

**IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
WACO DIVISION**

ZANOPRIMA LIFESCIENCES LTD.,

Plaintiff,

v.

HANGSEN INTERNATIONAL GROUP LTD,

Defendant.

Case No. 6:22-cv-00268-ADA

**HANGSEN INTERNATIONAL GROUP LTD'S
FINAL INVALIDITY CONTENTIONS**

Pursuant to the Amended Scheduling Order (ECF No. 52) and the Standing Order Governing Patent Proceedings (OGP) 4.2, Defendant Hangsen International Group Ltd. ("Hangsen") hereby submits its Final Invalidity Contentions with respect to the claims of U.S. Patent No. 10,913,962 (the "'962 patent").

RESERVATION OF RIGHTS

Discovery is ongoing, and the Court indicated that an order more fully explaining its claim constructions is forthcoming. (ECF No. 54.) Hangsen's final invalidity contentions are based, at least in part, on Hangsen's present understanding of the asserted claims and the limited discovery that the parties have taken to date. Hangsen reserves all rights to further supplement or amend these contentions to the extent permitted. For example, Hangsen reserves the right, to the extent that the Court allows and in accordance with the schedule, to identify additional evidence supporting, and otherwise supplement or amend, these contentions because Hangsen's positions on invalidity of particular claims may depend on, for example, Plaintiff's infringement allegations,

the Court's final claim construction order, and party and third-party discovery yet to be taken. Hangsen intends to introduce expert testimony to more fully support its contentions, including to provide motivations to combine prior art and to explain why a person of ordinary skill in the art ("POSA") would have had a reasonable expectation of success in doing so.

Hangsen reserves the right to incorporate by reference any publications, reports, opinions, and/or contentions produced by Plaintiff and/or amend its invalidity contentions to include and assert any prior art or invalidity theories identified in any such publications, reports, opinions, and/or contentions.

INVALIDITY

Hangsen sets forth the following contentions with respect to invalidity of the asserted claims. These contentions are based upon Plaintiff's infringement contentions and Hangsen's understanding of Plaintiff's interpretation, as well as Hangsen's interpretation, of the scope of the asserted patents and the claim limitations found in the asserted claims of the asserted patents. Accordingly, nothing herein shall be interpreted as setting forth any particular claim construction or as an admission that: (1) the asserted claims are infringed by Hangsen; (2) any particular feature or component practices any limitation of the asserted claims; (3) there is 35 U.S.C. § 112 support for any limitation of the asserted claims; or (4) Hangsen concedes the propriety of any claim construction.

I. INVALIDITY BASED ON PRIOR ART

Hangsen contends that each of the asserted claims of the '962 patent is invalid as anticipated under Section 102 and obvious under Section 103. Hangsen's contentions regarding the prior art are set forth below.

1. Anticipation

At this stage, Hangsen is not aware of any anticipatory, documentary prior art under 35 U.S.C. § 102. Hangsen expressly recognizes that discovery may reveal anticipatory prior art, documentary or otherwise, and reserves all rights to assert any such art that later comes to light.

Hangsen also anticipates taking further discovery regarding one or more of the following products, and other potential prior art products, which may also be found to anticipate and/or render obvious one or more of the asserted claims: synthetic nicotine products made by (a) Zanoprime Lifesciences Ltd. or any affiliate, (b) Raymond McCague, (c) Ashok Srinivasan Narasimhan, (d) McCague Scientific Consulting, (e) Enzymicals AG or any affiliate, and/or (f) Almac Group Ltd. or any affiliate.

2. Obviousness

a) Prior Art

Hangsen further contends that each of the claims of the '962 patent is invalid as obvious over the prior art, either alone, in addition to the common sense possessed and applied by those of ordinary skill in the art, or in combination with other prior art and/or the knowledge of those of ordinary skill in the art. To the extent any single reference is found not to render the claims obvious, Hangsen reserves the right to identify other combinable references, in addition to those set forth below, that demonstrate the obviousness of the claimed subject matter.

Hangsen has provided certain combinations of the prior art demonstrating that each claim of the '962 patent is invalid as obvious. These certain combinations are appended to these contentions as Exhibits A1-A15 and B1-B15. Moreover, Hangsen hereby incorporates by reference the Petition and supporting exhibits in IPR2023-00503. Further still, Hangsen hereby incorporates by reference the Korean invalidation petition produced as HANGSEN0003977-4015 and any exhibits supporting the petition and any documents cited therein.

Hangsen may rely on one or more of the prior art references below to demonstrate that the claims of the '962 patent would have been obvious under 35 U.S.C. § 103. In addition to the documentary prior art mentioned below, Hangsen also intends to, and reserves its right to rely upon, the admitted prior art to demonstrate obviousness of the asserted claims when combined with the identified prior art or prior art combinations. For example, the specification of the '962 patent admits that numerous claimed aspects were known in the prior art.

- Aceto et al, Optically Pure (+)-Nicotine from (±)-Nicotine and Biological Comparisons with (-)-Nicotine, *J. Med. Chem.* 1979, 22, 174-177 (“Aceto”)
- Aleku et al., Stereoselectivity and Structural Characterization of an Imine Reductase (IREC) from *Amycolatopsis orientalis*, *ACS Catal.* 2016, 6, 3880–3889 (“Aleku 2016”)
- Aleku-A reductive aminase from *Aspergillus oryzae*. *Nat. Chem.* 9, 961–969 (May 29, 2017) (“Aleku 2017”)
- Alkaloids - Secrets of Life. 2007.
- Bowman et al., A convenient method for the preparation of racemic nicotine, *Synthetic Communications*, 1982, 12,871-879 (“Bowman”)
- Chavdarian et al., Synthesis of optically active nicotinoids, *J. Org. Chem.* 1982, 41, 1069-1073 (“Chaydarian”)
- DeTraglia and Tometsko, *Applied and Environmental Microbiology*, 1980, 39, 1067-1069 (“DeTraglia and Tometsko”)
- Dubon et al., Enantioselective Syntheses of 2-Substituted Pyrrolidines from Allylamines by Domino Hydroformylation–Condensation: Short Syntheses of (S)-Nicotine and the Alkaloid 225C, *Synlett* 2009, 9, 1413-1416 (“Dubon”)

- Dunsmore et al., A Chemo-Enzymatic Route to Enantiomerically Pure Cyclic Tertiary Amines, *JACS*, 2006, 128, 2224-2225 (“Dunsmore”)
- Enzymicals, Portfolio Enzymicals – Chemicals & Enzymes (2017) (“Enzymicals”)
- France, “Biocatalytic Imine Reduction and Reductive Amination,” Thesis at University of Manchester (2017) (“France II”)
- France et al., Identification of Novel Bacterial Members of the Imine Reductase Enzyme Family that Perform Reductive Amination, *ChemCatChem* 10, 510 (2018). (published September 21, 2017) (“France”)
- Heath et al., Combined Imine Reductase and Amine Oxidase Catalyzed Deracemization of Nitrogen Heterocycles, *ChemCatChem* 2015, 8, 117-120 (“Heath”)
- Hussain et al., An (R)-Imine Reductase Biocatalyst for the Asymmetric Reduction of Cyclic Imines. *ChemCatChem*, **2015**, 7(4), 579–583 (“Hussain”)
- Jones et al., The Binding and Regioselectivity of Reaction of (R)- and (S)-Nicotine with Cytochrome P-450cam: Parallel Experimental and Theoretical Studies, *J. Amer. Chem. Soc.*, 1993, 115, 381-387 (“Jones”)
- Leipold et al., Asymmetric Reduction of Cyclic Imines Catalyzed by a Whole-Cell Biocatalyst Containing an (S)-Imine Reductase. *ChemCatChem*, **2013**, 5(12), 3505–3508 (“Leipold”)
- Li et al., A Novel (R)-Imine Reductase from *Paenibacillus lactis* for Asymmetric Reduction of 3H-Indoles, *ChemCatChem* **2016**, 8, 724 – 727 (“Li”)

- Loh et al., A novel reductive aminocyclization for the syntheses of chiral pyrrolidines: stereoselective syntheses of (S)-nornicotine and 2-(2'-pyrrolidyl)-pyridines, *Tetrahedron Letters*, 1999, 40, 7847-7650 (“Loh”)
- Mangas-Sanchez et al., Imine reductases (IREDs), *Current opinion in Chemical Biology*, 2017, 37, 19-25 (“Mangas-Sanchez”)
- Matzel, “Synthese optisch aktiver Amine mittels Iminreduktase-katalysierter reduktiven Aminierung,” Thesis at Universität Greifswald.
- Mitsukura et al., Asymmetric synthesis of chiral cyclic amine from cyclic imine by bacterial whole-cell catalyst of enantioselective imine reductase, *Org. Biomol. Chem.*, **2010**, 8, 4533–4535 (“Mitsukura 2010”)
- Mitsukura, A NADPH-dependent (S)-imine reductase (SIR) from *Streptomyces* sp. GF3546 for asymmetric synthesis of optically active amines: purification, characterization, gene cloning, and expression, *Appl Microbiol Biotechnol* (2013) 97:8079–8086 (“Mitsukura 2012”).
- Mitsukura et al. , Future Directions in Biocatalysis, Chapter 5-IMINE REDUCTASES FOR CHIRAL AMINE SYNTHESIS, **2017**, 97-117 (“Mitsukura 2017”)
- Moody, “Biocatalysis: Genes to GMP,” *Speciality Chemicals Magazine*, Vol. 36, No. 1 (January 2016)
- U.S. 2,459,696 (“the ’696 Patent”)
- U.S. 5,668,295 (“the ’295 Patent”)
- U.S. 9,556,142 (“Arnold” or “the ’142 Patent”)
- U.S. 8,367,837 (“Divi” or “the ’837 Patent”)

- Velikogne et al., Sequence-Based In-silico discovery, characterization, and biocatalytic application of a set of imine reductases, *Chemcatchem*, 2018, Vol. 10, pp. 3236-3246 and supplemental materials (June 2018) (“Velikogne”)
- Wells, Biocatalytic Imine Reduction: Isolation, Application, Structure and Mechanism of Imine Reductases, **2017** (“Wells”)
- Wetzl et al., “Asymmetric Reductive Amination of Ketones Catalyzed by Imine Reductases,” *ChemCatChem*, 2016, 8, 2023-2026 (“Wetzl II”)
- Wetzl et al., Expanding the Imine Reductase Toolbox by Exploring the Bacterial Protein-Sequence Space, *ChemBioChem* **2015**, 16, 1749 – 1756 and supplemental materials (“Wetzl”)
- WO2013/170050 (“Chen”)
- WO2014/174505 (“Sheldon”)
- WO2015/073555 (“Agard”)
- WO2016/065209 (“Arnold 209”)

Hangsen further reserves its right to assert any prior art combination of the above references that render obvious each of the asserted claims of the '962 patent under 35 U.S.C. § 103. As required by the Standing Order Governing Proceedings 4.2, charts setting forth where in the prior art references each element of the asserted claim(s) are found are attached as Exhibits A1-A15 and B1-B15.

b) Example Reasons to Combine the Prior Art and Reasonable Expectations of Success

A person of ordinary skill in the art at the time of the alleged invention of the '962 patent would have been motivated to combine each of the prior art references, or subsets of the prior art references, at least for the following reasons.

The reasons to combine the references in the specific manner shown come from many sources, including, but not limited to, the teachings of the prior art itself, the knowledge and common sense of those of ordinary skill in the art, the body of knowledge presumed to be known to those of skill in the art, the common field of technology of the references, and the teachings in the references directed to solving the purported problems that the '962 patent was allegedly directed to solving, including the synthesis of (S)-nicotine. The cited prior art references identify and address many of the same technical issues and suggest similar solutions to those issues, including using catalysts to convert myosmine to nornicotine and then using formaldehyde or using formaldehyde in formic acid for reductive methylation of the nornicotine to (S)-nicotine (*see e.g.* Arnold, Divi, Sheldon). Further, the art taught distillation of nicotine for purity and a POSA would be motivated to do so. *See* Arnold, Divi.

As Zanoprima's patent acknowledges, several prior art references such as Arnold and Divi describe chemical syntheses of nicotine via myosmine and nornicotine. The result is a racemic mixture. Thus, a POSA would have appreciated that myosmine was a good starting point. In fact, Divi provides a direct motivation for adopting myosmine as a starting point: Divi describes its synthesis of nicotine as "efficient" and "an attractive and economical method for the production of synthetic (S)-nicotine." Divi at 2:21-25. A POSA would have looked to one of the known syntheses of (S)-nicotine, including Arnold and Divi, and recognized that the reaction is a logical starting point and that avoiding a resolution or isolation step would further improve the reaction. Further, the '962 patent admits that the POSA was familiar with myosmine, further supporting references such as Divi and Arnold as logical starting points. '962 Patent at 3:29-31.

A POSA would have recognized that myosmine is a prochiral imine that is subject to reduction to form its corresponding chiral amine product, (S)-nornicotine, (R)-nornicotine, or a

mixture of the enantiomers. A POSA would have recognized that preferential reduction of myosmine to (S)-nornicotine could lead to a favorable production of (S)-nicotine, as the standard N-methylation of nornicotine to nicotine would not change the chirality of the molecule.

The '962 patent admits that a POSA is familiar with imine reductases. '962 patent at 3:31-41. As a person familiar with imine reductases, the POSA would have known that imine reductases were capable of reducing imines to their corresponding amines, often yielded the amine reduction product in significant enantiomeric excess (often up to 99%) and accepted a broad scope of imine substrates. As such, a POSA would have been motivated to use an imine reductase to catalyze the asymmetric reduction of myosmine to (S)-nornicotine.

The prior art also shows that a POSA seeking to modify the known myosmine-based synthesis to preferentially yield (S)-nicotine would have known to use an imine reductase ("IRED"), and would have thought it likely to succeed. The 2017 Enzymicals catalog lists several IREDs, some said to be (R)-specific and some said to be (S)-specific. The catalog states that they are "a promising alternative for the synthesis of chiral amines" and that they "offer [a] quantitative asymmetric route to amine products of high optical purity." Enzymicals at 39. The catalog further sold a kit of IREDs for a small, do-it-yourself enzyme screen, offered in-house screening capabilities against a broader set of enzymes, and advertised the ability to selectively mutate enzymes to better target a specific substrate or yield higher enantiomeric excess. Additionally, Moody, a publication from Almac Group, disclosed that "[t]he paradigm shift for the acceptance of biocatalysts is persistent and at the forefront of research within the fine chemicals and pharmaceuticals industries." Moody at 12. According to Moody, "[b]iocatalysis has become the workhorse of the chemists' toolbox for chiral chemistry." *Id.* Moody stated that "[e]nzyme processes are now at the epicentre of key drivers in process design, scale-up and economics" and

that “[t]he synthetic power of enzymes is their unequalled selectivity for the chemical reactions they catalyse.” *Id.* Moody disclosed a successful screen for imine reductases active on a customer-provided imine substrate that would reduce the imine selectively to the target (S)-amine product. *Id.* at 12-13 and Fig. 3.

The '962 patent admits that commercially available sources of imine reductases, including Enzymicals and Almac Group, were known. '962 patent at 4:7-14 (disclosing that nine imine reductases disclosed to reduce myosmine to (S)-nornicotine were “available from Enzymicals” and that another was “available from Almac Group”). A POSA would have also known from Enzymicals and Moody that imine reductases were widely available commercially. And a POSA would have been motivated by the disclosures of Enzymicals and Moody to use an imine reductase to reduce myosmine to (S)-nornicotine. *Id.* Further, a POSA would have understood from Moody and Enzymicals that commercial services could analyze a “customer substrate” imine (such as myosmine), build a custom enzyme screen of imine reductases targeting the reduction of myosmine, and identify an imine reductase “for the enantioselective reduction of the imine.” Moody at 12. A POSA also would have appreciated from Moody that Almac Group had successfully screened imine reductases for a customer-provided imine substrate to identify an IRED that yielded the (S)-amine product with 100% ee.

Accordingly, a POSA, knowing that the Divi or Arnold reaction could be made stereoselective where myosmine is reduced to nornicotine, would have been motivated to use an imine reductase to reduce myosmine to (S)-nornicotine. A POSA would have been motivated to apply the teachings of Enzymicals and/or Moody to use Enzymicals or Almac to identify an imine reductase capable of reducing myosmine to (S)-nornicotine asymmetrically and use that imine reductase to catalyze the reduction of myosmine to (S)-nornicotine.

As to Arnold, a POSA would have looked to Arnold's synthesis of nicotine by way of myosmine and nornicotine for, among other things, acceptable reaction conditions. Since the reaction sequence from myosmine to nornicotine to nicotine is what is also disclosed in Divi, a POSA would have expected success in making a combination.

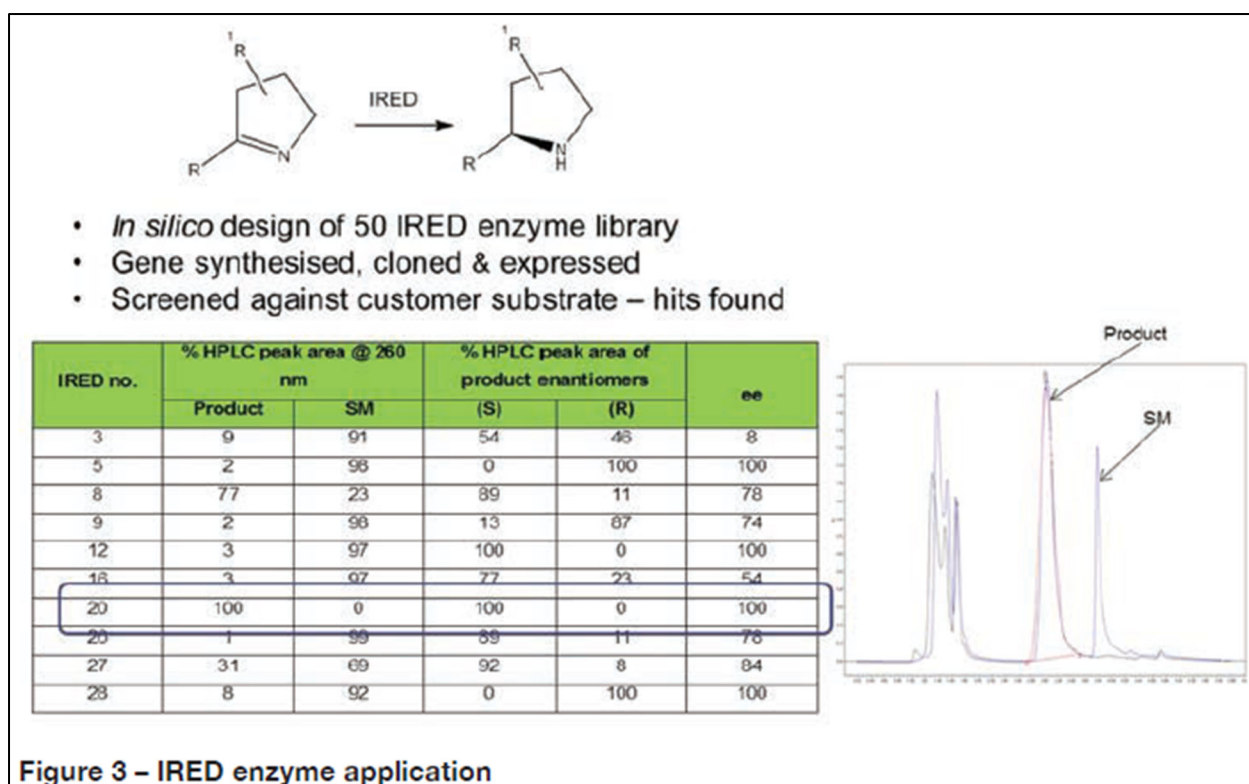
Sheldon disclosed a synthesis of (S)-nicotine using an imine reductase enzyme. Sheldon at 18. Sheldon disclosed that an imine reductase "refers to an enzyme that catalyzes the reduction of an imine, or of an iminium cation, optionally in a stereoselective manner." *Id.* Sheldon teaches that imine reductases have activity in aqueous solution that "is preferably water (as is known in the art, an aqueous salt solution or a buffer may be used as needed in order to avoid denaturation of the reductase enzymes)." *Id.* at 21. A POSA would have understood from Sheldon that imine reductases should be used in an aqueous solution, such as water or a buffered solution, to avoid denaturing the enzyme. A POSA catalyzing the reduction of myosmine to (S)-nornicotine using an imine reductase would have recognized that the reaction should take place in aqueous solution to avoid denaturing the imine reductase. A POSA would have been motivated to look to Sheldon and apply its teachings because Sheldon is in the field of nicotine synthesis and biocatalytic synthesis and discloses employing imine reductases in the synthesis of nicotine. The '962 patent admits both that the "field of the invention" is "a process for synthetically producing (S)-nicotine" and that a POSA was "familiar" with imine reductases. '962 patent at 1:5-7 and 3:31-41. A POSA would have been motivated to look to Sheldon's teachings about using an imine reductase as a biocatalyst in a synthesis of nicotine and would have had a reasonable expectation of success in using an aqueous solution to form (S)-nornicotine from the imine reductase-catalyzed reduction of myosmine, as Sheldon taught that an imine-reductase-catalyzed synthesis of nicotine should proceed in aqueous solution to avoid denaturing the enzyme.

Disclosures from Velikogne and Wetzl would have further motivated a POSA to catalyze the reduction of myosmine to (S)-nornicotine using an imine reductase. Wetzl recognized the motivation to use a biocatalyst to synthesize chiral amines asymmetrically to improve yield and reduce the need for an enantiomeric resolution—one of the issues the '962 patent recognized. Wetzl at 1749-50. Wetzl described imine reductases as having utility “for the asymmetric reduction of a broad panel of cyclic imines producing chiral secondary and tertiary amines,” and characterized imine reductases as “synthetically useful enzymatic tools” in the “IRET toolbox” “for the asymmetric synthesis of amines.” *Id.* at 1749-50, 1753. The descriptions of imine reductases as “synthetically useful enzymatic tools for the asymmetric synthesis of amines” by Wetzl and Velikogne would have motivated a POSA to use an imine reductase in the Divi reaction to reduce myosmine to (S)-nornicotine. Velikogne disclosed that “a large number of imine reductases have been identified and heterologously expressed, and their substrate scope ... and their applicability in preparative-scale reactions have been investigated.” Velikogne at 3236. Velikogne demonstrated that a screen of 14 imine reductases reduced a broad panel of imines to their corresponding amines. *Id.* at 3240. Velikogne’s Figure 3 illustrates the activities and stereoselectivities of the 14 imine reductases across the imine substrates.

A POSA would have had a reasonable expectation of success that Enzymicals or Almac would identify an imine reductase to reduce myosmine to (S)-nornicotine asymmetrically. Enzymicals sold a screening kit of four imine reductases and disclosed that it would screen a given substrate such as myosmine “to find out the most suitable enzyme for your desired reaction.” Enzymicals at 38, 40, 48. Enzymicals further disclosed that it offered mutant enzymes with “enhanced substrate specificity and/or increased stereoselectivity towards appropriate substrates” that were “available on request” and that “an in-house screening with suitable enzyme classes

about all available enzymes from public or private panel” was available. *Id.* at 52. A POSA would have had a reasonable expectation of success that Enzymicals, through its screening kit or in-house screening service, would identify an imine reductase to reduce myosmine to (S)-nornicotine asymmetrically.

A POSA would have further known from Moody that Almac could analyze a “customer substrate” imine, build a custom enzyme screen of imine reductases specifically targeting the reduction of the imine, and identify an imine reductase “for the enantioselective reduction of the imine.” Moody at 12. A POSA would have had a reasonable expectation of success that Almac’s enzyme screen would yield an imine reductase that reduced myosmine to (S)-nornicotine asymmetrically, as Moody disclosed that Almac had successfully identified an imine reductase from an enzyme screen to reduce a customer-supplied target imine to the (S)-amine with 100% ee. Moody at 12, Fig. 3. The IRED enzyme screen yielded a high-activity, high-selectivity imine reductase that asymmetrically reduced a customer-identified imine. *Id.* at 12-13, Fig. 3. Moody summarized the successful imine reductase screen as follows:



Velikogne demonstrated that by screening a limited, diverse set of imine reductases, a POSA would likely find an imine reductase that would selectively reduce an imine to the (S)-amine. Velikogne described how a POSA could create and run a custom enzyme screen to test the activity of numerous imine reductases against an imine substrate. Wetzl disclosed that “[t]he vast majority of the tested IRED candidates displayed good conversions (>90%) against nearly all of the tested substrates as well as good to excellent enantioselectivities, often yielding the corresponding product with an enantiomeric excess >90%.”

A POSA would have known that imine reductases reduced prochiral imines like myosmine to chiral amines across a broad range of substrates. Wetzl at 1749; Velikogne at 3240. Velikogne’s Figure 3 illustrates the activities and stereoselectivities of the 14 imine reductases across the range of imine substrates. Velikogne’s screen resulted in every single screened imine substrate being selectively reduced to the corresponding (S)-amine by multiple imine reductases with at least 99%

enantiomeric excess. A POSA following Velikogne's teachings would have had a reasonable expectation of success of finding at least one enzyme reducing myosmine to (S)-nornicotine selectively.

Therefore, a POSA would have had a reasonable expectation of success that a screen by Enzymicals or Almac would identify an appropriate imine reductase to reduce myosmine to (S)-nornicotine asymmetrically. Moody described how Almac designed an imine reductase screen to identify an imine reductase that reduced a customer-provided imine substrate to a target imine with high activity and high selectivity. *Id.* As Moody disclosed a specific experience in identifying an imine reductase that reduced an imine provided by a customer to the target (S)-amine with 100% ee, a POSA would have had a reasonable expectation of success that Enzymicals or Almac would successfully identify an imine reductase capable of reducing myosmine to (S)-nornicotine asymmetrically.

Separately, Wetzl, Wetzl II, and France II disclose some of the exact same IREDs that are disclosed in the '962 patent. A POSA would have been motivated to use one of those IREDs to catalyze the stereoselective reduction of myosmine to (S)-nornicotine.

Accordingly, the teachings of the individual prior art references, combined with the knowledge of a person of ordinary skill in the art at the time of the alleged invention of the '962 patent, would render obvious the asserted claims of this patent. Furthermore, the combinations above reflect predictable variations of known devices and systems, combinations that would be obvious to try, the use of known techniques to improve similar devices and systems, improvements that are no more than predictable uses of prior art elements according to their established functions, and combinations of familiar elements according to known methods to yield predictable results. For example, a person of ordinary skill would have reasonably predicted that the reduction of

myosmine's imine moiety with an imine reductase would have been successful because the prior art reports on the successful reduction of the imine or iminium moiety of pseudooxynicotine with imine reductase to form nicotine. *See, e.g.,* Sheldon at page 18, Example 6, claim 50.

In addition, as to each of the prior art combinations, one of ordinary skill in the art at the time of the alleged invention would have had reason to combine the many familiar elements such as enzymes with imine reductase activity and/or stereoselectivity, methylation of nornicotine with formaldehyde and a reductant, and, according to known methods because the asserted claims of the '962 patent yielded predictable results. In other words, reason to combine any two or more of the identified references comes from the fact that all of the references disclose processes for making nicotine, including synthetic nicotine, and one of ordinary skill in the art would have been motivated by considerations of efficiency, usability, convenience, cost-savings, and/or accessibility, to combine the various teachings. At a minimum, it would have been obvious to try to combine the various teachings of the existing methods because the combinations represent the known potential options with a reasonable expectation of success.

Additional rationales are present in Exhibits A1-A15 and B1-B15. However, the above rationales are hereby incorporated into each charted combination to the extent applicable.

In addition to the above reasons, Hangsen may also rely on other publications and the testimony of experts to establish that a person of ordinary skill in the art would have had a reason to modify or combine the cited references to render each of the asserted claims obvious. Also, fact and expert discovery are ongoing. Thus, while Hangsen discusses representative reasons to combine different prior art, Hangsen reserves the right to assert different or additional bases for an obviousness assertion in accordance with the guidelines provided by the Supreme Court in *KSR* and other applicable precedent to the extent permitted under this Court's rules.

B. Other Invalidity Defenses

Hangsen identifies the following grounds of invalidity under 35 U.S.C. § 112 for each asserted claim of the '962 patent based on Hangsen's current understanding of the patent and current understanding of Plaintiff's Infringement Contentions.

1. Indefiniteness

The asserted claims are invalid under 35 U.S.C. § 112 for indefiniteness because they fail to inform those skilled in the art "with reasonable certainty . . . about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014). The meaning of the terms and the scope of claims that include them could not be reasonably determined by a person of ordinary skill in the art at the time of the invention reading the specification and the intrinsic record, including the prosecution history of the '962 patent. To date, claim 1 has been identified to render the asserted claims indefinite because it fails to inform those skilled in the art with reasonable certainty about the scope of the invention, particularly for the term "enzyme with imine reductase activity" (claim 1). Further, claim 9 does not reasonably inform one skilled in the art of the scope of the claim: "[t]he process of claim 1, wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%, preferably at least 95%, more preferably at least 98%, most preferably at least 99%." The person of ordinary skill would not be able to discern if a product having 90%-98% enantiomeric excess is within the claim, as the "preferably" clauses within the claim language fail to provide reasonable certainty about the scope of the invention.

In addition, the asserted claims are invalid under 35 U.S.C. § 112 because they include step-plus-function claim terms under 35 U.S.C. § 112(f) without disclosing sufficient corresponding structures in the claims or specification. *Caterpillar Inc. v. Detroit Diesel Corp.*, 961 F. Supp. 1249, 1255 (N.D. Ind. 1996), *aff'd*, 194 F.3d 1336 (Fed. Cir. 1999) ("... § 112 applies to functional method claims where the element at issue sets forth a step for reaching a particular

result, but not the specific technique or procedure used to achieve the result.”) At least each of the following step-plus-function claim terms are indefinite under § 112(f):

- “(i) reducing myosmine with an enzyme with imine reductase activity to form (S)-nornicotine” (claim 1)
- “wherein the process is carried out without isolation of the (S)-nornicotine formed from step (i)” (claim 6)
- “wherein in step (i) the (S)-nornicotine is formed as part of an aqueous solution” (claim 7)
- “wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%, preferably at least 95%, more preferably at least 98%, most preferably at least 99%.” (claim 9)
- “A process for producing a pharmaceutical composition, comprising forming (S)-nicotine according to the process of claim 1, and including the (S)-nicotine in the pharmaceutical composition together with one or more pharmaceutical excipients.” (claim 10)
- “A process for producing a formulation for an electronic cigarette device, comprising forming (S)-nicotine according to the process of claim 1, and including the (S)-nicotine in a solvent with one or more additives.” (claim 12)

In addition, the asserted claims are invalid under 35 U.S.C. § 112(b) because the claims fail to particularly point out and distinctly claim the subject matter which the inventor or joint inventor regards as the invention. The applicant repeatedly describes the invention as having a “very high enantiomeric and chemical purity” at the “reduc[tion of] myosmine with an enzyme with imine reductase activity to for (S)-nornicotine”. For example:

It was surprisingly found that by way of steps (i) and (ii) of this process, where myosmine is used as the starting material, a very high enantiomeric and chemical purity was achieved for (S)-nicotine. This indicates that step (i) is a highly enantiomeric selective synthetic step with preference for the (S) isomer, and that step (ii) is such that this preference is retained in the final nicotine product, whilst also maintaining high chemical purity. This allows the production of (S)-nicotine without having to resort to resolution of a racemic mix. The high chemical purity is particularly advantageous; a reduced level of the undesirable impurities typically associated with nicotine results in a reduced risk of potential impurity-related negative effects.

'962 patent, 2:37-51; *see also* 7:7-12; Tables 1-5; 6:57-62. None of the claims require a “very high enantiomeric and chemical purity” at the myosmine to nornicotine reaction. Indeed, the claims use “comprising” language that captures a racemic mix, which is expressly taught against in the specification of the '962 patent. *Id.* at 1:31-2:26. During prosecution, the applicant further argued that the claimed method produces (S)-nicotine with “high stereoselectivity”. Oct. 30, 2020, Reply to Office Action, p. 10. Indeed, other dependent claims fail to capture this invention. For example, claims 6 and 9 do not require that step (i) is a highly enantiomeric selective synthetic step with preference for the (S) isomer: it only requires that the process is carried out without isolation of the (S)-nornicotine (claim 6), or that the *final product* has a required percentage of enantiomeric excess (claim 9). Thus, the claims expressly allow isolation or purification of racemic mixes by other methods not contemplated by the inventors.

2. Lack of Written Description

The asserted claims are invalid for lack of written description because they seek to claim a process of making (S)-nicotine, but the specification fails to disclose processes for how the purported steps are performed. Thus, the claimed inventions are not sufficiently described to clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed. Although Hangsen may raise additional bases at trial or otherwise during the case, it provides the following exemplary bases for its contentions as to lack of written description:

Claim 1 recites “an enzyme with imine reductase activity to form (S)-nornicotine.” Because the patent defines the enzyme using only functional language, the patent specification needs to describe a sufficient number of species to support claims that recite the functionally-defined enzyme. *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299 (Fed. Cir. 2014). The ‘962 patent does not describe enough species to support the functionally-defined genus of “imine reductase” enzymes that are capable of converting myosmine to (S)-nornicotine. For example, the specification states that the enzyme may include IRED_A, IRED_B, IRED_C, IRED_D, IRED_E, IRED_F, IRED_P, IRED_X, IRED_AB, IRED-20 or their homologues. ‘962 patent, 4:7-31. Although the microbial sources and amino acid sequences of IRED_A and IRED_B are listed in the examples of this patent, the specification fails to provide that information for IRED_C, IRED_D, IRED_E, IRED_F, IRED_P, IRED_X, IRED_AB and IRED-20. These are not common indications of an imine reductase and do not provide a POSA with any idea of their sequences or how to express them. In other words, these labels appear to have been made up and may or may not correspond to real-world enzymes; there is no way to tell from the patent. Likewise, the specification makes a distinction between other enzymes and those that give a specific enantiomeric purity, yet provides no guidance as to which enzymes would work. The art contains thousands of enzymes, yet the inventors seemed to have possessed a limited set. This is especially true in light of claim 9. The specification provides no teaching about how a POSA would go about selecting one IRED over another, yet claim 1 appears to attempt to functionally claim any IRED that might work.

Further, the POSA would not reasonably discern from the specification that the inventors possessed the full scope of the invention, as broadly claimed. For example, claim 1 describes “an enzyme with imine reductase activity,” which could be any one of thousands of available enzymes.

But the specification only discloses limited examples and sequence listings. The enzymes the inventors possessed were naturally derived. '962 patent at 8:1-9:7 (describing naturally derived enzymes); 3:63-4:14 (“[S]uch enzymes can be isolated or derived from sources such as *Streptomyces*, *Verrucosispora*, *Mesorhizobium*, *Yersinia*, *Pseudomonas*, *Candida albicans*, *Eschscholzia*, and *Papaver*.”). Yet the claims are such that nonnatural enzymes may be encompassed. A person skilled in the art would not reasonably conclude that the inventor had possession of a claimed invention that covered the scope of the claims.

3. Lack of Enablement

The asserted claims are also invalid for lack of enablement under 35 U.S.C. § 112(a). To fulfill the enablement requirement, the patent must disclose the claimed invention in sufficient detail for a person of ordinary skill in the art to carry out the full scope of that claimed invention. Here, the asserted claims are invalid for lack of enablement because the claimed inventions seek to claim a process of making (S)-nicotine by “reducing myosmine with an enzyme with imine reductase activity to form (S)-nornicotine” (claim 1), such that a person of ordinary skill in the art would not have been able to carry out the full scope of the claimed invention. For example, the specification provides for a broad disclosure of any enzyme that reduces myosmine to form (S)-nicotine (3:63-4:6), but provides amino acid sequences only for particular species IRED_A and IRED_B. '962 patent, 8:2-9:8. The specification fails to provide sequences for IRED_C, IRED_D, IRED_E, IRED_F, IRED_P, IRED_X, IRED_AB and IRED-20, and their homologues. *See also* Aleku at 3886 (“the studies of AoIRED again reveal that stereochemical control in these enzymes is complex, and the prediction of selectivity is especially difficult and has to be investigated on a case-by-case basis”). The specification fails to provide for “enzymes [] isolated or derived from sources such as *Streptomyces*, *Verrucosispora*, *Mesorhizobium*, *Yersinia*, *Pseudomonas*, *Candida albicans*, *Eschscholzia*, and *Papaver*.” *Id.* at 3:63-4:14. A POSA would

need to conduct undue experimentation to find the enzymes that would work within the scope of claim 1. Thus, all asserted claims are invalid for lack of enablement.

Further claim 9 requires undue experimentation, claiming “[t]he process of claim 1, wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%, preferably at least 95%, more preferably at least 98%, most preferably at least 99%.” Claim 9. Similarly, for claim 1, a POSA would need to conduct undue experimentation to find a process where the (S)-nicotine is obtained with an enantiomeric excess of more than 50%. Indeed, Tables 1-4 show that enantiomeric excess may vary by enzyme (with thousands of enzymes possibly available), and a POSA would need to unduly experiment to discover which ones were within the scope of the claim. Claim 1 (from which claim 9 depends) claims an entire class of enzymes, encompassing tens of thousands—perhaps more—of enzymes, some of which work, some of which would not work. All that the ’962 Patent provides is a sequence of two enzymes that (presumably) work. The claims of the ’962 Patent are therefore not enabled across their full scope.

4. Lack of Patentable Subject Matter

Section 101 of the Patent Act defines patentable subject matter. It says:

“Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.” 35 U.S.C. § 101.

The Supreme Court has long held that this provision contains an important implicit exception. “[L]aws of nature, natural phenomena, and abstract ideas” are not patentable. *Mayo Collaborative Servs. v. Prometheus Lab’ys, Inc.*, 566 U.S. 66, 70 (2012). “Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work.” *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972).

And monopolization of those tools through the grant of a patent might tend to impede innovation more than it would tend to promote it. *Mayo*, 566 U.S. at 70.

In *Diehr*, the Court pointed out that “a process is not unpatentable simply because it contains a law of nature or a mathematical algorithm.” *Diamond v. Diehr*, 450 U.S. 175, 187 (1981). As the Court has also made clear, to transform an unpatentable law of nature into a patent-eligible application of such a law, one must do more than simply state the law of nature while adding the words “apply it.” *See, e.g., Benson*, 409 U.S. at 71–72.

Here, the asserted claims are directed to a natural law or phenomena regarding using an enzyme with imine reductase activity. Step 1 of claim 1 involves “reducing myosmine with an enzyme with imine reductase activity to form (S)-nornicotine.” It claims the natural consequence of combining myosmine with an enzyme with imine reductase activity, namely, that it will make (S)-nornicotine by natural law. The reaction, and the relation to any particular enantiomeric mix, is a consequence of the way myosmine interacts with the enzyme—an entirely natural process, such that the patent claims simply describe a natural process. Indeed, the patentee admits that the “prior art of a synthetic process for producing (S)-nicotine using an enzyme as a biocatalyst [exists] (WO 2014/174505); [and] the use of biocatalysts in enantiomerically selective processes in general are known [].” ’962 patent, 2:14-22; *see also* 3:31-41; 3:51-62.

For step 2 of the *Mayo* analysis, the asserted claims do not do significantly more than the recited law of nature. The asserted claims merely recite generic or conventional limitations required in implementing the natural law of using an enzyme. Whether analyzed alone or in combination, the elements of the asserted claims fail to provide practical limitations on the claims and do nothing more than recite generic limitations. Indeed, the applicant admits that the POSA

would “appreciate” the aspects of step 2 such that they are routine. For example, the applicant admits that:

The skilled person will appreciate that this means the formaldehyde-based compound is added to the reaction mixture, and then subsequently breaks down to release formaldehyde (and other related compounds) which may then react with the (S)-nornicotine to form (S)-nicotine. In the case of the addition of a formaldehyde-based compound, the skilled person will be familiar with how to tailor the appropriate amount of the formaldehyde-based compound added in order to achieve the release of a particular amount of formaldehyde in situ.

5:60-6:3. Thus, “any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately.” *Mayo*, 566 U.S. at 79–80.

Finally, the process lacks additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself. Preemption is a tell-tale sign that claims may be invalid under Section 101. Here, the applicant claimed a process that was broad enough to cover any newly discovered enzyme—either naturally occurring or synthetic—that would make (S)-nicotine. Like in *Mayo*, the “laws of nature at issue here are narrow laws that may have limited applications, but the patent claims that embody them nonetheless implicate this concern.” 566 U.S. at 86. The claims are not directed to, for example, the particular discovery of certain enzymes with a highly enantiomeric excess of (S)-nornicotine, but encompass any enzyme with imine-reductase activity for use in the process of making (S)-nicotine.

C. Unenforceability

The claims of the '962 patent may be unenforceable due to inequitable conduct. Hangsen is presently conducting discovery and intends to amend its pleading to state an inequitable conduct defense. One or more individuals associated with the prosecution of the application that became the '962 patent (a) buried material prior art by glossing over references to the prior art but not

citing the prior art in an information disclosure statement; (b) failed to cite material prior art (including an enzyme catalog by Enzymicals); (c) misleadingly described Sheldon and omitted that Sheldon taught a synthesis of nicotine using an imine reductase enzyme; and (d) relabeled enzyme labels provided by an enzyme provider into meaningless labels (e.g., “IRED_C”) after discovering that the enzymes may have been publicly available and sold by the enzyme provider in an attempt to conceal prior-art status of those enzymes. Each of the foregoing rationales independently supports a defense of inequitable conduct, but together the conduct constitutes a deceptive pattern that provides a fifth combined basis for inequitable conduct. Additionally, on information and belief, had the examiner had the information that the applicant should have disclosed, the examiner would not have allowed the patent to issue. On information and belief, this conduct was undertaken with the intent to deceive the U.S. Patent and Trademark Office.

Hangsen believes additional discovery will further support these example rationales.

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Respectfully Submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on March 21, 2023, a true and correct copy of the foregoing has been served via electronic mail on the known counsel of record.

/s/ Kevin P. Flynn
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