applicants argued that "[t]he claim phrase 'by HPLC' means the purity value for the compound measured and obtained using high performance liquid chromatography (HPLC), *which one skilled in the art recognizes to be a standard technique to obtain purity values for drug substances and drug products*." (*Id.*, 120-121 (emphasis added).)

This definition, however, does not provide clarity with respect to the scope of the challenged claims. The Board may consider evidence other than just the express definition in construing the claims. *See, e.g.*, *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1338 (Fed. Cir. 2009) (not directly adopting express definition from patent where "evidence of accepted practice within the art, [that was] not at variance with the intrinsic evidence, is relevant to the question of how a person of skill in the pertinent field would understand a term").

Here, a POSITA would understand the phrase "having a purity of at least 99% by HPLC" to mean the composition, when analyzed by HPLC under appropriate conditions, results in "a peak [representing ISB] having at least 99.0%

of the area under the curve ('AUC') on a chromatogram." (Cox Decl., ¶97; *see also id.*, ¶48.) This construction is consistent with the Applicants' acknowledgement that a POSITA would choose the proper HPLC conditions to optimize the accuracy of the peak representing entirely (or almost entirely) the compound of interest. ('050 File History, 120–121.); *see also Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015) (prosecution history informs claim construction under BRI) (citation omitted).

Furthermore, where a POSITA describes a chromatogram as having a "single peak," and/or where a chromatogram shows a single peak for a given component, the POSITA would recognize that it is pure (*i.e.*, very close to 100%) by HPLC. (*Id.*, ¶48.) In an analytical separation, it is routine for a POSITA to identify peaks with between 0.05% and 0.1% of the area of the major component—so a single peak could represent a component having 99.9% purity. (*Id.*) If a compound is described as, for example, "99% pure," the POSITA would understand that there would be other peaks in the chromatogram that represent the remaining 1% of the impurities. Finally, the POSITA would recognize that there may be components that are not detectable or resolvable by HPLC; however, the POSITA would understand that a purity of "at least 99.0% by HPLC" refers to the components that *are* detectable by HPLC. (*Id.*, ¶97.)

B. Level of Ordinary Skill in the Art

A POSITA at the time of the alleged invention would have had an advanced degree (an M.S., Ph.D., or equivalent) in organic, medicinal, or process chemistry or related discipline, including analytical methodology relating to testing active pharmaceutical ingredients, as well as at least about 2 years of experience in developing drug candidates or analyzing pharmaceuticals. (*Id.*, ¶25.) This description is approximate, so a lesser degree with more experience may suffice, and vice versa. (*Id.*)

VI. Ground 1: Kulkarni in View of Snyder Renders Claims 1–18 Obvious

A. Kulkarni discloses a process for making ISB (sodium salt) and its uses as a pharmaceutical product, along with an inherent purity of 86.4% by HPLC.

Kulkarni is titled "[a] process for the preparation of isosulphan blue," and it "relates to an improved process for the manufacturing of Isosulphan Blue, which avoids usage of a stronger oxidizing agent for the oxidation reaction." (Ex. 1007, Kulkarni, [0001].) Kulkarni discloses synthesis of the sodium salt of ISB. (*Id.*, [0010]; Cox Decl., ¶78.) Kulkarni describes a reaction where "ammonium dichromate is used as a mild oxidizing agent." (Kulkarni, [0050].) Thus, Kulkarni does not rely on silver dioxide as the oxidizing agent, as the Applicants do in the '050 patent. (Cox Decl., ¶78.)

Kulkarni recognizes that ISB can be used in human patients "as a contrast agent to identify lymphatic vessels" for a variety of reasons. (Kulkarni, [0073].) In

the Examples, which describe the details of the synthetic method, Kulkarni repeatedly states that after each step in the synthetic method the "reaction was monitored by HPLC." (*Id*., [0055], [0060], [0064].) Kulkarni also discloses that after the final synthesis step, the [r]eaction was monitored by [thin layer chromatography]." (*Id*., [0071].)

Kulkarni does not expressly disclose the level of purity of the synthesized ISB product. (Cox Decl., ¶80.) However, Kulkarni submitted a declaration during prosecution of his application on October 15, 2008. (*See* Ex. 1031, Kulkarni Decl.) Kulkarni declared (under penalty of a fine, imprisonment, or both) that his claimed process for synthesizing ISB using ammonium dichromate resulted in a crude product of 86.3689% purity, as assessed by analytical HPLC. (*Id*., 2; Cox Decl., ¶80.)[2] Thus, the process described in Kulkarni (filed on April 4, 2006 and published on October 5, 2006), inherently produces an ISB product of around 86% purity. (Cox Decl., ¶80.) Any POSITA could have readily performed the same

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[2] Kulkarni further averred that he purified the crude ISB using preparative HPLC to an ultimate purity of 98.473%. (Kulkarni Decl., 3; Cox Decl., ¶80.) In a second experiment, Kulkarni even purified ISB to 99.4%. (*Id*.; *see also* Cox Decl., ¶80, n.6.)

analytical HPLC test to determine the purity level of the crude ISB. (*Id.*)

B. Snyder discloses a roadmap to scale up an analytical HPLC method to a preparative HPLC method to obtain a purified compound like ISB of at least 99.0% by HPLC.

Dr. Lloyd R. Snyder is one of a small group of principals in the development of HPLC and is very well known to those working in the field. (Cox Decl., ¶¶83–85.) Snyder co-authored one of the "go-to" reference works for anyone in the field, titled "Practical HPLC Method Development." (Ex. 1008, "Snyder"; Cox Decl., ¶85.) A POSITA would have consulted this book in developing a preparative HPLC separation process in 2007. (*Id.*, ¶86.) Snyder provides logical, practical, and basic procedures that would have been familiar to a POSITA in the preparative chromatography field as of the critical date. (*Id.*)

Snyder detailed a roadmap for designing a preparative chromatography method—a mature science already by 1997: "There exists today a good practical understanding of chromatographic separation and how it varies with the sample and with experimental conditions. *Any systematic approach to HPLC method development should be based on this knowledge of the chromatographic process.*" (Snyder, 1 (emphasis added); Cox Decl., ¶87.) Furthermore, "[w]hereas individual approaches may exhibit considerable diversity, method development often follows the series of steps summarized in Fig. 1.1," shown below:

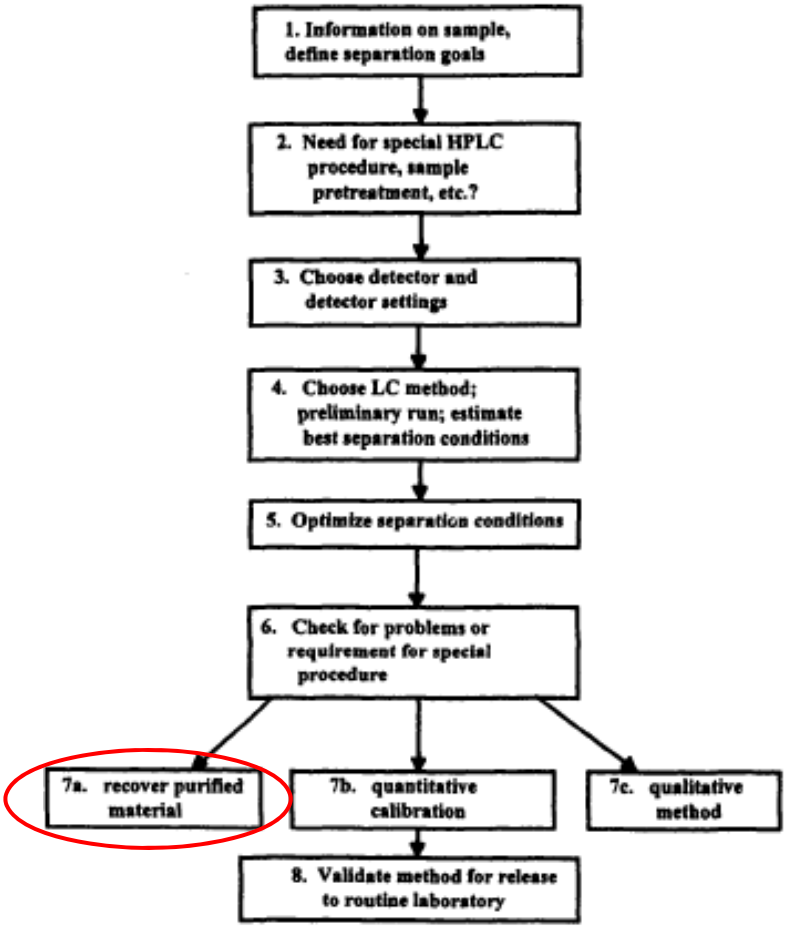

FIGURE 1.1 Steps in HPLC method development.

(Cox Decl., ¶88; Snyder, 1–2; Fig. 1.1 (emphasis added).) Snyder provides step-by-step guidance regarding this Figure in his book to guide the POSITA in developing a chromatography method that results in the desired separation and to recover the purified material. (Cox Decl., ¶89; Snyder, Chapter 1, *et seq*.)

A POSITA could have used Snyder to scale up known analytical HPLC conditions into a preparative HPLC method to obtain a purified product. (Cox Decl., ¶92.) An analytical HPLC method usually "will be developed first and can be used as the starting point for a preparative method." (Snyder, 618; Cox Decl.,

¶90.) Although reciting HPLC purity in the claims, the '050 patent does not disclose how to assess ISB purity by HPLC, thereby admitting that the use of HPLC was well known in the art at the critical date. In the previous litigation between Patent Owner and Aurobindo Pharma, the district court and Patent Owner's expert, Dr. Sessler, agreed:

> 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.

(Ex. 1032, Report & Recommendation ("R&R"), 17, 18.) The Federal Circuit found no error with this finding. *See* 857 F.3d 858, 871–72 (Fed. Cir. 2017). Patent Owner also admitted as much during prosecution. ('050 File History, 120-121.)

Thus, a POSITA readily could have developed the analytical HPLC starting point. According to Snyder, "[m]ethod development for a preparative *should be carried out in the same general way* as for an analytical procedure[.]" (Snyder, 620 (emphasis added); Cox Decl., ¶90.) Snyder provides a table comparing the

methods of analytical versus preparative HPLC:

TABLE 13.1 Analytical vs. Preparative HPLC: Differences in Goals and Characteristics

Analytical HPLC	Preparative HPLC
Goals	
Information about sample composition	Recovery of purified product
Most or all sample components often of interest	Usually only one or a few sample components (products) of interest
Characteristics	
Sample weight just large enough for adequate detection	Largest possible sample weight for maximum yield of pure product
Reversed-phase HPLC most convenient	Normal-phase HPLC most convenient
Column ID 1–5 mm	Column ID 1–10 cm (or larger)
Column particles 5 μm or smaller	Column particles 7 μm or larger
HPLC pumps provide up to 10 mL/min	HPLC pumps provide >> 10 mL/min
Sample injection usually not a problem	Sample injection more difficult, requires more attention
Detection conditions selected for maximum sensitivity	Detection conditions often selected for reduced sensitivity
Solubility of sample in mobile phase usually not important	Sample solubility usually very important
Mobile-phase volatility unimportant	Mobile phase should be volatile; no involatile additives

(Snyder, 617 (emphasis added); Cox Decl. ¶91.) As shown in Table 13.1 above, the goals of analytical HPLC include "[i]nformation about sample composition" and "[m]ost or all sample components often [are] of interest." (Snyder, 617; Cox Decl., ¶92.) Preparative HPLC, on the other hand, is directed to the goals of "[r]ecovery of purified product" and "[u]sually only one or a few sample components (products) [are] of interest." (*Id.*)

To achieve these different goals, the POSITA would understand that the characteristics of each process do not differ in kind, just by degree. (Snyder, 617; Cox Decl., ¶92.) For example, during preparative HPLC, the column is larger and

the HPLC pumps operate at a higher rate. The POSITA would appreciate, however, that for each process, she must consider, for example, detection conditions, sample solubility, and mobile phase, all by exercising only routine skill in the art. (*Id.*) In this case, the POSITA would understand that preparative HPLC could be used to purify ISB, even from its known isomers that were generated during synthesis. (*Id.*)

C. Independent Claim 1

1. The combination of Kulkarni and Snyder teaches or suggests an ISB compound "having a purity of at least 99.0% by HPLC."

The combination of Kulkarni and Snyder teaches or suggests an ISB compound "having a purity of at least 99.0% by HPLC" as required by claim 1. (Cox Decl., ¶98.)

Kulkarni discloses "a compound, [ISB]" as a sodium salt, as required by claim 1. (*Id.*, ¶99; Kulkarni, [0010].) Although Kulkarni does not describe the final purity of the crude ISB prepared by his procedure, such purity would have been inherent in the product itself. (Cox Decl., ¶100.) Although not prior art, Kulkarni signed a declaration in 2008 stating that his process results in crude ISB having a purity level of 86.4%, as assessed by analytical HPLC. (Kulkarni Decl., 2; Cox Decl., ¶100.)

Snyder provides a roadmap for the POSITA to follow in developing a

preparative HPLC method for purifying ISB to 99.0% or higher. (Cox Decl., ¶¶101–102.) Snyder teaches the use of preparative HPLC for "[c]onvenient recovery of highly purified (99%+) product." (Snyder, 621; *see also id*., 617, 625, 632, and 634 (additional references to preparative HPLC techniques generating purities of 99% or greater); Cox Decl., ¶103.)

2. A POSITA would have been motivated to combine the teachings of Kulkarni with the roadmap from Snyder.

It would have been obvious to a POSITA to purify the ISB disclosed in Kulkarni using the roadmap provided by Snyder to make a preparative HPLC method to purify ISB to at least 99.0%. This proposed modification to the purity of ISB is nothing more than applying known methods to yield predictable results. (Cox Decl., ¶104.) *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1303 (Fed. Cir. 2007). In *Aventis*, the court found obvious a method of purifying a mixture from its enantiomers because the POSITA would have known how to perform such steps. The Federal Circuit stated:

> Ordinarily, one expects a concentrated or purified ingredient to retain the same properties it exhibited in a mixture, and for those properties to be amplified when the ingredient is concentrated or purified; isolation of interesting compounds is a mainstay of the chemist's art. 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. at 1302 (quoting *KSR Int'l Co. v. Teleflex Inc*., 127 S. Ct. 1727, 1742 (2007).

The same is true here.[3]

Kulkarni describes ISB as a useful pharmaceutical tracing product for humans. (Kulkarni, [0073].) The POSITA also would have been familiar with Lympazurin®, the ISB product that was FDA approved for "subcutaneous administration," that "delineates the lymphatic vessels draining the region of injection [as] an adjunct to lymphography[.]" (Ex. 1033, Lymphazurin® Label, 1; Cox Decl., ¶105.) A publication describing this product in 1982 disclosed that ISB "was prepared in high purity of 94.5% dye content of the 2,5 isomer as determined by high-pressure liquid chromatography. The remaining 5.5% consists of closely-related isomers produced during synthesis." (Ex. 1010, Hirsch, 1061–62; Cox Decl., ¶105.)

As of the critical date, the POSITA would have been motivated to improve the purity of the ISB disclosed by Kulkarni for the following reasons. *First*, it is

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[3] The district court contrasted the holding in *Aventis* to decide that the '050 patent was *not* invalid, but that was based on its finding that "it is more likely than not that the state of the art was such that a [POSITA] would not have been able to purify isosulfan blue to at least 99% purity before the priority date." (R&R, 38.) Luitpold presents extensive evidence to undercut that finding in this Petition.

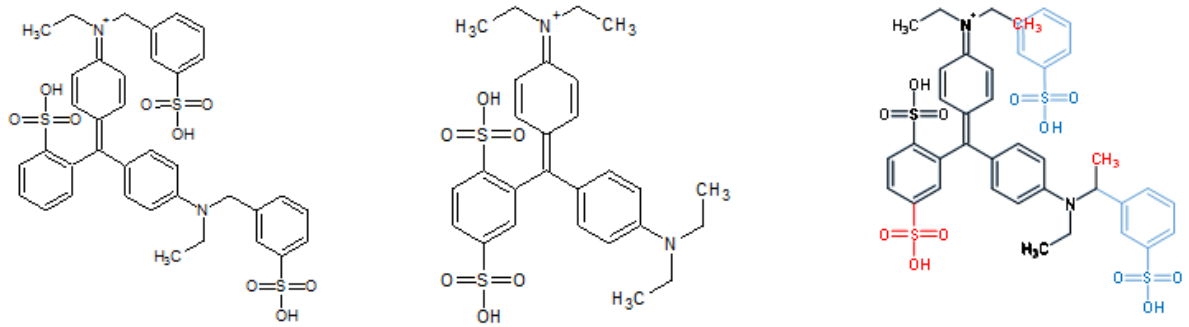
well-known that a POSITA always is motivated to find a more pure form of a pharmaceutical product that is directed for human use. (Cox Decl., ¶106; Ex. 1005, Moreton Decl., ¶22.) For example, a review article published contemporaneously with the priority date of the challenged claims explains that controlling impurities in drug substances is essential. (*See* Ex. 1034, Argentine, Abstract; Cox Decl., ¶106.)

Furthermore, pharmaceutical regulations drive drug manufacturers to make more pure drug substances. (*See, e.g.*, Ex. 1035, ICH Q3A Guidelines 2002, 8; Cox Decl., ¶106; Moreton Decl., ¶¶26–28.) As Dr. Moreton explains, these guidelines impose step-wise regulatory burdens on manufacturers for drug substances that include individual impurities greater than 0.05% (reporting threshold), 0.10% (identification threshold), and 0.15% (qualification threshold). (Ex. 1037, ICH Q3A Guidelines 1995, 8; Moreton Decl., ¶26.) As expected, drug manufacturers would be highly motivated to avoid any additional regulatory burden, if possible, by eliminating or reducing impurities in a finished drug substance, particularly below the thresholds identified in the guidance. (Moreton Decl., ¶27.) In 2007, the POSITA would have understood that the ICH Q3A Guidelines 2002 reflected FDA's current thinking and upcoming requirements, and would have designed drug substances to comply with such recommendations. (*Id.*, ¶28.)

Second, a POSITA would have understood the disclosure of analytical

HPLC in Kulkarni and Hirsch to be a "starting point" for developing a preparative HPLC method based on Snyder, and would have been motivated to do so. (Cox Decl., ¶107.) Applicants admitted as much during prosecution and prior litigation. (*See* Cox Decl., ¶107; R&R, 17–18; '050 File History, 120-121.)

Third, the POSITA would have been motivated to purify ISB to at least 99.0% purity as assessed by HPLC based on Brown. (Cox Decl., ¶108.) Brown synthesized, then purified a radio-labeled compound that is structurally similar to ISB, known as FD&C Blue No. 1, to "more than 99.0%" purity assessed by HPLC. (Brown, 3, Fig. 2; Cox Decl., ¶94.) FD&C Blue No. 1 has many features in common with ISB, being a triarylmethane dye with both amine and sulfonic acid functionality. (Cox Decl., ¶93.) Cox Figure 1 demonstrates similar structures (shown in black) between the compounds, while showing groups particular to ISB in red, and those particular to FD&C Blue No. 1 in blue.



FD&C Blue No. 1 Isosulfan Blue Overlay

Cox Figure 1

Brown disclosed use of conventional preparative HPLC conditions. (Cox Decl., ¶109.) Brown utilized consecutive runs on a preparative HPLC column until the product collected had a purity of "more than 99%." (Brown, 3.) Brown's procedure, involving repeated purification, collection, and re-purification using sequential preparative HPLC runs, is conventional and would have been routine to a POSITA. (Cox Decl., ¶109.)

Brown demonstrates this high purity of the radio-labeled dye in a chromatogram, where the FD&C Blue No. 1 is shown as having a single, significant peak:

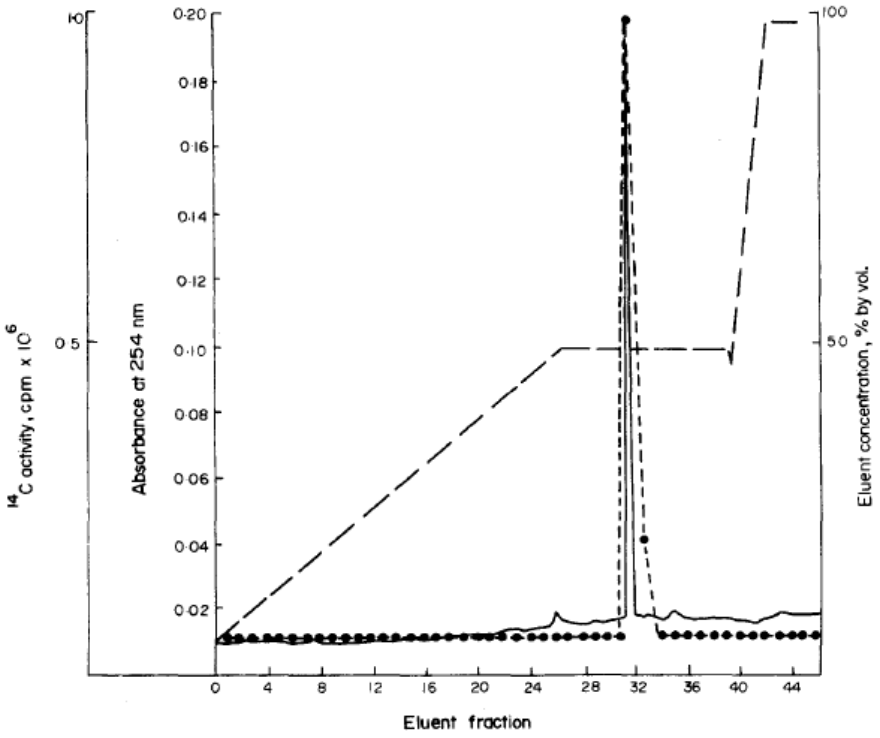


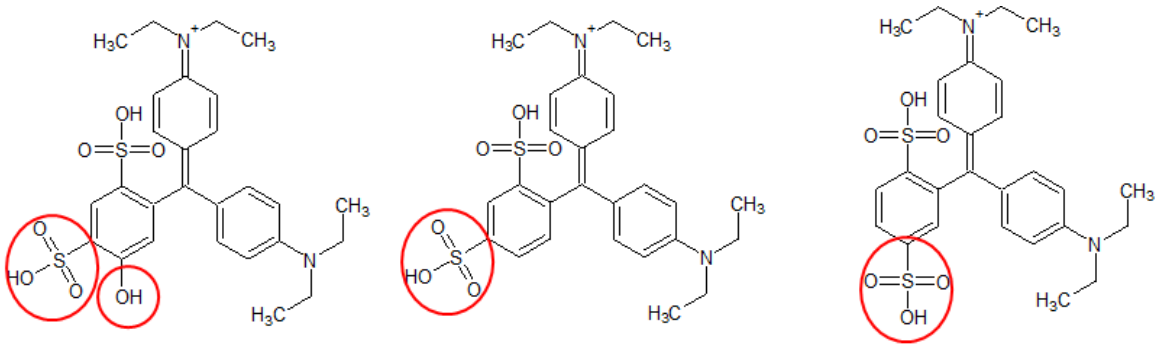
Fig. 2. HPLC purification of [^{14}C]FD & C Blue No. 1: absorbance of effluent at 254 nm (—); ^{14}C activity (---●---); eluent gradient (——).

(Brown, Fig. 2.) As the chromatogram demonstrates and Brown concludes, there is

a single peak having more than 99% of the AUC of the radio-labeled FD&C Blue No. 1, *i.e.*, the compound is more than 99% pure as determined by HPLC. (Cox Decl., ¶94.) The POSITA would have understood from Brown that it was possible to obtain a high purity for ISB (*i.e.*, more than 99%) using conventional HPLC conditions. (*Id.*)

Fourth, the POSITA would have been aware of literature describing the successful separations of triarylmethane dyes like Patent Blue VF and Patent Blue V (Lee), FD&C Blue No. 1 (Kusaka), and Food Green No. 3 (Ngang), which are structurally very similar to ISB, from closely-related isomers of the respective compounds. (Cox Decl., ¶¶51–54.) These examples, described below, would have given the POSITA confidence that ISB could be separated from its isomers by HPLC as well. (*Id.*, ¶55.)

As shown below in Cox Figure 2 (*see* Cox Decl., ¶112), Lee attempted the separation of two compounds, known as Patent Blue V and Patent Blue VF, that differ from ISB and each other only by the addition of a single hydroxyl group adjacent to a sulfonyl group (Patent Blue V), or the arrangement of the sulfonic acid groups on the 2,4 carbons instead of the 2,5 carbons (Patent Blue VF):



Patent Blue V | Patent Blue VF (Sulfan Blue) | Isosulfan Blue

Cox Figure 2

Using conventional conditions (Cox Decl., ¶113), and as shown below in Figure 2, Lee successfully separated Patent Blue V (Sample 3) from Patent Blue VF (Sample 2), along with four other closely-related isomers, using HPLC:

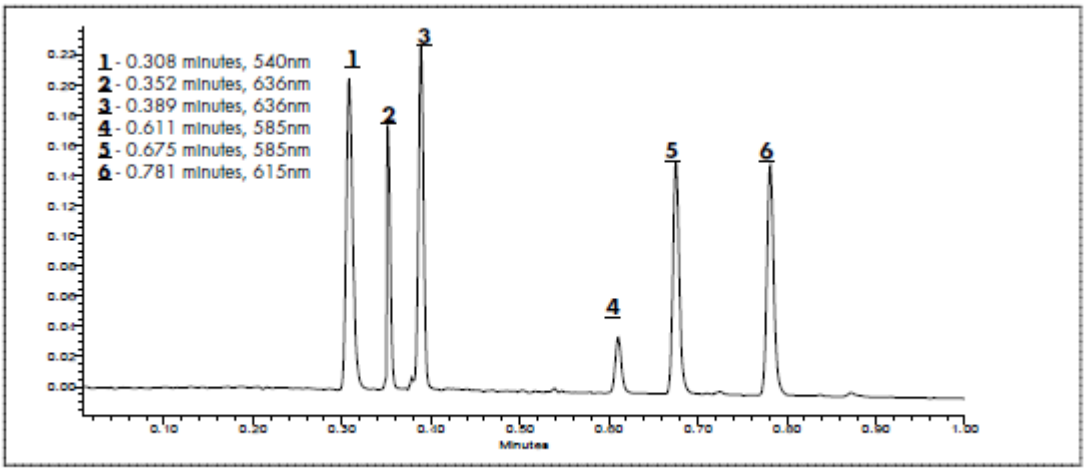
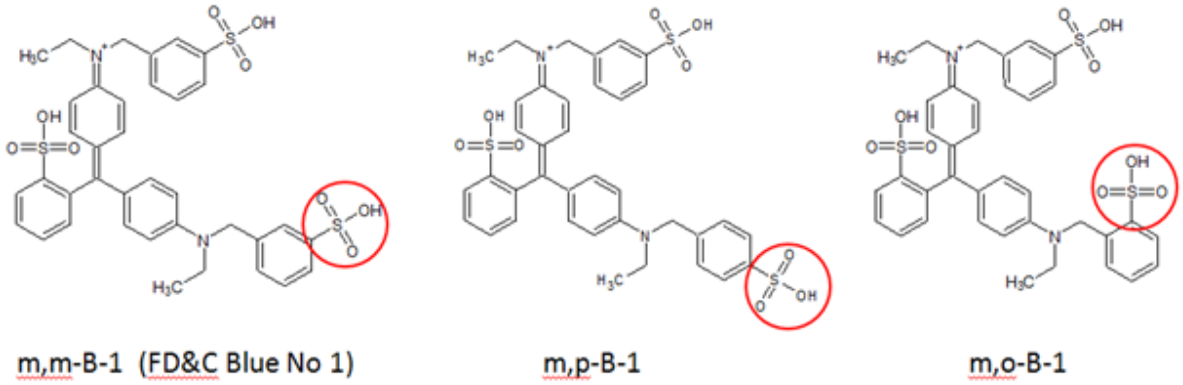


Figure 2. PDA timed wavelength chromatogram of UPLC separation of 6 triarymethane dyes at 1 µg/mL.

(Lee, Fig. 2.) Because of the close structural relation between the dyes separated in Lee and ISB, a POSITA would have reasonably expected, based upon Lee's successful separation, that ISB would elute from the column and could be isolated from related compounds, including isomers, under similar conditions. (Cox Decl.,

¶119.)

Decades before the critical date, several publications demonstrated the separation of closely related isomers from FD&C Blue No. 1. (*See, e.g.*, Brown, *supra*; Kusaka, Fig. 4; Cox Decl., ¶114.) Kusaka showed that closely related isomers of FD&C Blue No. 1 could be resolved by HPLC from the dye. (Cox Decl., ¶114.) Kusaka describes the separation of two known isomers of FD&C Blue No. 1 (*o,m*-B-1 and *m,p*-B-1), each an isomer that differed only in the position of a sulfonic acid group in the o, m, or p position on the benzene ring. (Id.) Cox Figure 3 compares these structures:



Cox Figure 3

(*See* Kusaka, Fig. 4 (excerpt).)

Because FD&C Blue No. 1, and *o,m*-B-1 and *m,p*-B-1 are dyestuffs, each are readily detectible using HPLC, showing the power of chromatography to separate such closely related species. (Cox Decl., ¶115.) The Kusaka chromatogram shows the successful separation of each of *o,m*-B-1 and *m,p*-B-1 from FD&C Blue No. 1

(identified below as *m,m*-B-1):

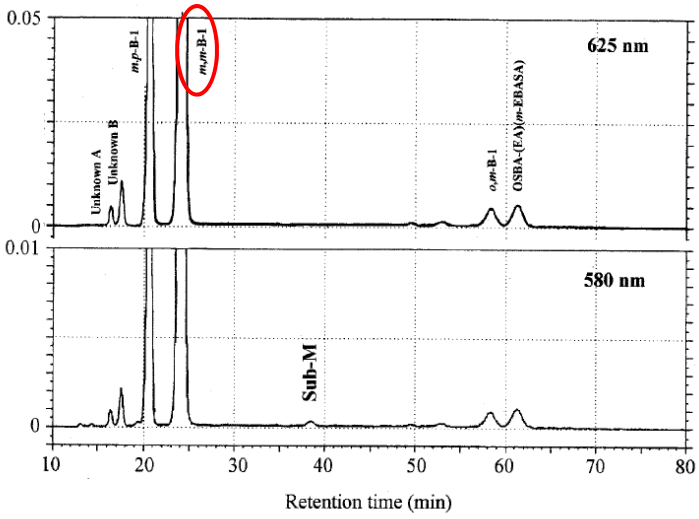
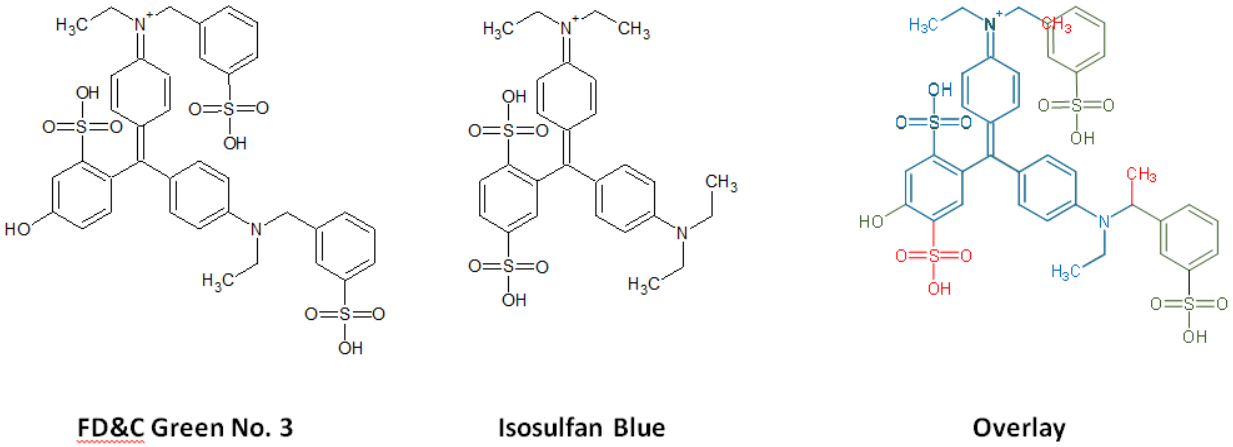


*Figure 2. Analytical HPLC of commercial B-1 at 625 nm (upper) and 580 nm (lower). OSBA-(EBA)(*m*-EBASA), a subsidiary colour reported elsewhere, was not observed in our study, although synthetic OSBA-(EBA)(*m*-EBASA), supplied kindly by Dr Kamikura, eluted at 48.0 min under other conditions (methanol/0.5% ammonium carbonate (50 : 50)) and was easily seen. As for unknowns A and B, we are continuing to investigate their chemical structures.*

(Kusaka, Fig. 2 (emphasis added).) Kusaka also used the same, conventional repeat purification steps of preparative HPLC runs to separate another triarylmethane related impurity known as Sub-M from the blue dye "until the chromatography *indicated a single peak*." (*Id.*, 503 (emphasis added); Cox Decl., ¶116.) The POSITA would expect the "single peak" described by Kusaka to have a purity of at least 99.0%, but closer to 100%, by HPLC. (Cox Decl., ¶¶116, 48.) The POSITA would have been motivated to purify ISB from its closely-related isomers based upon the successful preparative HPLC purification of Sub-M described in Kusaka. (*Id.*)

Finally, Ngang shows the successful separation and purification of closely-related o, m, and p isomers from a highly-similar triarylmethane dye (FD&C Green

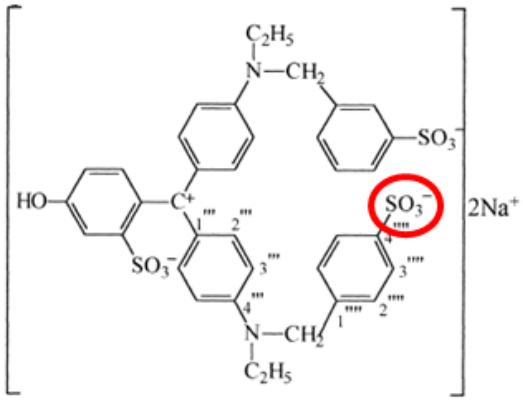
No. 3) by preparative HPLC. (Cox Decl., ¶117.) Cox Figure 4 shows the close structural relationship between FD&C Green No. 3 (shown in green) and ISB (shown in red):



Cox Figure 4

(*Id.*)

Ngang reports the separation of one closely-related isomer named "Sub-C" that differs from the green dye only by the p-position of the sulfonic acid groups. Cox Figure 5 below, which is an annotated excerpt of Ngang Figure 3, highlights this one distinction:



Cox Figure 5

(*Id.*, ¶118.)

Ngang utilizes the same repetitive preparative HPLC procedure as Brown and Kusaka, where "[t]he fractions of observed peaks were collected and concentrated, and each residue was rechromatographed under the same conditions until the chromatogram *indicated a single peak*." (Ngang, 299 (emphasis added).) This iterative process would have been routine for a POSITA. (Cox Decl., ¶118.) A POSITA would understand that a single peak means the AUC for the given peak on the chromatogram is close to 100% of the AUC under the entire chromatogram. (Cox Decl., ¶¶118, 48.) The POSITA readily could separate these dyestuffs—despite their very close chemical structures—because Food Green No. 3 (*i.e.*, *m,m*-G-3) and Sub-C each are readily detectable on a chromatogram. (*Id.*)

Collectively, because of the close structural relationship between each of the dyes separated in Lee (Patent Blue V and Patent Blue VF), Kusaka (Food Blue No.

1), and Ngang (Food Green No. 3), on the one hand, and ISB (sodium salt) on the other, a POSITA would have been motivated to apply the conventional conditions and preparative HPLC as represented in each of these studies to separate ISB from its closely-related isomers and other impurities, such as synthetic byproducts or degradation products, to a purity of at least 99.0%, but likely closer to 100%. (Cox Decl., ¶¶118–119.)

Fifth, armed with the motivation to produce a more pure form of ISB using preparative HPLC, the POSITA would have consulted Snyder because it was a seminal text in the field of chromatography, and was largely regarded as the "go-to" work for a POSITA to consult in developing chromatographic conditions. (Cox Decl., ¶120; *see also id.*, ¶¶87–92.) Based on Snyder's disclosure to use HPLC for "[c]onvenient recovery of highly purified (99%+) product," a POSITA would have been motivated to obtain that "highly purified (99%+) product" using the preparative HPLC techniques and conditions described by Snyder. (Cox Decl., ¶120.) The Board should consider the "routine steps" that a POSITA would take, including preparative HPLC, when trying to obtain a more pure ISB product. *See, e.g.*, *Ball Aerosol & Specialty Container, Inc. v. Limited Brands, Inc.*, 555 F.3d 984, 993 (Fed. Cir. 2009) (reversing finding of non-obviousness where the prior art contained all the elements needed to solve a known problem because the court failed to account for the "routine steps" the POSITA would take to combine them).

3. The POSITA would have had a reasonable expectation of success to purify the ISB of Kulkarni to at least 99.0% purity by HPLC using the roadmap from Snyder.

Applicants admitted that a POSITA readily could have developed analytical HPLC conditions for ISB. Using the roadmap described by Snyder (*see, e.g.*, Fig. 1.1), and the teachings that "[m]ethod development for a preparative HPLC method *should be carried out in the same general way* as for an analytical procedure" (*see id.,* 619 (emphasis added); Table 13.1), the POSITA could purify the ISB of Kulkarni to at least 99.0% using preparative HPLC. (Cox Decl., ¶121.) The POSITA would have appreciated that analytical chromatography can be scaled up to a preparative HPLC method for "the isolation of purified material (product) for further use." (*Id.*; Snyder, 616.)[4]

By 2007, preparative HPLC was a mature technique that would have been routine to the POSITA, as demonstrated by Brown, Kusaka, and Ngang, *supra*.

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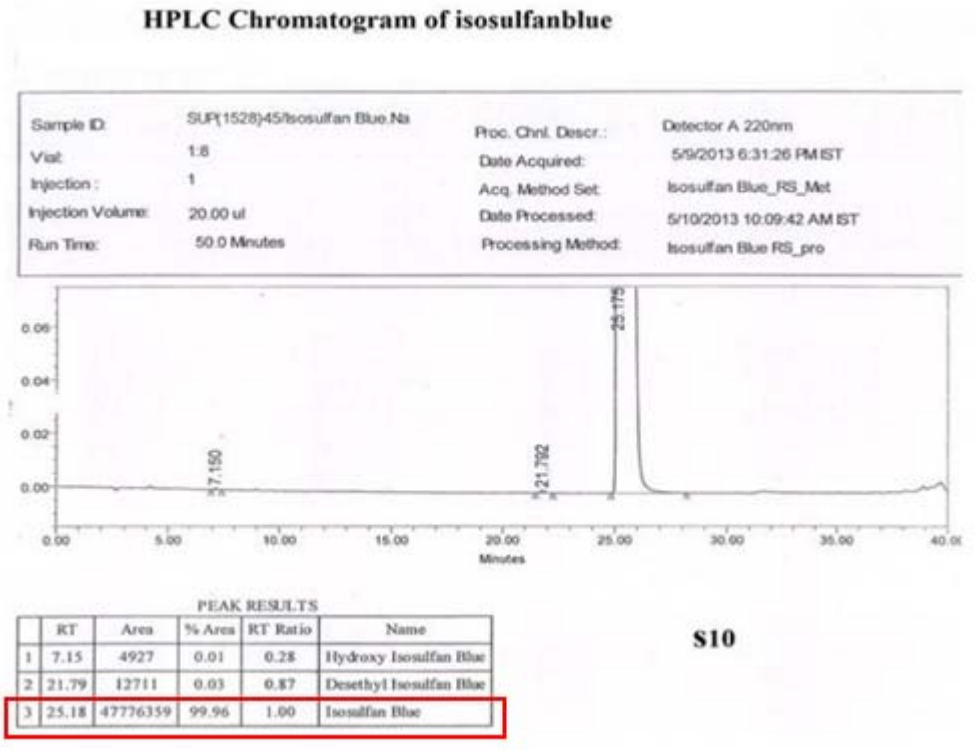
[4] In the previous IPR Petition directed to the '050 patent, Auromedics' expert agreed. *See* IPR2017-00762, Exhibit 1009 thereto at 41–42 ("The difference between measuring the purity of a compound—an analytical test—and preparing a pure compound—a preparative technique—is only one of scale."). (Cox Decl., ¶121.)

(Cox Decl., ¶122.) A POSITA reasonably could have expected those techniques to purify ISB to at least 99.0%, but closer to 100%, by HPLC. (*Id.*) Moreover, there are no fundamental differences between analytical and preparative chromatography, and a POSITA could have exercised routine skill to scale up an analytical HPLC method to a preparative HPLC method. (*Id.*, ¶39.)

Post-filing evidence confirms that the preparative HPLC procedures described in Snyder would have worked. The Kulkarni Declaration demonstrates that a POSITA could have (and would have) purified the crude ISB product in Kulkarni using preparative chromatography. (Kulkarni Decl., 2; Cox Decl., ¶123.) Indeed, the Kulkarni Declaration reports purifying ISB by column chromatography to 98.5%, and 99.4% by analytical HPLC, respectively. (*Id*.) The data presented in the Kulkarni Declaration support the ease that a POSITA could have purified the ISB to 99% purity using HPLC. (*Id.*, ¶124.) The peaks in the analytical chromatograms are very well separated: the ISB eluted at 11.4 minutes (in experiment I) while the nearest impurities eluted at 6.23 minutes and 17.88 minutes. (Kulkarni Decl., 3.) Based upon this degree of separation, it would have been routine for the POSITA to scale this method up to preparative HPLC. (*Id*.)

Additionally, a 2017 paper utilizes preparative HPLC conditions from the teachings of Snyder to purify ISB to a purity of 99.96%. (*See* Ex. 1036, Nethinti, 20; Cox Decl., ¶125.) Cox Figure 6 shows "peak results" reporting ISB as having

99.96% purity by HPLC, along with the chromatogram showing fully resolved peaks:



Cox Figure 6

Thus, the POSITA, relying only on the guidance in Snyder and routine skill, would have successfully purified ISB with the claimed purity of at least 99.0% using HPLC. (Cox Decl., ¶125.)

D. Independent Claim 11

1. The combination of Kulkarni and Snyder teaches or suggests a "solution containing [ISB] having a purity of at least 99.0% by HPLC."

In addition to the reasons set forth above in Section VI.C.1, Kulkarni teaches or suggests a "solution containing [ISB]" as required by claim 11. (Cox Decl.,

¶126.) Kulkarni states that "Isosulphan Blue is a reagent used in diagnostic kits for detecting cancer cells." (Kulkarni, [0009].) "Like the term 'comprising,' the terms 'containing' and 'mixture' are open-ended." *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376 (Fed. Cir. 2004).[5] A POSITA would understand that the ISB produced by the methods disclosed in Kulkarni would be used in solutions that could be injected into a human, and a POSITA would be knowledgeable of appropriate solvents to dissolve ISB. (Cox Decl., ¶126.) Moreover, ISB was commercially available as a 1% solution in 2007 (Lymphazurin® Label), and the POSITA would have been aware of that FDA-approved preparation. (*Id.*)

2. A POSITA would have been motivated to combine the teachings of Kulkarni with the roadmap from Snyder.

As described in Section VI.C.2 above, the POSITA would have been motivated to combine the teachings of Kulkarni and Snyder to purify ISB to a purity of "at least 99.0% by HPLC." (Cox Decl., ¶127.)

3. The POSITA would have had a reasonable expectation of success to purify the ISB of Kulkarni to at least 99.0% by HPLC using the roadmap from Snyder.

As described in Section VI.C.3 above, a POSITA would have had a

[5] Even if the Board construes the term "containing" to be closed, a solution containing only ISB sodium salt would have been obvious for the same reasons.

reasonable expectation of success to arrive at the claimed purity by combining Kulkarni and Snyder. (Cox Decl., ¶128.)

E. Independent Claim 15

1. The combination of Kulkarni and Snyder teaches or suggests a "composition consisting essentially of [ISB] having a purity of at least 99.0% by HPLC."

In addition to the reasons set forth above in Section VI.C.1, the combination of Kulkarni and Snyder teaches or suggests a "composition consisting essentially of [ISB] having a purity of at least 99.0% by HPLC" as required by claim 15. (Cox Decl., ¶129.) The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551–52 (C.C.P.A. 1976). For the purposes of searching for and applying prior art under 35 U.S.C. §§ 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." *See, e.g., PPG Indus. v. Guardian Indus.*, 156 F.3d 1351, 1355 (Fed. Cir. 1998). A solution containing ISB does not materially differ from ISB alone because it was known that ISB is soluble in, for example, methanol and other polar solvents. (Cox Decl., ¶130.)

Kulkarni states that "[i]sosulphan [b]lue is a reagent used in diagnostic kits

for detecting cancer cells." (Kulkarni, [0009].) A POSITA would understand that the ISB produced by the methods disclosed in Kulkarni would be used in solutions that could be injected into a human, and a POSITA further would understand the proper solvent to use that could form a solution with ISB. (Cox Decl., ¶130.) Moreover, ISB was commercially available as a 1% solution in 2007 (Lymphazurin® Label), and the POSITA would have been aware of that FDA-approved preparation. (*Id*.)

2. A POSITA would have been motivated to combine the teachings of Kulkarni with the roadmap from Snyder.

As described in Section VI.C.2 above, the POSITA would have been motivated to combine the teachings of Kulkarni and Snyder to purify ISB to a purity of "at least 99.0% by HPLC." (Cox Decl., ¶131.)

3. The POSITA would have had a reasonable expectation of success to purify the ISB of Kulkarni to at least 99.0% by HPLC using the roadmap from Snyder.

As described in Section VI.C.3 above, a POSITA would have had a reasonable expectation of success to arrive at the claimed purity by combining Kulkarni and Snyder. (Cox Decl., ¶132.)

F. Dependent Claims 2, 12, and 16

Claims 2, 12, and 16 require that the purity level of the claimed ISB compound fall "between 99.0% and 99.5% by HPLC." Each of these claims depend from independent claims 1, 11, and 15, respectively. To the extent the

Board adopts Luitpold's claim construction, a purity of "at least 99.0% by HPLC" would cover the claimed range of "between 99.0% and 99.5%." (Cox Decl., ¶133.); *see also In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (partially overlapping ranges establish *prima facie* obviousness). Accordingly, for the same reasons as described above in Section VI.C, it would have been obvious to the POSITA to arrive at the claimed purity based on Kulkarni in view of Snyder.

G. Dependent Claims 3, 13, and 17

Each of claims 3, 13, and 17 require that the claimed ISB compound has "less than 20 ppm silver." It was well known as of the critical date in May 2007 that use of heavy metal oxidizing agents, like lead oxide or potassium dichromate, would pose toxicity issues for the resulting ISB product. (*See, e.g.*, Kulkarni, [0015–16]; Cox Decl., ¶134). The '050 patent specification itself recognizes that the "literature is replete with methods of preparing triarylmethane dyes, [but] most of the methods involve…hazardous oxidizing agents (lead oxide, chloranil, iron phthalocyanine/oxone) for converting to triarylmethane dyes[.]" ('050 patent, 1:64–2:4.)

The POSITA would have recognized the need to reduce the amount of metal ions left behind from any oxidation catalyst. The USP-NF (2006) includes a test for heavy metals, and a common injectable product (sodium chloride injection) has a 10 ppm limit for heavy metals like silver. (*See* USP-NF (2006), 1858, 1529;

Moreton Decl., ¶35-37.) To comply with these standards, the POSITA would have been motivated to separate out any metal ions, including silver, that remained as a result of the oxidation reaction using HPLC. (Cox Decl., ¶135; Moreton Decl., ¶¶33-37.) Accordingly, it would have been obvious to make an ISB product having less than 20 ppm silver as of the critical date.

Furthermore, had the POSITA relied upon the synthetic method described in Kulkarni, there would be no silver ions to remove, since Kulkarni uses ammonium dichromate as the oxidizing agent, not silver dioxide. (Kulkarni, [0030]; Cox Decl., ¶136.) To the extent any prior art process would have included the use of silver, preparative HPLC would readily separate out those foreign ions such that the resulting ISB (sodium salt) product would be free of silver ions. (Cox Decl., ¶136.)

H. Dependent Claims 4, 14, and 18

Each of claims 4, 14, and 18 require that the purity level of the claimed ISB compound is "greater than 99.5% by HPLC." Each of these claims depend from claims 3, 13, and 17, respectively. To the extent the Board adopts Luitpold's claim construction, a purity of "at least 99.0% by HPLC" would cover the claimed range of "greater than 99.5% by HPLC." (Cox Decl., ¶137.); *see also Peterson*, 315 F.3d at 1329. Accordingly, for the same reasons as described above in Section VI.C, it would have been obvious to the POSITA to arrive at the claimed purity based on Kulkarni in view of Snyder.

I. Dependent Claims 5–10

Claims 5–10 are product-by-process claims. "The general rule when determining the patentability of a product-by-process claim is to 'focus [] on the product and not on the process of making it.'" *Fresenius Kabi USA LLC v. Cubist Pharms. LLC*, Case IPR2015-01566, Paper No. 20 at 8 (P.T.A.B. Jan. 28, 2016) (quoting *Amgen, Inc. v. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009)). That is because "an old product is not patentable even if it is made by a new process." *Amgen*, 580 F.3d at 1370. "An exception applies only when process steps recited in the claim impart unrecited 'structural and functional differences' to the claimed product." *Fresenius*, Paper 20 at 8 (quoting *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1267–68 (Fed. Cir. 2012)).

Just as in *Fresenius*, the rule—not the exception—applies here. In *Fresenius*, the claims were directed to a "pharmaceutical composition […] comprising daptomycin obtained by a process comprising the steps of forming a daptomycin aggregate, the composition having daptomycin with greater than or about 93% *purity relative to impurities 1–14* defined by peaks 1–14 shown in FIG. 12." *Fresenius*, Paper 20 at 5 (emphasis original). Just as here, the Board determined that the process limitations directed to the purity of the claimed compound relative to specified impurities do not "add any unrecited structural or functional feature that distinguishes the claimed product from the prior art." *Id.* at 8.

The process described in claims 5–10 allegedly result in an ISB (sodium salt) product having a purity of "at least 99.0% by HPLC." The process limitations, therefore, do not add anything additional to what the claims already require. *Id*. at 9. Accordingly, and for the same reasons as described above in Sections VI.C, (*see* Cox Decl., ¶138), Kulkarni in view of Snyder renders claims 5–10 obvious.

VII. Ground 2: Kulkarni in View of Snyder, or Further in View of Brown Renders Claims 1–18 Obvious.

A. Brown purified closely-related isomers from a triarylmethane dye with a highly similar chemical structure to ISB to "more than 99%" purity by HPLC.

As described above in Section VI.C.2, Brown synthesized, then purified a radio-labeled compound that is structurally similar to ISB, known as FD&C Blue No. 1, to "more than 99.0%" purity assessed by HPLC. (Brown, 3, Fig. 2; Cox Decl., ¶¶93–94, 140–142.) Brown disclosed conventional chromatographic conditions, using consecutive runs on a preparative HPLC column until the product collected had a purity of "more than 99%." (Cox Decl., ¶141.) Brown's procedure, involving repeated purification, collection, and re-purification using repetitive preparative HPLC runs, is conventional and would have been routine to a POSITA. (*Id.*)

B. Independent Claim 1

1. The combination of Kulkarni and Snyder, or further in view of Brown, teaches or suggests an ISB compound "having a purity of at least 99.0% by HPLC."

As described in Section V.C.1 above, the combination of Kulkarni and Snyder teaches or suggests an ISB compound "having a purity of at least 99.0% by HPLC," as required by claim 1. (Cox Decl., ¶¶139–141.) To the extent the Board determines that the POSITA would not have been able to arrive at a purity of "at least 99.0% by HPLC" from Kulkarni in view of Snyder, Brown provides the additional disclosure of the claimed purity. (*Id*., ¶142)

2. A POSITA would have been motivated to combine the teachings of Kulkarni with the roadmap from Snyder, together with the example of Brown.

As described in Section VI.C.2 above, the POSITA would have been motivated to combine Kulkarni and Snyder to arrive at the claimed invention. (Cox Decl., ¶143.) The same POSITA also would have combined the teachings of Brown with Kulkarni and Snyder to purify ISB to "at least 99.0% by HPLC." (*Id.*) The POSITA would have been motivated to combine the teachings of Brown because it is an experimental example of how to arrive at the claimed purity using preparative HPLC for a related dye. (*Id*., ¶144.) Brown took crude FD&C Blue No. 1 and used repeated runs on a preparative HPLC column, recollecting, and re-purifying the dye until he arrived at a highly-purified compound (*i.e.*, more than 99%). (*Id.*) The chromatogram disclosed in Brown Figure 2 demonstrates a single

peak where more than 99% of the AUC is under the peak. (*Id.*; Brown, Fig. 2.) Accordingly, the POSITA seeking to purify ISB would have looked to Brown as an example. (*Id*.)

3. The POSITA would have had a reasonable expectation of success to purify ISB from Kulkarni to at least 99.0% by HPLC using the roadmap from Snyder, in light of the example from Brown.

For the same reasons described above in Section VI.C.3, the POSITA would reasonably have expected success for purifying ISB sodium salt to a purity of at least 99.0% by HPLC. (Cox Decl., ¶145.) The addition of Brown only would have increased that expectation because it shows the successful purification of a closely related triarylmethane dye, FD&C Blue No. 1, to "more than 99%" using preparative HPLC. (*Id.*)

C. Independent Claim 11

1. The combination of Kulkarni and Snyder teaches or suggests a "solution containing [ISB] having a purity of at least 99.0% by HPLC."

For the same reasons set forth above in Section VI.D.1, the combination of Kulkarni and Snyder teaches or suggests a "solution containing [ISB]" as required by claim 11. (Cox Decl., ¶146.)

2. A POSITA would have been motivated to combine the teachings of Kulkarni with the roadmap from Snyder and the example of Brown.

As described in Section VII.B.2 above, the POSITA would have been

motivated to combine the teachings of Kulkarni and Snyder to purify ISB to a purity of "at least 99.0% by HPLC." (Cox Decl., ¶147.)

3. The POSITA would have had a reasonable expectation of success to purify ISB to at least 99.0% by HPLC using the roadmap from Snyder, in light of the example of Brown.

As described in Section VII.B.3 above, a POSITA would have had a reasonable expectation of success to arrive at the claimed purity by combining Kulkarni and Snyder in light of the example of Brown. (Cox Decl., ¶148.)

D. Independent Claim 15

1. The combination of Kulkarni and Snyder teaches or suggests a "composition consisting essentially of [ISB] having a purity of at least 99.0% by HPLC."

For the same reasons set forth above in Section VI.E.1, the combination of Kulkarni and Snyder teaches or suggests a "solution containing [ISB]" as required by claim 11. (Cox Decl., ¶149.)

2. A POSITA would have been motivated to combine the teachings of Kulkarni with the roadmap from Snyder and the example of Brown.

As described in Section VII.B.2 above, the POSITA would have been motivated to combine the teachings of Kulkarni and Snyder with the example of Brown to purify ISB to a purity of "at least 99.0% by HPLC." (Cox Decl., ¶150.)

3. The POSITA would have had a reasonable expectation of success to purify the ISB of Kulkarni to at least 99.0% by HPLC using the roadmap from Snyder, in light of the example of Brown.

As described in Section VII.B.3 above, a POSITA would have had a reasonable expectation of success to arrive at the claimed purity by combining Kulkarni and Snyder in light of the example of Brown. (Cox Decl., ¶151.)

E. Dependent Claims 2, 12, and 16

Each of claims 2, 12, and 16 require that the purity level of the claimed ISB compound fall "between 99.0% and 99.5% by HPLC." For the same reasons described above in Section VI.F (*see* Cox Decl., ¶152), these dependent claims would have been obvious to a POSITA.

F. Dependent Claims 3, 13, and 17

Each of claims 3, 13, and 17 require that the claimed ISB compound has "less than 20 ppm silver." For the same reasons described above in Section VI.G (*see* Cox Decl., ¶153; Moreton Decl., ¶¶34-37), these dependent claims would have been obvious to a POSITA.

G. Dependent Claims 4, 14, and 18

Each of claims 4, 14, and 18 require that the purity level of the claimed ISB compound is "greater than 99.5% by HPLC." For the same reasons described above in Section VI.H (*see* Cox Decl., ¶154), these dependent claims would have been obvious to a POSITA.

H. Dependent Claims 5–10

For the same reasons as described above in Sections VI.I (*see* Cox Decl., ¶155), Kulkarni in view of Snyder, or further in view of Brown renders claims 5–10 obvious.

VIII. Ground 3: Hirsch in View of Snyder Renders Claims 1–18 Obvious.

A. Hirsch discloses that ISB had been FDA-approved for pharmaceutical use and ultimately had a purity of 83.4% as assessed by HPLC.

Hirsch discloses an FDA-approved ISB product named Lymphazurin® that reports a purity of 94.5% by HPLC. (Cox Decl., ¶81; Hirsch, 1061–1062.) Hirsch states that "[i]sosulfan blue injection (1%) is a safe and efficacious drug for the identification of lymphatics during lymphangiography." (*Id.*, 1064.) Later, it was determined that the same lot of ISB from Hirsch contained only 83.4% ISB and 8.2% "other organics." (R&R, 3–4 (quoting Dkt. No. 80-18); Cox Decl., ¶82.) In a letter to FDA on June 8, 1990, Dr. Hirsch assured FDA that his company remained "committed to conduct studies designed to identify and/or remove the organic compound" found in the ISB product and welcomed the FDA's "advice as to the best approach to achieve this." (*Id.*)

B. Independent Claim 1

1. The combination of Hirsch and Snyder teaches or suggests an ISB compound "having a purity of at least 99.0% by HPLC."

The combination of Hirsch and Snyder teaches or suggests an ISB

compound "having a purity of at least 99.0% by HPLC" as required by claim 1. (Cox Decl., ¶156.) In 1982, Hirsch described the first FDA-approved use of ISB (as monosodium salt) in humans for "identification of lymphatic vessels before cannulation." (Hirsch, Abstract, 1061; Cox Decl., ¶157.) Hirsch reported that "[i]sosulfan blue injection (1%) is a safe and efficacious drug for the identification of lymphatics during lymphangiography. FDA approval for human use has been obtained. Commercial introduction of this drug is forthcoming under the trade name Lymphazurin (1%)." (Hirsch, 1064.) Hirsch then stated that a sample containing ISB was subjected to HPLC, and it was determined that the sample was 94.5% ISB and 5.5% "closely related isomers produced during synthesis." (*Id.*, 1061–1062.)

By 1990, the purity of this crude ISB product ultimately was found to be around 83.4%, and Dr. Hirsch welcomed FDA's advice in seeking a more purified pharmaceutical product. (R&R, 3–4 (quoting Dkt. No. 80-18); Cox Decl., ¶158.)[6] While Hirsch does not disclose a method of making ISB, the '050 patent admits that a POSITA would have known methods to synthesize ISB before the critical

[6] This purity is consistent with Kulkarni, which discloses that crude ISB has a purity of 86.4% by HPLC. (Kulkarni Decl., 2.)

date. (’050 patent, 1:63–2:8; Cox Decl., ¶158.)

As described more fully above in Section VI.B, Snyder provides a roadmap for the POSITA to follow in developing a preparative HPLC method for purifying ISB to 99.0% or higher. (Cox Decl., ¶¶159–161.) Snyder teaches the use of preparative HPLC for “[c]onvenient recovery of highly purified (99%+) product.” (Snyder at 621; *see also id*. at 617, 625, 632, and 634 (additional references to preparative HPLC techniques generating purities of 99% or greater); Cox Decl., ¶161.)

2. A POSITA would have been motivated to combine the teachings of Hirsch with the roadmap from Snyder.

It would have been obvious to a POSITA in 2007 to purify the ISB disclosed in Hirsch using the roadmap provided by Snyder to make a preparative HPLC method to purify ISB to at least 99.0% by HPLC. This proposed modification to the purity of ISB is nothing more than applying known methods to yield predictable results. (Cox Decl., ¶162.) *See Aventis*, 499 F.3d at 1303 (finding obvious a method of purifying a mixture from its enantiomers because the POSITA would have known how to perform such steps). The same is true here.

The POSITA in 2007 would have been familiar with Lympazurin®, the ISB product that was FDA approved for “subcutaneous administration,” that “delineates the lymphatic vessels draining the region of injection [as] an adjunct to lymphography[.]” (Lymphazurin® Label, 001; Cox Decl., ¶163.) This product had

a purity of around 83%,[7] and its makers welcomed FDA's "advice as to the best approach" to further purify the dye. (R&R, 3–4 (quoting Dkt. No. 80-18).)

As of the critical date, the POSITA would have been motivated to improve the purity of the ISB disclosed by Hirsch for the same five reasons she would have been motivated to combine Kulkarni with Snyder, described above in Section VII.B.2. *First*, a POSITA always is motivated to find a more pure form of a pharmaceutical product that is directed for human use. (Cox Decl., ¶164; Moreton Decl., ¶22; Argentine, Abstract.) Furthermore, pharmaceutical regulations drive drug manufacturers to make more pure drug substances. (*See, e.g.*, ICH Q3A Guidelines 2002, 8; Cox Decl., ¶106; Moreton Decl., ¶¶26–28.)

This especially was true for Hirsch, since the paper published in 1982, and Lymphazurin® had been on the market for 20 years or more. (Cox Decl., ¶165.) During the period between 1982 and 2007, the art of preparative chromatography advanced significantly. (*Id.*) For example, Snyder published in 1997, and it was regarded as a seminal work in the industry. (*Id.*; *see also id.*, ¶¶85–92.) Other

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[7] The POSITA would have been motivated to combine Hirsch and Snyder to arrive at the claimed purity regardless of whether the known purity was 94.5% or 83.6%. (Cox Decl., ¶¶162–163.)

significant advances in chromatography were catalyzed during the mid-1980s by the development of computers that allowed rapid solution of the differential equations that describe the interactions in chromatography using numerical methods. (Cox Decl., ¶165; *see also* Guiochon 1994.) In light of these advances, the POSITA would have been motivated to apply new preparative HPLC techniques to further purify an old pharmaceutical product. (*Id.*)

Second, a POSITA would have understood the disclosure of analytical HPLC in Hirsch (and Kulkarni) to be a "starting point" for developing a preparative HPLC method based on Snyder, and would have been motivated to do so. (Cox Decl., ¶166.) Applicants admitted during prosecution and litigation of the '050 patent that it was within the skill of the POSITA to design an analytical HPLC method for ISB. (*See id.*; R&R, 17–18; '050 File History, 120-121.)

Third, the POSITA would have been motivated to purify ISB to at least 99.0% purity as assessed by HPLC based on Brown. (Cox Decl., ¶¶167–169.) As described more fully above in Section VI.C.2, the POSITA would have understood from Brown that it was possible to attain a high purity for ISB (*i.e.*, more than 99%) using preparative HPLC. (*Id.*, ¶169.)

Fourth, the POSITA would have been aware of literature describing the successful separations of triarylmethane dyes like Patent Blue VF and Patent Blue V (Lee), FD&C Blue No. 1 (Kusaka), and Food Green No. 3 (Ngang), which are

structurally very similar to ISB, from closely-related isomers of the respective compounds. (Cox Decl., ¶170; *see also* Section VI.C.2, *supra*.)

Fifth, armed with the motivation to produce a more pure form of ISB using preparative HPLC, the POSITA would have consulted Snyder. (Cox Decl., ¶171; *see also id.*, ¶¶87–92.) It would have been routine for the POSITA to arrive at the claimed purity. (Cox Decl., ¶¶166–168); *see Ball Aerosol*, 555 F.3d at 993.

3. The POSITA would have had a reasonable expectation of success to purify the ISB of Hirsch to at least 99.0% purity by HPLC using the roadmap from Snyder.

For the same reasons described above in Section VI.C.3, the POSITA would have had a reasonable expectation of success to purify ISB to at least 99.0% by HPLC. (Cox Decl., ¶172.)

C. Independent Claim 11

1. The combination of Hirsch and Snyder teaches or suggests a "solution containing [ISB] having a purity of at least 99.0% by HPLC."

For the same reasons as set forth above in Section VIII.B.1, Hirsch teaches or suggests a solution containing ISB. "Like the term 'comprising,' the terms 'containing' and 'mixture' are open-ended." *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376 (Fed. Cir. 2004). By 2007, Lymphazurin® had been sold in the United States as a 1% solution for more than 20 years. (Cox Decl., ¶173; Lymphazurin® Label.) Furthermore, a POSITA would be knowledgeable of appropriate solvents to dissolve ISB. (Cox Decl., ¶173.)

2. A POSITA would have been motivated to combine the teachings of Hirsch with the roadmap from Snyder.

As described in Section VIII.B.2 above, the POSITA would have been motivated to combine the teachings of Hirsch and Snyder to purify ISB sodium salt to a purity of "at least 99.0% by HPLC." (Cox Decl., ¶174.)

3. The POSITA would have had a reasonable expectation of success to purify ISB to at least 99.0% purity by HPLC using the roadmap from Snyder.

As described in Section VIII.A.3 above, a POSITA would have had a reasonable expectation of success to arrive at the claimed purity by combining Hirsch and Snyder. (Cox Decl., ¶175.)

D. Independent Claim 15

1. The combination of Hirsch and Snyder teaches or suggests a "composition consisting essentially of [ISB] having a purity of at least 99.0% by HPLC."

In addition to the reasons set forth above in Section VIII.B.1, the combination of Hirsch and Snyder teaches or suggests a "composition consisting essentially of [ISB] having a purity of at least 99.0% by HPLC" as required by claim 15. (Cox Decl., ¶176.) Here, "consisting essentially of" will be construed as equivalent to "comprising." *See, e.g., PPG Indus.*, 156 F.3d at 1355. A solution containing ISB does not materially differ from ISB alone because it was known that ISB is soluble in, for example, methanol and other polar solvents. (*Id*., ¶177.) Moreover, ISB was commercially available as a 1% solution in 2007

(Lymphazurin® Label), and the POSITA would have been aware of that FDA-approved preparation. (*Id*.) The POSITA would have understood that the necessary ingredients to make an ISB sodium salt solution would not affect the basic and novel characteristics of ISB itself. (*Id*.)

2. A POSITA would have been motivated to combine the teachings of Hirsch with the roadmap from Snyder.

As described in Section VIII.B.2 above, the POSITA would have been motivated to combine the teachings of Hirsch and Snyder to purify ISB sodium salt to a purity of "at least 99.0% by HPLC." (Cox Decl., ¶178.)

3. The POSITA would have had a reasonable expectation of success to purify the ISB of Hirsch to at least 99.0% purity by HPLC using the roadmap from Snyder.

As described in Section VIII.B.3 above, a POSITA would have had a reasonable expectation of success to arrive at the claimed purity by combining Hirsch and Snyder. (Cox Decl., ¶179.)

E. Dependent Claims 2, 12, and 16

Claims 2, 12, and 16 require that the purity level of the claimed ISB compound fall "between 99.0% and 99.5% by HPLC." Each of these claims depend from independent claims 1, 11, and 15, respectively. To the extent the Board adopts Luitpold's claim construction, "having a purity of at least 99.0% by HPLC" would cover the claimed range of "between 99.0% and 99.5%." (Cox Decl., ¶180.); *see also Peterson*, 315 F.3d at 1329. Accordingly, for the same

reasons as described above in Section VIII.B, it would have been obvious to the POSITA to arrive at the claimed purity based on Hirsch in view of Snyder.

F. Dependent Claims 3, 13, and 17

Each of claims 3, 13, and 17 require that the claimed ISB compound has "less than 20 ppm silver." For the same reasons described above in Section VI.G (*see* Cox Decl., ¶¶181–183; Moreton Decl., ¶¶34-37), it would have been obvious to make an ISB product having less than 20 ppm silver.

G. Dependent Claims 4, 14, and 18

Each of claims 4, 14, and 18 require that the purity level of the claimed ISB compound is "greater than 99.5% by HPLC." Each of these claims depend from claims 3, 13, and 17, respectively. To the extent the Board adopts Luitpold's claim construction, the term "having a purity of at least 99.0% by HPLC" would have covered the same range as "greater than 99.5% by HPLC." (Cox Decl., ¶184.); *see also Peterson*, 315 F.3d at 1329. Accordingly, for the same reasons as described above in Section VIII.B, it would have been obvious to the POSITA to arrive at the claimed purity based on Kulkarni in view of Snyder.

H. Dependent Claims 5–10

Claims 5–10 are product-by-process claims. For the same reasons as described above in Section VII.F (*see* Cox Decl., ¶185), Hirsch in view of Snyder renders claims 5–10 obvious.

IX. Ground 4: Hirsch in View of Snyder, or Further in View of Brown Renders Claims 1–18 Obvious.

A. Independent Claim 1

1. The combination of Hirsch and Snyder, or further in view of Brown, teaches or suggests an ISB compound "having a purity of at least 99.0% by HPLC."

As described in Section VIII.B.1 above, the combination of Hirsch and Snyder teaches or suggests an ISB compound "having a purity of at least 99.0% by HPLC," as required by claim 1. To the extent the Board determines that the POSITA would not have been able to arrive at a purity of "at least 99.0% by HPLC" from Hirsch in view of Snyder, Brown provides the additional disclosure of the claimed purity. (Cox Decl., ¶¶186–189.)

2. A POSITA would have been motivated to combine the teachings of Hirsch with the roadmap from Snyder, together with the example of Brown.

As described in Section VIII.B.2 above, the POSITA would have been motivated to combine Hirsch and Snyder to arrive at the claimed invention. The same POSITA also would have combined the teachings of Brown with Hirsch and Snyder to purify ISB to "at least 99.0% by HPLC." (Cox Decl., ¶190.) The POSITA would have been motivated to combine the teachings of Brown because it is an experimental example of how to arrive at the claimed purity using preparative HPLC for a related dye. (*Id.*, ¶191) Brown took crude FD&C Blue No. 1 and used repeated runs on a preparative HPLC column, recollecting, and re-purifying the

dye until arriving at a highly purified compound (*i.e.*, more than 99%). (*Id.*) The chromatogram disclosed in Brown Figure 2 demonstrates a single peak where more than 99% of the AUC is under the peak. (*Id.*; Brown, Fig. 2.) Accordingly, the POSITA seeking to purify ISB would have looked to Brown as an example. (Cox Decl., ¶191.)

3. The POSITA would have had a reasonable expectation of success to purify ISB from Hirsch to at least 99.0% by HPLC using the roadmap from Snyder, in light of the example from Brown.

For the same reasons described above in Section VIII.B.3, the POSITA would reasonably have expected success for purifying ISB sodium salt to a purity of at least 99.0% by HPLC. The addition of Brown only would have increased that expectation because it shows the successful purification of a closely related triarylmethane dye, FD&C Blue No. 1, to "more than 99%" purity using preparative HPLC. (Cox Decl., ¶192; Brown, 3, Fig. 2.)

B. Independent Claim 11

1. The combination of Hirsch and Snyder, or further in view of Brown, teaches or suggests a "solution containing [ISB] having a purity of at least 99.0% by HPLC."

For the same reasons set forth above in Section VIII.C.1, the combination of Hirsch and Snyder, or further in view of Brown, teaches or suggests a "solution containing [ISB]" as required by claim 11. (Cox Decl., ¶193.)

2. A POSITA would have been motivated to combine the teachings of Hirsch with the roadmap from Snyder and the example of Brown.

As described in Section VIII.C.2 above, the POSITA would have been motivated to combine the teachings of Hirsch and Snyder in view of the example of Brown to purify ISB to a purity of "at least 99.0% by HPLC." (Cox Decl., ¶194.)

3. The POSITA would have had a reasonable expectation of success to purify the ISB of Hirsch to at least 99.0% by HPLC using the roadmap from Snyder, in light of the example of Brown.

As described in Section VIII.C.3 above, a POSITA would have had a reasonable expectation of success to arrive at the claimed purity by combining Hirsch and Snyder, in light of the example of Brown. (Cox Decl., ¶195.)

C. Independent Claim 15

1. The combination of Hirsch and Snyder, or further in view of Brown, teaches or suggests a "composition consisting essentially of [ISB] having a purity of at least 99.0% by HPLC."

For the same reasons set forth above in Section VIII.D.1 above, the combination of Hirsch and Snyder, or further in view of Brown, teaches or suggests a "solution containing [ISB]" as required by claim 11. (Cox Decl., ¶196.)

2. A POSITA would have been motivated to combine the teachings of Hirsch with the roadmap from Snyder and the example of Brown.

As described in Section VIII.D.2 above, the POSITA would have been

motivated to combine the teachings of Hirsch and Snyder in light of the example of Brown to purify ISB to a purity of "at least 99.0% by HPLC." (Cox Decl., ¶197.)

3. The POSITA would have had a reasonable expectation of success to purify the ISB of Hirsch to at least 99.0% by HPLC using the roadmap from Snyder, in light of the example of Brown.

As described in Section VIII.D.3 above, a POSITA would have had a reasonable expectation of success to arrive at the claimed purity by combining Hirsch and Snyder, in light of the example of Brown. (Cox Decl., ¶198.)

D. Dependent Claims 2, 12, and 16

Each of claims 2, 12, and 16 require that the purity level of the claimed ISB compound fall "between 99.0% and 99.5% by HPLC." For the same reasons described above in Section VIII.E (*see* Cox Decl., ¶199), these dependent claims would have been obvious to a POSITA.

E. Dependent Claims 3, 13, and 17

Each of claims 3, 13, and 17 require that the claimed ISB compound has "less than 20 ppm silver." For the same reasons described above in Section VIII.F, (*see* Cox Decl., ¶200; Moreton Decl., ¶¶34-37), these dependent claims would have been obvious to a POSITA.

F. Dependent Claims 4, 14, and 18

Each of claims 4, 14, and 18 require that the purity level of the claimed ISB compound is "greater than 99.5% by HPLC." For the same reasons described

above in Section VIII.G, (*see* Cox Decl., ¶201), these dependent claims would have been obvious to a POSITA.

G. Dependent Claims 5–10

For the same reasons as described above in Sections VIII.H, (*see* Cox Decl., ¶202), Hirsch in view of Snyder, or further in view of Brown, renders claims 5–10 obvious.

X. Secondary Considerations of Non-Obviousness Do Not Outweigh Obviousness Here.

In the prior litigation, the district court did not attribute secondary considerations to the ’050 patent alone. (R&R, 41.) Instead, the court was balancing the validity of two additional patents not before the Board here. Specifically, at the preliminary injunction stage, the magistrate judge considered whether any objective considerations supported the non-obviousness of *three* asserted patents: U.S. Patent Nos. 7,662,992 and 8,969,616—both directed to a method of synthesizing ISB (sodium salt) using silver dioxide—and the ’050 patent, which is directed to ISB (sodium salt), having at least 99.0% purity by HPLC. (R&R, 41.) The court analyzed the following secondary considerations of non-obviousness: long-felt need, failure of others, commercial success, copying and praise of others, and unexpected results and teaching away (*see id.* at 41–47), but none support the validity of the ’050 patent here.

The district court expressly relied upon objective indicia that support the

non-obviousness of the *process patents* in upholding the validity of the ’050 patent. (*Id.*, 41 (“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.”) (emphasis added).) For example, Apicore put on lengthy evidence regarding the commercial success of its ISB product in the marketplace, and the court stated that “Plaintiffs’ commercial success is sufficiently tied to the invention claimed in at least the [’992] and ’616 patents.” (*Id.*, 44.) The court further recognized that, “even if Aurobindo is correct that the market demand for ISB is not sufficiently tied to the 99% purity limitation of the ’050 patent, the nonobviousness of the [’992] and ’616 patent claims supports the patentability of the ’050 patent claims.” (*Id.* (citing *Aventis*, 499 F.3d at 1301–02).)

Luitpold is aware of no legal authority—including *Aventis*—that permits a court to rely on objective indicia of *another patent* to support the commercial success of the claims at issue. That is because “[e]vidence of secondary considerations is only significant if there is a nexus with respect to the *claimed invention*.” *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311–12 (Fed. Cir. 2006) (emphasis added). Patent Owner may argue that a nexus is presumed where, as here, its ISB product is “coextensive” with the ’050 patent. The Board has held, however, that—even for such a pharmaceutical product—the Patent Owner must

show a nexus to the asserted patent, separate and apart from other patents covering the same product. *See, e.g.*, *Mylan Labs. Ltd. v. Aventis Pharma S.A.*, IPR2016-00712, Paper 99 at 44 (P.T.A.B. Sept. 21, 2017) (rejecting patent owner's attempt to rely on presumption of nexus to commercial success where multiple patents cover the product); *see also, e.g.*, *Lutron Elecs. Co. v. Crestron Elecs., Inc.*, 970 F. Supp. 2d 1229, 1240 (D. Utah 2013) (citing 2–5 Chisum on Patents § 5.05[2][f] [ii] (2013)) ("When a product is marked with multiple patents, however, it is more difficult to establish a nexus between commercial success and the relevant claimed invention.") (internal citation omitted).

Likewise, the district court painted with the same broad brush in finding that long-felt need and unexpected results support the claimed invention. The court found 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." (R&R, 42.) The court also stated that "there is no dispute that suppliers such as Sigma-Aldrich had a long-felt need for a *reliable* supply of high-purity ISB" and that "the claimed invention reliably provides high-purity ISB." (*Id.*, 41–42 (emphasis added).)

The claims of the '050 patent, however, do not require the production of a "reliable" amount of ISB—nor do they require any specific amount whatsoever. *See Ormco Corp.*, 463 F.3d at 1312 (objective indicia is "irrelevant" if due to an

unclaimed feature of the device). With respect to unexpected results, the court found that "there is significant evidence that the purity levels achieved by the claimed invention were unexpected," but did not attribute that factor to any of the three asserted patents. *Id*.

The other factors considered by the district court also do not support the validity of the '050 patent. First, the district court rejected Apicore's argument that failure of others applied, calling its argument, "too general." (R&R, 42.) Second, the district court relied upon evidence of copying of the patented process *by Aurobindo* to support the objective indicia of copying and praise of the invention. (*Id.*, 45–46.) Third, "the Court [did] not find that the record supports Plaintiffs' assertion of teaching away[.]" (*Id.*, 46.)

No secondary considerations support the '050 patent claims, separate and apart from any that support the process patents not at issue here. Furthermore, in cases where there is a strong showing of obviousness, like here, the Federal Circuit has repeatedly held that even relevant secondary considerations supported by substantial evidence do not outweigh the *prima facie* case. *See, e.g.*, *Leapfrog Enters., Inc. v Fisher-Price Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). Thus, secondary considerations do not outweigh the obviousness of the '050 patent.

XI. The Board Should Institute Trial Based on Luitpold's Petition (35 U.S.C. §§ 314(a) and 325(d)).

The Board should not exercise its discretion pursuant to either 35 U.S.C.

§§ 314(a) or 325(d) to deny institution of Luitpold's Petition here based on prosecution or the Petition for *inter partes* review filed by Auromedics Pharma Ltd. *et al*. (the "Auromedics Petition"). (*See* Section XII "Related Matters," *infra.*)

35 U.S.C. § 325(d). The Board should institute the Petition because the art and arguments presented by Luitpold's Petition are substantially different than those relied upon during prosecution and in the Auromedics Petition, which the Board never ruled upon. The Board considers a number of non-exclusive factors in applying its discretion under Section 325(d). *See Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017) (designated as "informative" on Mar. 21, 2018). None of these factors support dismissal.

The Examiner did not consider any of the references from the Luitpold Petition during prosecution of the '050 patent. (*See* '050 File History.) During prosecution of a *parent* application (the '291 application), however, the Examiner rejected the pending claims over Kulkarni. (*See* Ex. 1029, '291 Application File History, 020.) The claims subject to the Kulkarni rejection in the parent application were *method* claims directed to a process of synthesizing ISB using silver dioxide. (*Id.*, 111-115.) The Applicants abandoned the '291 application. During prosecution of a continuation, however, the Applicants overcame the same Kulkarni rejection, arguing that Kulkarni does not teach the use of silver dioxide to synthesize ISB

(sodium salt). (Ex. 1042, ’057 Application File History, 038–040.) That was because Kulkarni discloses the use of ammonium dichromate as the oxidizing agent. (*Id.*; *see also* Kulkarni, [0030].) The ’050 claims at issue here are directed to a *product*—ISB “having a purity of at least 99.0% by HPLC.” (’050 patent, claim 1.) The Examiner never rejected the pending claims of the ’050 patent based on Kulkarni, so there is no basis for the Board to exercise its § 325(d) discretion based on prosecution.

Likewise, the Board never issued an institution decision, so the Auromedics Petition was never “considered by” the Office. 35 U.S.C. § 325(d); *see also*, *Cultech, Inc. v. Stormtech LLC*, IPR2017-00777, Paper 7 at 8 (P.T.A.B. Aug. 22, 2017) (informative) (interpreting whether the “same or substantially the same prior art or arguments previously were presented to the [Patent and Trademark] Office” as whether those references “were presented to, and considered by, the Office.”).

Moreover, the Board has declined to exercise its Section 325(d) discretion in a follow-on petition where parties to the prior petition settled before the Board could issue a final written decision. *See, e.g.*, *Frontier Therapeutics, LLC v. medac Gesellschaft fur klinische Spezialpraparate mbH*, IPR2016-00649, Paper 10 at 7 (P.T.A.B. Sept. 1, 2016) (declining to exercise Section 325(d) discretion and instituting trial in light of settlement in prior proceeding); *Square, Inc. v. Protegrity Corp.*, CBM2014-00182, Paper 16 at 8 (P.T.A.B. Mar. 5, 2015) (same). The same

logic applies here—with even stronger force—because the Board did not issue an institution decision based upon the Auromedics Petition, let alone provide a final written decision.

35 U.S.C. § 314(a). The Board's precedential opinion in *General Plastics Industrial Co., Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 (P.T.A.B. Sept. 6, 2017), does not apply here. In *General Plastics*, the Board listed nonexclusive factors that bear on the issue of whether it should invoke its discretion to deny institution of an *inter partes* review, based on a follow-on petition for the same patent, under 35 U.S.C. § 314(a). *General Plastics*, at 9–10.

The first *General Plastics* factor is dispositive: this is Luitpold's *first* Petition challenging the '050 patent. "[T]he fact that Petitioner differs from the petitioners in the [prior IPR] weighs against, rather than in favor of, a discretionary denial of the Petition. *Alcatel-Lucent USA, et al v. Oyster Optics, LLC*, IPR2018-00070, Paper 14 at 14 (P.T.A.B. May 10, 2018) (declining to exercise its Section 314(a) discretion to institute a trial based on prior petitions on the same patents filed by other parties). The Board need not consider factors 2–5 absent extenuating circumstances, none of which are present here. *Id.*

The remaining two *General Plastics* factors also do not weigh in favor of denial because the Board never issued an institution decision on the Auromedics Petition in light of a settlement. An institution decision is a prerequisite for a

discretionary denial pursuant to 35 U.S.C. § 314(a). *General Plastics* at 15 ("There is no *per se* rule precluding the filing of follow-on petitions *after the Board's denial* of one or more first-filed patents on the same patent.") (first emphasis in original, second emphasis added).

Finally, there are no "undue inequities and prejudices" to the Patent Owner based on the filing of serial petitions by a challenger. *Id.* at 17–18. While the Board is understandably wary of petitioners that file serial petitions, shoring up their grounds each time in light of the patent owners' responses (*see id.*), that is not the case here. Unlike in *General Plastics* and many of its progeny, this is Luitpold's first Petition challenging the '050 patent.

XII. Mandatory Notices (37 C.F.R. § 42.8(a)(1))

REAL PARTIES-IN-INTEREST: Luitpold Pharmaceuticals, Inc. is a real party-in-interest. Luitpold Pharmaceuticals, Inc. is a Daiichi Sankyo Group Company.

RELATED MATTERS: The '050 patent was the subject of the following civil action: *Mylan Institutional LLC et al. v. Aurobindo Pharma Ltd. et al.*, No. 2:16-cv-491 (E.D. Tex. filed May 11, 2016). The district court entered a preliminary injunction against Aurobindo Pharma Ltd. *et al*. based, in part, on the '050 patent. *See id.*, Doc. No. 122 (E.D. Tex. Feb. 7, 2017). The Court of Appeals for the Federal Circuit affirmed. *See Mylan Institutional LLC et al. v. Aurobindo Pharma*

Ltd. et al., No. 2017-1645 (Fed. Cir. May 19, 2017). The Court granted the parties' joint motion to dismiss the action pursuant to settlement on August 1, 2017.

Auromedics Pharma LLC also filed a Petition for *inter partes* review for the '050 patent on January 24, 2017 (*see* IPR2017-00762), but the Board terminated the proceedings before any decision on institution pursuant to a settlement on August 3, 2017.

LEAD AND BACK-UP COUNSEL: Pursuant to 37 C.F.R. §§ 42.8(b)(3) and 42.10(a), Luitpold appoints Margaret B. Brivanlou, Ph.D. (Reg. No. 40,922) as its lead counsel at: KING & SPALDING LLP, 1185 Avenue of the Americas, New York, NY 10036, phone number (212) 556-2270 and fax number (212)556-2222; Luitpold appoints Abby L. Parsons (Reg. No. 61,473) as its backup counsel at: KING & SPALDING LLP, 1100 Louisiana Street, Suite 4000, Houston, TX 77002, phone number (713) 751-3294 and fax number (713) 751-3900.

SERVICE INFORMATION: Luitpold consents to electronic service by email at the following email addresses: pbrivanlou@kslaw.com, aparsons@kslaw.com, and Luitpold-PTAB@kslaw.com.

XIII. Conclusion

Based on the grounds specified above, *inter partes* review of the challenged claims is respectfully requested.

Respectfully submitted,

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CERTIFICATION OF WORD COUNT

The undersigned hereby certifies that the portions of the above-captioned **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,353,050** specified in 37 C.F.R. § 42.24 has 13,903 words, in compliance with the 14,000 word limit set forth in 37 C.F.R. § 42.24. This word count was prepared using Microsoft Word 2010.

Respectfully submitted,

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CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,353,050,** Luitpold's Power of Attorney, and all supporting exhibits were served via UPS Express on August 31, 2018, in their entireties on the following:

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