

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HANGSEN INTERNATIONAL GROUP LTD.,

Petitioner

v.

ZANOPRIMA LIFESCIENCES, LTD.,

Patent Owner.

IPR2023-00503

U.S. Patent No. 10,913,962

PETITION FOR *INTER PARTES* REVIEW

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EXHIBIT LIST

Exhibit No.	Description¹
1001	U.S. Patent No. 10,913,962
1002	Declaration of Jeffrey D. Winkler, Ph.D. (“Winkler”)
1003	U.S. Patent No. 8,367,837 (“Divi”)
1004	Tom Moody, “Biocatalysis: Genes to GMP,” Speciality Chemicals Magazine, pp. 12-14 (January 2016) (“Moody”)
1005	Declaration of Andrew Warmington, Ph.D.
1006	Enzymicals, 2017 Portfolio (“Enzymicals”)
1007	Declaration of Nathaniel E. Frank-White from the Internet Archive
1008	U.S. Patent No. 9,556,142 (“Arnold”)
1009	Dennis Wetzl et al., “Expanding the Imine Reductase Toolbox by Exploring the Bacterial Protein-Sequence Space,” <i>ChemBioChem</i> 2015, 16, 1749-1756 (“Wetzl”)
1010	Declaration of Sylvia D. Hall-Ellis, Ph.D., with attachments 1a-1f, 2a-2c, and 3a-3g
1011	Stefan Velikogne et al., “Sequence-Based <i>In-silico</i> Discovery, Characterization, and Biocatalytic Application of a Set of Imine Reductases,” <i>ChemCatChem</i> 2018, 10, 3236-3246 (“Velikogne”)
1012	<i>Reserved</i>

¹ Descriptions are for convenience only and are not admissions or evidence.

Exhibit No.	Description ¹
1013	International Patent Application Publication WO 2014/174505 (“Sheldon”)
1014	October 30, 2020, Response to Office Action
1015	Complaint from <i>Zanoprima Lifesciences, Ltd. v. Hangsen Int’l Grp. Ltd.</i> , No. 6:22-cv-00268-ADA (W.D. Tex.)
1016	“Chemical and physical basics of routine formaldehyde fixation,” <i>J. of Oral and Maxillofacial Pathology</i> , Vol. 16, Issue 3, pp. 400-405 (Sep. – Dec. 2012)
1017	Dictionary Definition of “polyoxymethylene” from <i>McGraw-Hill Dictionary of Scientific and Technical Terms</i>
1018	Dictionary Definition of “excipient” from <i>McGraw-Hill Dictionary of Scientific and Technical Terms</i>
1019	August 7, 2020, Office Action
1020	United States District Courts — National Judicial Caseload Profile
1021	Curriculum Vitae of Dr. Jeffrey D. Winkler
1022	Francis A. Carey, <i>Organic Chemistry</i> (6th ed. 2006), Chapter 7
1023	Letter from Tony Corsini of the British Library Regarding the Public Availability of January 2016 Issue of <i>Speciality Chemicals Magazine</i>

I. INTRODUCTION

Hangsen International Group, Ltd. (“Hangsen”) requests *inter partes* review (“IPR”) of claims 1-14 (“the Challenged Claims”) of U.S. Patent No. 10,913,962 (“the ’962 Patent”) (Ex. 1001).

This is a textbook case of obviousness. The Challenged Claims recite nothing more than the routine, expected development of the art. The Challenged Claims recite a known synthesis of (S)-nicotine using an enzyme called an imine reductase. A person of ordinary skill in the art (“POSITA”) would have had the ability and motivation to catalyze the known reaction as claimed.

To be clear, the inventors of the ’962 Patent did not discover a new imine reductase enzyme, nor did they invent a new reaction pathway to (S)-nicotine. They simply applied commercially available imine reductase enzymes to catalyze the imine-reduction step of a known reaction sequence.

Before the effective filing date, working imine reductase enzymes were available from at least two enzyme companies, Enzymicals and Almac Group—a fact the ’962 Patent admits. Enzymicals and Almac Group not only advertised imine reductases available for production-scale use, but also offered screening services to find the specific enzymes that would work in a target reaction. Enzymicals and Almac Group had proven successes using enzyme screening techniques to identify

which specific imine reductases worked on a target imine substrate to yield a particular chiral amine.

The prior art shows that it would have been obvious to screen for an imine reductase to catalyze the reduction of an imine in a known reaction and that a POSITA would have had a reasonable expectation of success in doing so. The disclosure and claims of the '962 Patent follow naturally from the prior art. The Challenged Claims are unpatentable, and Hangsen respectfully requests that the Board cancel the Challenged Claims.

II. MANDATORY NOTICES

A. 37 C.F.R. § 42.8(b)(1): Real Party-in-Interest

Parties who may be real parties-in-interest are Hangsen International Group Ltd.; Shenzhen Hangsen Star Technology Co., Ltd.; Hangsen E-Cig Technology Co., Ltd.; and Shandong Jincheng Pharmaceutical Chemical Co., Ltd.

B. 37 C.F.R. § 42.8(b)(2): Related Matters

The '962 Patent is asserted in *Zanoprima Lifesciences, Ltd. v. Hangsen Int'l Grp. Ltd.*, No. 6:22-cv-00268-ADA (W.D. Tex.) ("District Court Litigation"). Ex. 1015.

C. 37 C.F.R. § 42.8(b)(3) & (4): Counsel And Service Information

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Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney accompanies this Petition. Hangsen consents to electronic service by email at kkirsch@bakerlaw.com, kflynn@bakerlaw.com, asamuels@bakerlaw.com, and yli@bakerlaw.com.

III. PAYMENT OF FEES

Hangsen requests review of 14 claims. The Director may charge the request fee and post-institution fee listed in § 42.15(a) and any other necessary fees to Deposit Account No. 502036.

IV. CERTIFICATION OF STANDING

Hangsen certifies that the '962 Patent is available for IPR and that Hangsen is not barred or estopped from requesting an IPR of the Challenged Claims.

V. BACKGROUND

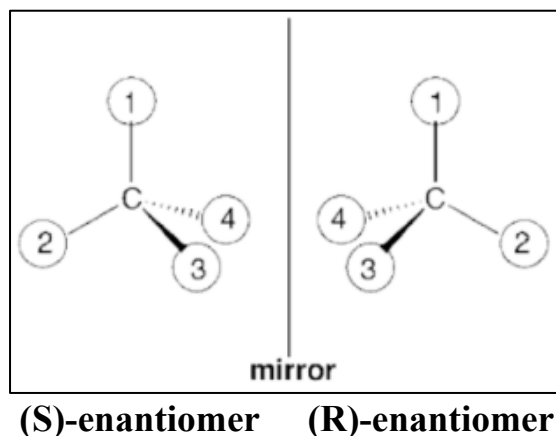
The '962 Patent is titled "Process of Making (S)-Nicotine," and issued from Application No. 16/336,024, filed on March 22, 2019. Ex. 1001, Cover. The '962 Patent claims priority to European Patent Application 18206826, filed on November 16, 2018. *Id.*

A. Stereochemistry

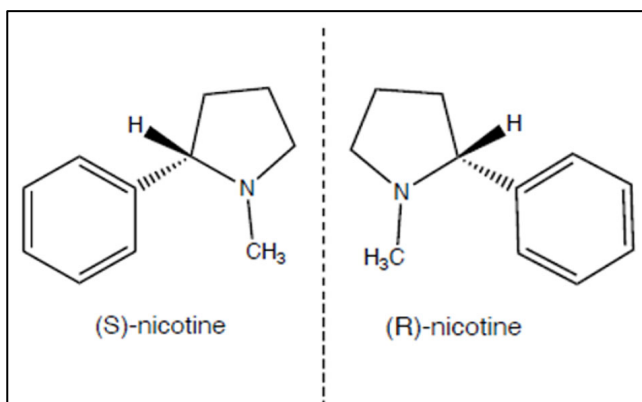
Molecules have three-dimensional structures. Ex. 1002 ("Winkler") ¶ 54. Carbon atoms may have a tetrahedral structure connected to four atoms or functional groups. *Id.* Molecules with a tetrahedral carbon having four different substituents can have the same chemical formula yet have different three-dimensional orientations; they may be non-superimposable mirror-images of each other. *Id.* These are "chiral" molecules, and each mirror-image molecule is an "enantiomer." *Id.* Chemists call one the (R)-enantiomer and the other the (S)-enantiomer. *Id.* ¶ 55.

When a 50/50 mixture of (R)- and (S)-enantiomers exists, the mixture is “racemic.”

Id. A generic chiral molecule showing its two enantiomers follows:



When drawing molecules to reflect three-dimensional orientations, normal lines are considered coplanar with the paper, solid wedges reach toward the reader, and dashes extend behind the paper. *Id.* ¶ 56. Nicotine has (R)- and (S)-enantiomeric forms:

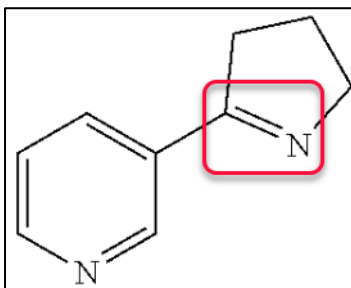


Id. ¶ 57.

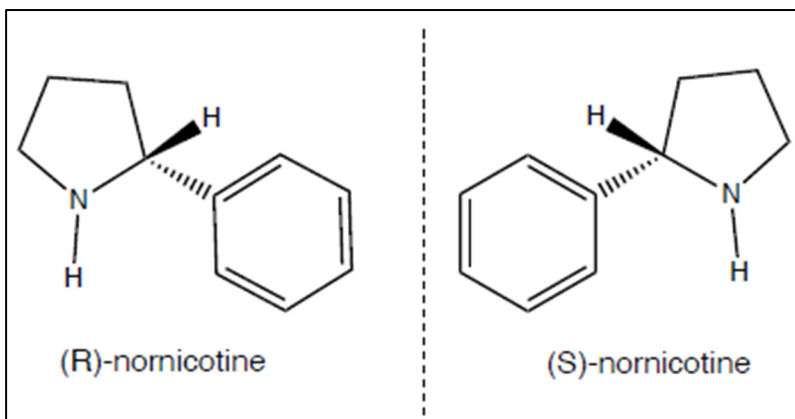
Enantiomers may have different properties when those properties depend on the three-dimensional arrangement of atoms. *Id.* ¶ 58; Ex. 1022 at 310. Biological

systems implement biological processes by receptors and enzymes, which may be specific to one enantiomer of a molecule—a concept called chiral recognition. Winkler ¶ 58; Ex. 1022 at 311. For example, “it is acknowledged that (S)-nicotine ... is significantly more active than (R)-nicotine.” Ex. 1001 at 1:36-41.

Myosmine is an imine. Winkler ¶ 60. An imine is characterized by a carbon-nitrogen double bond (C=N). *Id.* The imine bond in myosmine is indicated in red:



Id. Imines such as myosmine are “prochiral”; when a prochiral imine is reduced to its corresponding amine, the amine can take one of its two enantiomeric forms, the (R)-amine or the (S)-amine. *Id.* ¶ 61. The resulting amine is a chiral molecule. *Id.* When the imine bond of myosmine is reduced, it becomes either (R)-nornicotine or (S)-nornicotine:



Id.

B. Overview of the '962 Patent

The '962 Patent describes demand for “tobacco replacement products” driven by the addictive nature of (S)-nicotine, a chemical occurring naturally in tobacco, and a “growing concern around the detrimental impact of traditional cigarette products on consumer health.” Ex. 1001 at 1:11-27. Nicotine is used “to treat nicotine dependence.” *Id.* at 1:27-30.

The '962 Patent describes two problems with obtaining nicotine: enantiomeric purity and chemical purity because “(S)-nicotine ... is significantly more active than (R)-nicotine” and the pharmaceutical industry demands a high level of chemical purity (nicotine free from non-nicotine impurities). *Id.* at 1:31-51. Impurities in tobacco-derived nicotine might be carcinogenic. *Id.* at 1:51-60. Nicotine from tobacco “typically has a chemical purity of less than 95% due [to] the presence of related alkaloid impurities,” which are chemically similar to nicotine and “difficult to remove.” *Id.* at 1:61-2:4.

Chemical syntheses were known and produced a racemic mix of (R,S)-nicotine, requiring a separation step to obtain (S)-nicotine. *Id.* at 2:7-13. The '962 Patent aimed to “synthesiz[e] (S)-nicotine in preference to the (R)-enantiomer with high enantiomeric selectivity whilst also achieving high chemical purity.” *Id.* at 2:23-26.

To that end, the '962 Patent commandeered a well-known reaction sequence of reducing myosmine to form nornicotine and methylating the nornicotine to form nicotine, using a stereoselective enzyme catalyst instead of a metal catalyst to reduce myosmine. *See id.* at 2:30-51. And myosmine was known to a POSITA, as “[t]he skilled person will be familiar with appropriate reaction schemes to make myosmine.” *Id.* at 3:29-30.

A POSITA would have been familiar with enzymes having imine reductase activity (also known as “imine reductases” or “IREDs”). The '962 Patent states that “the enzyme with imine reductase activity ... is an enzyme capable of catalysing the conversion of myosmine to (S)-nornicotine” and admits that “[t]he skilled person is familiar with such enzymes.” Ex. 1001 at 3:35-39. Indeed, imine reductases were well-characterized before the '962 Patent was filed. As their name indicates, imine reductases reduce imines to form amines. Winkler ¶¶ 63, 71. Unlike reductions using hydrogen gas and a metal catalyst (which form racemic mixtures), reductions using imine reductases are characteristically stereoselective: an imine is reduced to either

the (R)-amine or the (S)-amine in high proportions. *Id.* ¶¶ 64, 71. Imine reductases were known to have a broad substrate scope, meaning that any given imine reductase tended to reduce a wide range of imines. *Id.*

Obtaining imine reductases was trivial before the effective filing date of the '962 Patent: the '962 Patent admits that working imine reductases were available commercially from Enzymicals and Almac Group. Ex. 1001 at 4:7-14. And it was a well-known technique to “screen” for imine reductases that would react with a given imine to yield a target amine, either the (R)- or (S)-amine, selectively. Winkler ¶¶ 65, 73. Enzyme screening services were available commercially through Enzymicals and Almac Group. *Id.*

The '962 Patent has 14 claims. Claim 1 is an independent claim. Claims 2-14 depend from claim 1. Claim 1 recites a synthesis of nicotine by reducing the imine myosmine to form the amine nornicotine, then methylating the nornicotine to form nicotine. The reduction of myosmine to (S)-nornicotine is catalyzed using any “enzyme with imine reductase activity” accepting myosmine as a substrate and forming the (S)-enantiomer of its amine, nornicotine.

Thus, the '962 Patent claims a well-known reaction pathway catalyzed by known, commercially available enzymes that reduce imines stereoselectively and have broad substrate scope. The claims of the '962 Patent are nothing more than the product of a routine application of enzymatic chemistry to a known reaction.

VI. OVERVIEW OF CHALLENGE

A. Grounds for Challenge

Hangsen challenges claims 1-14 as obvious as follows:

Ground	Claims	Basis
1	1-14	Obvious (35 U.S.C. § 103) by Divi, Moody, and Enzymicals
2	6, 12	Obvious (35 U.S.C. § 103) by Divi, Moody, Enzymicals, and Arnold
3	7-8	Obvious (35 U.S.C. § 103) by Divi, Moody, Enzymicals, and Sheldon
4	1-14	Obvious (35 U.S.C. § 103) by Divi, Moody, Velikogne, and Wetzl
5	6, 12	Obvious (35 U.S.C. § 103) by Divi, Moody, Velikogne, Wetzl, and Arnold
6	7-8	Obvious (35 U.S.C. § 103) by Divi, Moody, Velikogne, Wetzl, and Sheldon

B. Claim Construction

Term	Claims	Proposed Construction
“enzyme with imine reductase activity to form (S)-nornicotine”	1	“enzyme capable of reducing an imine group to form more (S)-nornicotine than (R)-nornicotine”
“wherein the (S)-nicotine is obtained	9	“wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%” ²

² Hangsen proposes a construction only if this term is not indefinite. *See* M.P.E.P. § 2173.05(c)(I) (providing prototypical indefiniteness examples). The “preferably” clauses must have meaning, yet the scope is unclear. *Nippon Suisan Kaisha Ltd. v.*

with an enantiomeric excess of at least 90%, preferably at least 95%, more preferably at least 98%, most preferably at least 99%”		
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First, “enzyme with imine reductase activity to form (S)-nornicotine” means “enzyme capable of reducing an imine group to form more (S)-nornicotine than (R)-nornicotine.” This construction is consistent with the express definition in the specification.

The ’962 Patent defines “enzyme with imine reductase activity to form (S)-nornicotine” as an enzyme capable of reducing an imine group to form more (S)-nornicotine than (R)-nornicotine:

As used herein, an “enzyme with imine reductase activity” refers to *an enzyme capable of asymmetrically reducing an imine group*, in particular a secondary imine group, to the corresponding amine group, in particular a secondary amine group.

Ex. 1001 at 3:31-35.

This construction is consistent with the prosecution history. Patent Owner contrasted the claims with the “fundamentally different” route of Arnold, stating that “the aim in Arnold is to produce a racemic mix, rather than achieve

Pronova Biopharma Norge, PGR2017–00033, Paper 7 at 21-22 (P.T.A.B. Jan. 17, 2018) (“preferably” clauses “more likely than not” indefinite).

stereoselectivity.” Ex. 1015 at 10. In context, “asymmetrically” thus means not racemic, or more (S)-enantiomer than (R)-enantiomer.³ Winkler ¶ 80.

While Patent Owner may offer constructions of “plain and ordinary meaning” or “enzyme capable of stereoselectively reducing an imine group to form more (S)-nornicotine than (R)-nornicotine,” those constructions do not affect whether the Petition should be instituted.

Second, the term “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%” should be construed as “wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%” if the claim is not indefinite.⁴

While Patent Owner may offer a construction of “plain and ordinary meaning,” such a construction does not affect whether the Petition should be instituted.

C. Evidence Supporting Challenge

Exhibits are identified on pages vi-vii of the Petition. The relevance and specific portions supporting the challenge are provided throughout the Petition.

³ For purposes of this Petition, “asymmetrically” is synonymous with “stereoselectively.”

⁴ Claims 1 and 9 do not preclude a separate isolation step (following the formation of (S)-nornicotine or following the formation of (S)-nicotine) to obtain the enantiomeric excess(es) claimed in claim 9, but this issue is immaterial to the Petition.

Hangsen submits a declaration from Jeffrey Winkler, Ph.D. as Ex. 1002 in support of this Petition.

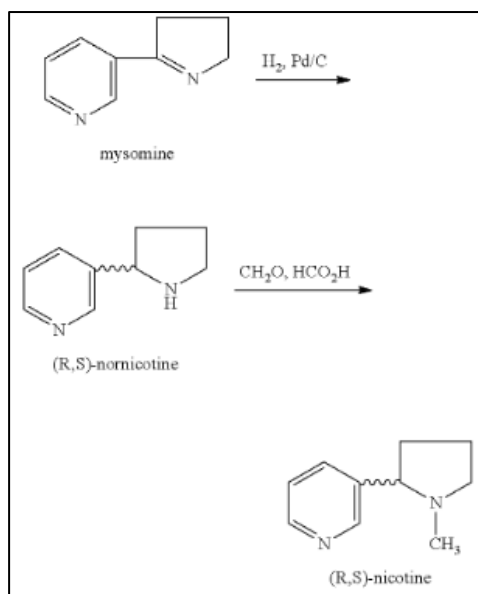
VII. LEVEL OF ORDINARY SKILL IN THE ART

A POSITA with respect to the '962 Patent would have had a Ph.D. in a relevant field of organic chemistry or biochemistry, with several years of research experience gained during those studies or afterwards in organic synthesis, including chiral synthesis, and the use of enzymes in reactions. Winkler ¶ 51. A POSITA could also include a person with a lesser academic degree, but with several years' experience sufficient to develop equivalent experience in synthetic organic chemistry, such as in pharmaceutical applications or in the chiral synthesis of compounds with biological activity. *Id.* Dr. Winkler was a POSITA as of the '962 Patent's earliest effective filing date. *Id.* ¶ 52.

VIII. OVERVIEW OF THE PRIOR ART

A. Divi (Ex. 1003)

Divi is not listed on the cover of the '962 Patent, and there is no evidence that the Examiner considered Divi. Divi is briefly mentioned in the specification. Divi disclosed a synthesis of (R,S)-nicotine by reducing myosmine to (R,S)-nornicotine and methylating the (R,S) nornicotine to (R,S)-nicotine:



Ex. 1003 at 2:35-3:15. Divi explained that “[c]atalytic hydrogenation of myosmine resulted in (R,S)-nornicotine.” *Id.* at 3:60-61. Then, “[c]onversion of (R,S)-nornicotine to (R,S)-nicotine was carried out by N-methylation using formaldehyde and formic acid as reported in the literature.” *Id.* at 4:8-11. Divi summarized that “[t]he most convenient way to prepare (R,S)-nicotine is through myosmine” and that “this process provides an attractive and economical method for the production of synthetic (S)-nicotine.” *Id.* at 2:21-25, 3:16-19. A POSITA would have recognized Divi as a logical starting point for synthesizing (S)-nicotine. Winkler ¶ 93.

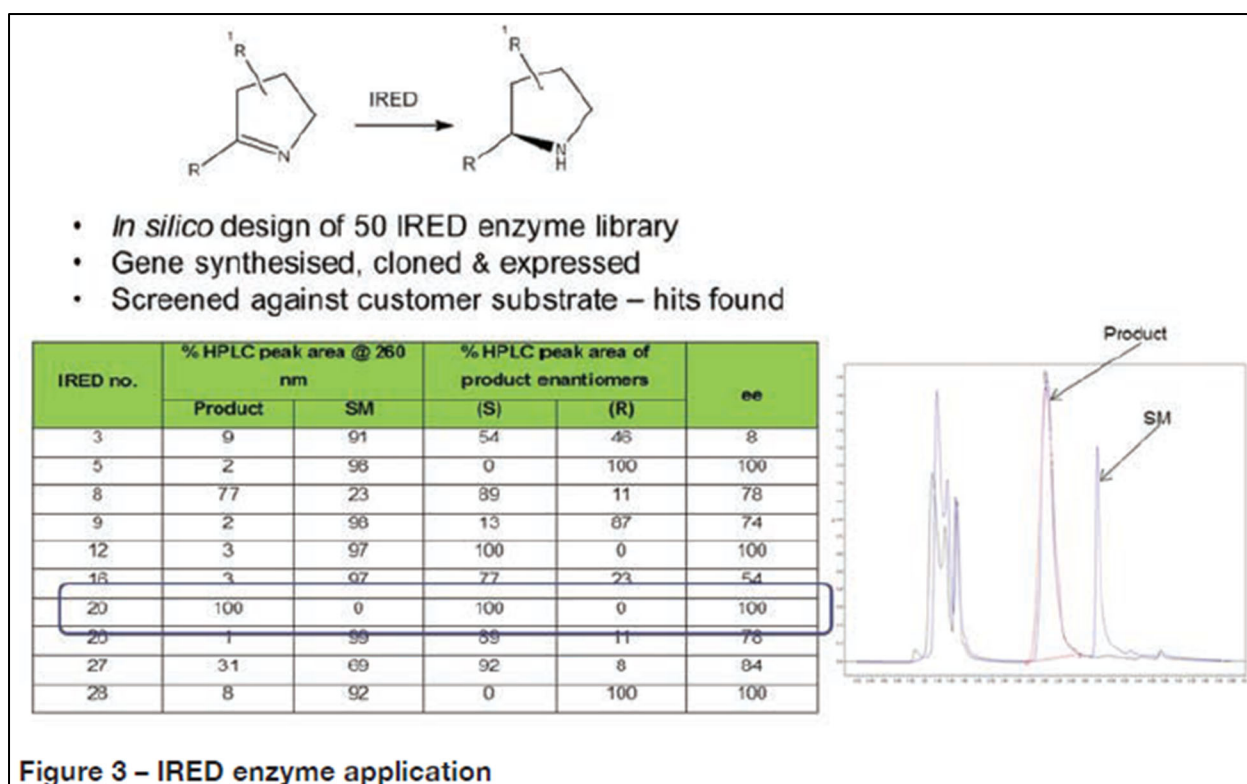
Divi disclosed that the “unwanted” (R)-nicotine is separated from the racemic (R,S)-nicotine mixture. A POSITA would have recognized that avoiding a separation step would improve the reaction. *Id.* ¶ 94.

Divi qualifies as prior art under 35 U.S.C. § 102(a)(1)-(2).

B. Moody (Ex. 1004)

Moody is not listed on the cover of the '962 Patent, and there is no evidence that the Examiner considered Moody. 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.” Ex. 1004 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. Moody summarized the successful imine reductase screen in the following figure:



Moody qualifies as prior art under 35 U.S.C. § 102(a)(1). It is a printed publication from *Speciality Chemicals Magazine* that was publicly available on or around January 29, 2016, and was distributed to between 30,000 and 40,000 readers. Ex. 1005; Ex. 1023; Ex. 1010 ¶¶ 44-53.

C. Enzymicals (Ex. 1006)

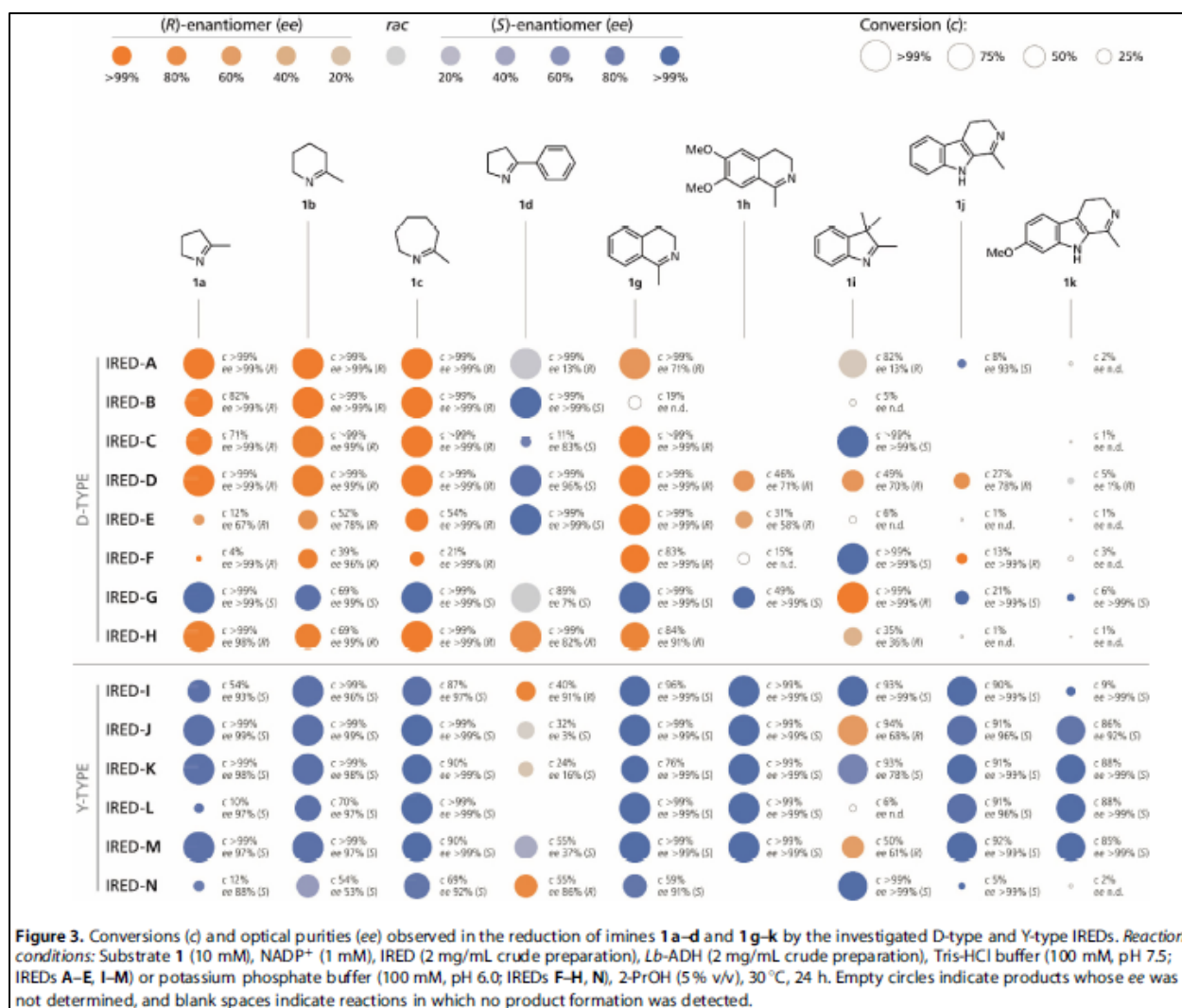
Enzymicals is not listed on the cover of the '962 Patent, and there is no evidence that the Examiner considered Enzymicals. Enzymicals disclosed a “continually expanding toolbox with innovative biocatalysts and a range of proteins,” including “Imine Reductases” in the “biocatalytic toolbox.” Ex. 1006 at 9. Enzymicals disclosed four separate imine reductases available to order, two of which were (R)-selective and two of which were (S)-selective, and an imine

reductase “screening kit” containing all four imine reductases. *Id.* at 38, 40. Enzymicals further advertised an in-house enzyme screening service that screens a given substrate “to find out the most suitable enzyme for your desired reaction,” that “[m]utants with enhanced substrate specificity and/or increased stereoselectivity towards appropriate substrates are 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 48, 52.

Enzymicals qualifies as prior art under 35 U.S.C. § 102(a)(1). It is a printed publication published and publicly available on the Enzymicals website as early as July 1, 2017. Ex. 1007.

D. Velikogne (Ex. 1011)

Velikogne is not listed on the cover of the '962 Patent, and there is no evidence that the Examiner considered Velikogne. 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.” Ex. 1011 at 3236. Velikogne demonstrated that a screen of 14 imine reductases reduced a broad scope of imines to their corresponding amines. *Id.* at 3239-3240. Figure 3 illustrates the activities and stereoselectivities of the screened imine reductases across the range of imine substrates:



Velikogne qualifies as prior art under 35 U.S.C. § 102(a)(1). It is a printed publication from the *ChemCatChem* journal that was publicly available as early as June 20, 2018. Ex. 1010 ¶¶ 54-63.

E. Wetzl (Ex. 1009)

Wetzl is not listed on the cover of the '962 Patent, and there is no evidence that the Examiner considered Wetzl. Wetzl disclosed that imine reductases reduced imines to chiral amines across “a broad range of substrates.” Ex. 1009 at 1749. Wetzl

ran an experimental enzyme screen to characterize about 20 imine reductases and found that the “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%.” *Id.* at 1750.

Wetzel qualifies as prior art under 35 U.S.C. § 102(a)(1). It is a printed publication from the *ChemBioChem* journal that was publicly available as early as September 23, 2015. Ex. 1010 ¶¶ 64-73.

F. Arnold (Ex. 1008)

Arnold was considered during prosecution. Arnold disclosed a synthesis of nicotine by forming myosmine, reducing myosmine to (R,S)-nornicotine, and methylating (R,S)-nornicotine using formaldehyde and formic acid to form (R,S)-nicotine. Ex. 1008 at 2:28-3:10. Examples 4 and 5 of Arnold disclose a synthesis of nicotine from myosmine that proceeds without isolating the nornicotine from the reaction mixture. *Id.* at 7:33-52.

Arnold qualifies as prior art under 35 U.S.C. § 102(a)(1)-(2).

G. Sheldon (Ex. 1013)

Sheldon is not listed on the cover of the '962 Patent, and there is no evidence that the Examiner considered Sheldon. Sheldon is briefly mentioned in the specification. While the specification coyly mentions that Sheldon teaches “a

synthetic process for producing (S)-nicotine using an enzyme as a biocatalyst,” Ex. 1001 at 2:14-16, Sheldon teaches a synthesis of (S)-nicotine from pseudooxynicotine using an imine reductase. Ex. 1013 at 18-21. Sheldon disclosed that “imine reductase enzymes are commercially available, for example, from Enzymicals AG.” *Id.* at 18. Sheldon teaches that the synthesis of nicotine using an imine reductase occurs in water or an aqueous salt solution or a buffer “to avoid denaturation of the reductase enzymes.” *Id.* at 21.

Sheldon qualifies as prior art under 35 U.S.C. § 102(a)(1)-(2).

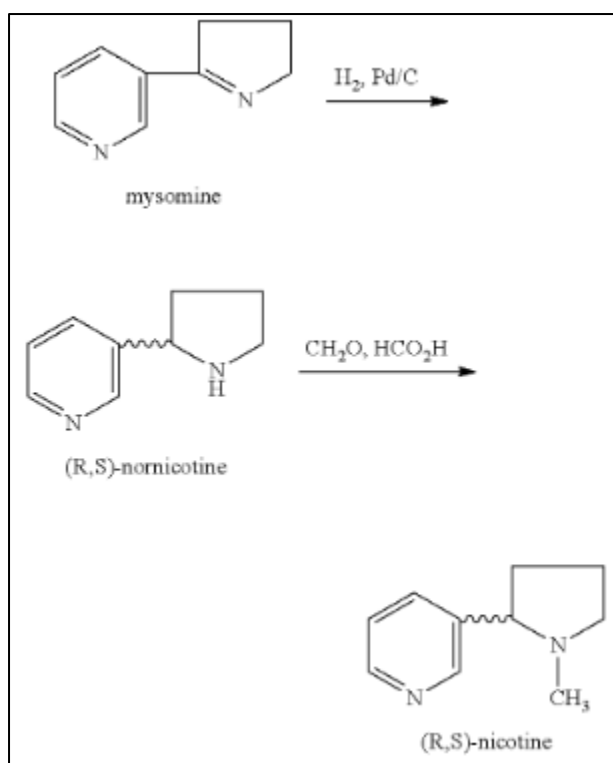
IX. SPECIFIC GROUNDS OF OBVIOUSNESS

A. Claims 1-14 Are Obvious by Divi, Moody, and Enzymicals.

1. Claim 1

a. “A process for making (S)-nicotine comprising the steps of:”

Divi disclosed that syntheses of (S)-nicotine were known in the art, and that using chiral reagents and chiral catalysts were also known but were expensive. Ex. 1003 at 1:64-2:3. Divi’s synthesis of (R,S)-nicotine is depicted as follows:



Id. at 2:35-3:15. Divi disclosed that the synthesized (R,S)-nicotine is followed by a resolution step to separate (S)-nicotine from the “unwanted” (R)-nicotine, which “provides an attractive and economical method for the production of synthetic (S)-nicotine.”. *Id.* at 2:8-11, 2:21-25. Accordingly, a POSITA would have looked at the reaction disclosed in Divi as a logical starting point, while recognizing that avoiding a resolution step would further improve the reaction. Winkler ¶¶ 119-120.

b. “(i) reducing myosmine with an enzyme with imine reductase activity to form (S)-nornicotine; and”

i. Divi disclosed that the reduction of myosmine by reducing the imine bond yields nornicotine.

Divi teaches that “[t]he most convenient way to prepare (R,S)-nicotine is through myosmine (Scheme 3). Myosmine is hydrogenated to (R,S)-nornicotine,

which on N-methylation gives (R,S)-nicotine.” Ex. 1003 at 3:16-19, 2:8-11, 2:21-25, 2:35-3:16, 4:8-11. Myosmine is reduced when it is “hydrogenated” to nornicotine. Winkler ¶ 122. A POSITA would have recognized that Divi disclosed an achiral reaction and, absent, a chiral reagent (such as an enzyme), the reaction results in a racemic product unless resolved. *Id.*

A POSITA would have recognized that the reduction of myosmine to nornicotine in Divi proceeded by reducing the C=N imine bond of myosmine, converting it to the corresponding amine, nornicotine. *Id.* ¶ 123.

ii. Moody disclosed that enzyme-catalyzed reactions proceeded to give selective formation of chiral products and were well-established in industrial applications.

Moody disclosed that the use of biocatalysts in modern chemical and pharmaceutical production is well-accepted. “The paradigm shift for the acceptance of biocatalysts is persistent and at the forefront of research within the fine chemicals and pharmaceuticals industries.” Ex. 1004 at 12. Moody disclosed that “[b]ioprocessing is now the norm rather than the exception at Almac.” *Id.*

Moody disclosed that “[o]ff-the-shelf and specifically designed enzymes can be accessed within days and weeks respectively. These timelines allow synthetic chemists to include enzyme processing in their synthetic toolbox.” *Id.* According to Moody, not only was biocatalysis accepted in synthetic chemistry, but “[b]iocatalysis has become the workhorse of the chemists’ toolbox for chiral

chemistry.” *Id.* Moody praised incorporating enzyme-catalysts into synthetic reactions, stating that “[e]nzyme processes are now at the epicentre of key drivers in process design, scale-up and economics.” *Id.*

Moody recognized that “[t]he synthetic power of enzymes is their *unequalled selectivity* for the chemical reactions they catalyse.” *Id.* at 12.

A POSITA would have known that enzymes were effective in the industrial production of chiral compounds, were available commercially, and were the “workhorse” in the “toolbox for chiral chemistry.” Winkler ¶ 127.

iii. Moody and Enzymicals disclosed that imine reductases reduce imines to chiral amines asymmetrically.

Enzymicals disclosed that “[i]mine reductases (IREDs) catalyze the reduction of imines to amines by using NAD(P)H as a hydride source.” Ex. 1006 at 39. Enzymicals disclosed that the “transformation of prochiral imines to chiral amines using IREDs offer quantitative asymmetric route to amine products of high optical purity. So these enzymes can have a valuable complementary role to play in chiral amine synthesis.” *Id.* Enzymicals disclosed four imine reductases and an imine reductase “screening kit” containing the four imine reductases, all available for purchase, two of which were (S)-selective. *Id.* at 38, 40. Similarly, Moody disclosed that imine reductases enabled “the enantioselective reduction of the imine.” Ex. 1004 at 12, Fig. 3.

A POSITA knew that imine reductases reduced imines to amines asymmetrically. Winkler ¶ 129. Additionally, a POSITA would have been exposed to papers from Enzymicals and Almac that offered imine reductases and described the utility of using imine reductases to asymmetrically reduce imines to chiral amines. *Id.*

- iv. *Enzymicals disclosed imine reductase screening kits and in-house screening services with a large set of enzymes; Moody disclosed the commercial availability of enzymes for a customer's target substrate.*

Enzymicals disclosed a “continually expanding toolbox with innovative biocatalysts,” including “Imine Reductases” in the “biocatalytic toolbox.” Ex. 1006 at 9. Enzymicals disclosed four separate imine reductases, two of which were (R)-selective and two of which were (S)-selective, as well as an imine reductase “screening kit” containing all four imine reductases available commercially. *Id.* at 38, 40. Enzymicals further disclosed an in-house enzyme screening service that would screen a given substrate “to find out the most suitable enzyme for your desired reaction.” *Id.* at 48. Enzymicals disclosed that it offered mutant enzymes with “enhanced substrate specificity and/or increased stereoselectivity towards appropriate substrates” and that “an in-house screening with suitable enzyme classes about all available enzymes from public or private panel” was available. *Id.* at 48, 52.

Moody described that “[o]ff-the-shelf and specifically designed enzymes can be accessed within days and weeks respectively” and that “enzyme processing” was a part of chemists’ “synthetic toolbox.” Ex. 1004 at 12. Moody disclosed that “Almac can rapidly access specifically built enzyme libraries for specific customer substrates.” *Id.* Moody stated that “[u]sing this technology, [Almac] can take customer substrates and by performing complex dockings studies can build tailored catalysts for the customer substrate.” *Id.* And Moody disclosed that Almac could build tailored imine reductases designed to reduce a specific customer imine substrate. *Id.*

A POSITA would have recognized that Enzymicals offered enzyme screens and screening services for identifying imine reductases to catalyze the reduction of imines on production scale. Winkler ¶ 132. A POSITA would have known that Enzymicals and Almac offered commercial screening services to screen a given imine substrate and identify an optimal imine reductase for the substrate. *Id.* And a POSITA would have understood that these services could specifically design imine reductases for activity against a given imine substrate and had done so successfully. *Id.*

- v. *A POSITA would have been motivated to screen imine reductases using Enzymicals or Almac to find an imine reductase catalyzing the asymmetric reduction of myosmine to (S)-nornicotine.*

A POSITA would have recognized that the Divi reaction provided an opportunity for a stereoselective reaction where myosmine is reduced to nornicotine. Winkler ¶ 133. A POSITA would have understood from reaction pathway disclosed in Divi that the conversion of myosmine, an imine, to nornicotine, the corresponding amine, requires reducing the imine bond of myosmine. *Id.* The '962 Patent admits that “[t]he skilled person is familiar with” imine reductases. Ex. 1001 at 3:32-41. A POSITA, familiar with imine reductases, would have known that imine reductases reduce imines to their corresponding amines asymmetrically. Winkler. ¶ 134. As such, a POSITA would have been motivated to use an imine reductase to catalyze the asymmetric reduction of myosmine to (S)-nornicotine. *Id.*

Moody disclosed that “[b]iocatalysis has become the workhorse of the chemists’ toolbox for chiral chemistry” and that “[t]he synthetic power of enzymes is their unequalled selectivity for the chemical reactions they catalyse.” Ex. 1004 at 12. And Enzymicals disclosed that the “transformation of prochiral imines to chiral amines using IREDs offer quantitative asymmetric route to amine products of high optical purity. So these enzymes can have a valuable complementary role to play in chiral amine synthesis.” Ex. 1006 at 39.

The '962 Patent admits that commercially available sources of imine reductases, including Enzymicals and Almac Group, were known. Ex. 1001 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 POSITA would have known from Enzymicals and Moody that imine reductases were widely available commercially. Winkler ¶ 136. And a POSITA 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 POSITA 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.” Ex. 1004 at 12; Winkler ¶ 136.

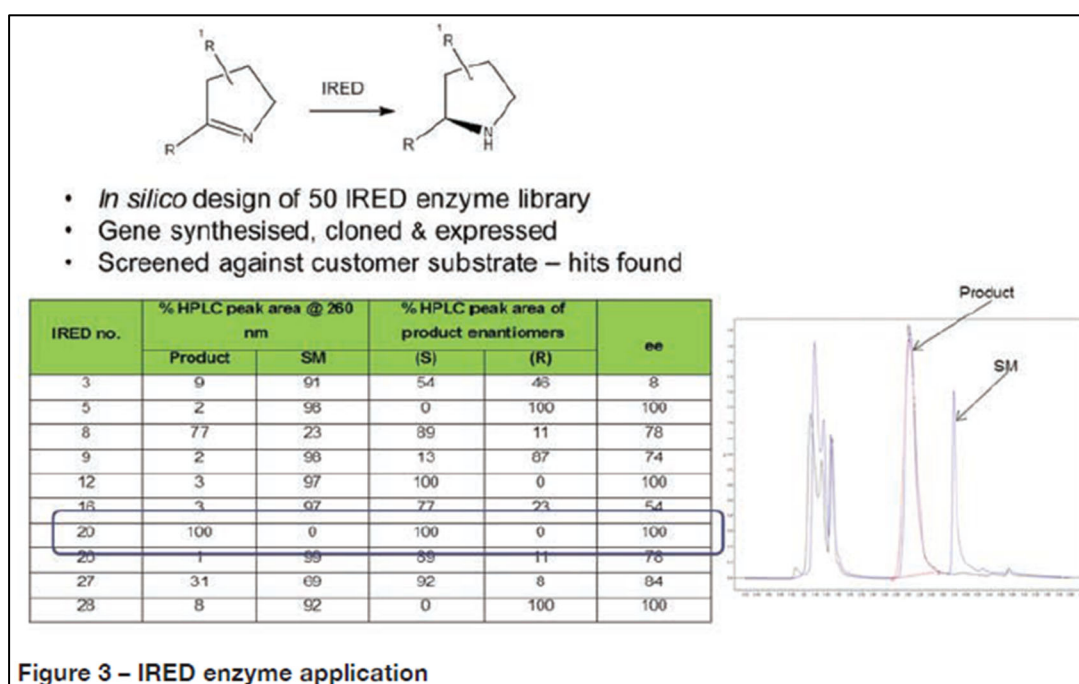
Accordingly, a POSITA, knowing that the Divi reaction could be made stereoselective where myosmine is reduced to nornicotine, would have been motivated to use an imine reductase to reduce myosmine to (S)-nornicotine. Winkler ¶ 137. A POSITA would have been motivated to apply the teachings of Enzymicals 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. Winkler ¶ 137.

- vi. *A POSITA would have had a reasonable expectation of success that Enzymicals or Almac would identify an imine reductase that would asymmetrically reduce myosmine to (S)-nornicotine.*

A POSITA would have had a reasonable expectation of success that Enzymicals or Almac would identify an imine reductase to reduce myosmine to (S)-nornicotine asymmetrically. Winkler ¶ 138. 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.” Ex. 1006 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 POSITA 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. Winkler ¶ 139.

A POSITA 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.” Ex. 1004 at 12; Winkler ¶ 140. A POSITA 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% enantiomeric excess (“ee”). *Id.*; Ex. 1004 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:



Therefore, a POSITA 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. Winkler ¶ 141. 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 POSITA 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. *Id.*

c. “(ii) methylating the (S)-nornicotine formed from step (i) to form (S)-nicotine;”

Divi disclosed methylating (R,S)-nornicotine to form (R,S)-nicotine. Ex. 1003 at 3:16-19, 4:8-11, 6:42-45; Winkler ¶ 142. A POSITA would have understood that the N-methylation step in Divi does not impart or change the chirality of the molecule. Winkler ¶ 143. The application of Divi’s N-methylation step to (S)-nornicotine would generate (S)-nicotine, in analogy to Divi’s conversion of (R,S)-nornicotine to (R,S)-nicotine. *Id.* A POSITA would have known that the chirality of nicotine is determined by the chirality of the nornicotine entering the N-methylation step. *Id.*

d. “wherein step (ii) is carried out by way of reductive methylation; and”

Divi disclosed methylating nornicotine to form nicotine by reductive methylation. *See* Section IX.A.1.c. The methylation disclosed in Divi is a reductive methylation using formaldehyde and formic acid. Winkler ¶ 144; Ex. 1003 at 4:8-11.

- e. **“wherein in step (ii) the (S)-nornicotine is reductively methylated, using formaldehyde or a formaldehyde-based compound in the presence of a reductant.”**

Divi disclosed reductively methylating nornicotine using formaldehyde in the presence of a reductant. *See* Section IX.A.1.d; Winkler ¶ 145. Divi disclosed methylating nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Formic acid is the reductant. Winkler ¶ 145.

2. Claim 2

- a. **“The process of claim 1”**

Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.1.

- b. **“wherein formaldehyde is introduced as part of an aqueous solution.”**

Divi disclosed introducing formaldehyde as part of an aqueous solution. Winkler ¶ 148. Divi disclosed: “To a solution of nornicotine (50 g 0.338 mol) in 100 ml water a mixture of 37% formaldehyde (49.7g, 1.656 mol) and 85% formic acid (37.26g 0.81 moles) was added and stirred at 85oC for 20 hrs.” *Id.* at 5:26-29; *id.* at 4:8-11. A POSITA would have understood that when Divi added the formaldehyde/formic acid, it was introduced as an aqueous solution. Winkler ¶ 148.

3. Claim 3

- a. **“The process of claim 1”**

Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.1.

- b. “wherein the formaldehyde-based compound is a dimer of formaldehyde, a polymer of formaldehyde, or an acetal of formaldehyde.”**

Divi disclosed that “the formaldehyde-based compound is a dimer of formaldehyde, a polymer of formaldehyde, or an acetal of formaldehyde.” Winkler ¶ 151. A “formaldehyde-based compound” is any compound capable of generating formaldehyde in-situ, and the ’962 Patent states that a formaldehyde-based compound is “preferably” a polymer of formaldehyde. Ex. 1001 at 5:58-6:14. A POSITA would have known that formaldehyde naturally forms polymers in aqueous solution. Winkler ¶ 151; Ex. 1016 at 401; Ex. 1017. Divi’s disclosure of formaldehyde solution thus inherently discloses a polymer of formaldehyde. Winkler ¶ 151.

4. Claim 4

- a. “The process of claim 1,”**

Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.1.

- b. “wherein the reductant is formic acid, sodium cyanoborohydride, or palladium/hydrogen.”**

Divi disclosed the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Formic acid is the reductant. Winkler ¶ 154.

5. Claim 5

- a. “The process of claim 1,”**

Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.1.

b. “wherein the reductant is formic acid.”

Divi disclosed the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Formic acid is the reductant. Winkler ¶ 157.

6. Claim 6

a. “The process of claim 1,”

Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.1.

b. “wherein the process is carried out without isolation of the (S)-nornicotine formed from step (i).”

A POSITA would have been motivated to reduce unnecessary isolation steps in any reaction sequence involving more than one chemical step. Winkler ¶ 160. In Divi’s nicotine synthesis, a POSITA would have recognized that there are two distinct chemical steps: (1) the reduction of myosmine to nornicotine, and (2) the reductive methylation of nornicotine to nicotine. *Id.* A POSITA would have been motivated to avoid isolating nornicotine and isolate only the nicotine at the end of the sequence if it could lead to comparable purity of the final product or an enhanced overall yield. *Id.* A POSITA would have been motivated to avoid that isolation step because it could have reduced costs and there would be a reasonable expectation that the overall yield would be higher. *Id.* It would have been obvious to a POSITA to try to prepare nicotine using the enzyme-catalyzed reaction without isolating the nornicotine intermediate but simply to proceed to the reductive methylation step to

reduce costs and solvent waste, and potentially improve the yield and efficiency of the process. *Id.*

Additionally, there are only two ways to run the reaction sequence from myosmine to nicotine: with isolation of the nornicotine, and without isolation of nornicotine. *Id.* ¶ 161. It would have been obvious to try the reaction without isolation of the (S)-nornicotine from step (i), as there were only two options and successfully completing the reaction without isolating the (S)-nornicotine would reduce costs and solvent waste, and potentially improve the yield and efficiency of the process. *Id.*

7. Claim 7

a. “The process of claim 1,”

Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.1.

b. “wherein in step (i) the (S)-nornicotine is formed as part of an aqueous solution, and wherein step (ii) comprises methylating the (S)-nornicotine contained within the aqueous solution.”

It would have been obvious to a POSITA that when using a biocatalyst to reduce myosmine to nornicotine, the reduction of myosmine would take place in aqueous solution because enzymes naturally function in aqueous solutions. Winkler ¶ 164. Consistently, Enzymicals disclosed that it provided enzymes as a “[c]oncentrated liquid aqueous culture supernatant.” Ex. 1006 at 51. Accordingly, a POSITA would have run the biocatalyzed reduction of myosmine to (S)-nornicotine

in aqueous solution to ensure that the imine reductase enzyme functions optimally. Winkler ¶ 164.

Further, Divi disclosed that the methylation of nornicotine to form nicotine was conducted while the nornicotine was in aqueous solution. Ex. 1003 at 5:26-29.

8. Claim 8

a. “The process according to claim 7,”

Claim 7 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.7.

b. “wherein in step (ii) the (S)-nornicotine is reductively methylated using formaldehyde introduced as part of an aqueous solution.”

Divi disclosed that the methylation of nornicotine to form nicotine was conducted by introducing formaldehyde as part of an aqueous solution. Ex. 1003 at 5:26-29.

9. Claim 9

a. “The process of claim 1,”

Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.1.

b. “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%.”

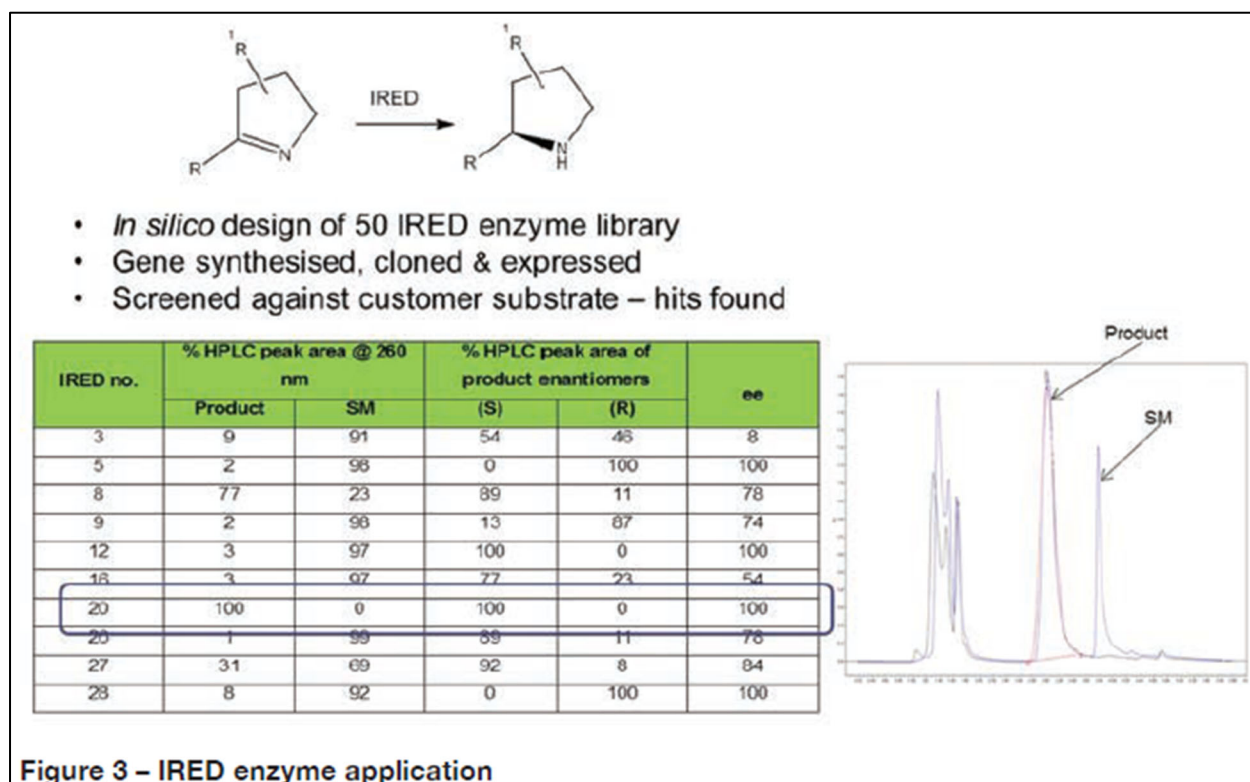
As presented in Section IX.A.1., a POSITA would have been motivated to improve the myosmine-nornicotine-nicotine reaction of Divi by using an imine

reductase as taught by Moody and Enzymicals to reduce myosmine and would have had a reasonable expectation of success in doing so. Winkler ¶ 171.

Enzymicals disclosed that the “transformation of prochiral imines to chiral amines using IREDs offer quantitative asymmetric route to amine products of high optical purity. So these enzymes can have a valuable complementary role to play in chiral amine synthesis.” Ex. 1006 at 39. Enzymicals disclosed that imine reductases offered by Enzymicals reduced three different imine substrates into chiral amines with 99% enantiomeric excess. *Id.* at 40. A POSITA would have understood from Enzymicals that imine reductases accept a broad range of imine substrates and convert those imines to their corresponding amines in a highly asymmetric manner—often with 99% enantiomeric excess. Winkler ¶ 172. A POSITA would have had a reasonable expectation of success that, even if their standard imine reductase screening kit did not reduce myosmine to (S)-nornicotine asymmetrically, Enzymicals could screen myosmine against a large panel of imine reductases to identify the imine reductases having high “substrate specificity” for myosmine and “increased stereoselectivity” toward (S)-nornicotine. Winkler ¶ 173.

Moody disclosed an enzyme screen of imine reductases for a customer-provided imine substrate, which “result[ed] in the identification of an active and selective IRED catalyst.” Ex. 1004 at 12-13. The imine reductase identified from the enzyme screen converted the customer-provided imine substrate to the (S)-amine

product with an enantiomeric excess of 100%—all of the amine obtained was the (S)-enantiomer:



Id. at Fig. 3; Winkler ¶ 174.

A POSITA would have had a reasonable expectation of success that a screen of imine reductases would identify an imine reductase that would reduce myosmine to (S)-nornicotine with an enantiomeric excess of at least 90%, as predicted and advertised by Enzymicals and demonstrated in Moody. Winkler ¶ 175.

A POSITA would have understood that the enantiomeric excess of (S)-nicotine would depend on the enantiomeric excess from the reduction of myosmine to (S)-nornicotine. Winkler ¶ 176. A POSITA would have known that the N-

methylation of nornicotine would not change the chirality of the molecule. *Id.* Thus, the proportion of (S)-nicotine to (R)-nicotine following methylation would be the same as the proportion of (S)-nornicotine to (R)-nornicotine. *Id.* Because a POSITA would have had a reasonable expectation of success that the reduction of myosmine to (S)-nornicotine using an imine reductase would result in an enantiomeric excess of (S)-nornicotine of at least 90% (and as high as 100%), the POSITA would expect to achieve (S)-nicotine in the same excess—at least 90%. *Id.*

10. Claim 10

- a. **“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.”**

The preamble (“A process for producing a pharmaceutical composition”) is not limiting. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.1. Thus, the step of “forming (S)-nicotine according to the process of claim 1” is also obvious. Winkler ¶ 178. Divi disclosed including (S)-nicotine in a pharmaceutical composition with one or more pharmaceutical excipients. *Id.* ¶ 179. Divi disclosed that “[t]reating nicotine dependence requires therapeutic use of nicotine. Nicotine is given to patients through dermal patches, gums, creams, lozenges, nasal sprays or electronic cigarettes to wean them away from smoking.” Ex. 1003 at 1:32-36. Here, Divi expressly refers to (S)-nicotine. *Id.* at 1:21-22;

Winkler ¶ 179. A POSITA would have understood that the compositions in Divi, such as gum, cream, and lozenges, include pharmaceutical excipients. Winkler ¶ 179; Ex. 1018 (defining excipient as “[a]ny inert substance combined with an active drug for preparing an agreeable or convenient dosage form”). Here, (S)-nicotine is the active drug, and things like gum base, flavors, emollients, emulsifiers, preservatives, and solvents are inert substances to prepare an agreeable or convenient dosage form. *Id.*

11. Claim 11

a. “The process of claim 10,”

Claim 10 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.10.

b. “wherein the pharmaceutical composition is a transdermal patch, a lozenge, or an inhalation formulation.”

Divi disclosed (S)-nicotine in a pharmaceutical composition in each of a transdermal patch, a lozenge, and an inhalation formulation. Ex. 1003 at 1:32-36; Winkler ¶ 183.

12. Claim 12

a. “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.”

The preamble (“A process for producing a formulation for an electronic cigarette device”) is not limiting. Claim 1 is obvious by Divi, Moody, and

Enzymicals. *See* Section IX.A.1. Thus, the step of “forming (S)-nicotine according to the process of claim 1” is also obvious. Winkler ¶ 185. Divi disclosed including (S)-nicotine in a solvent with one or more additives. Divi disclosed that “[n]icotine is given to patients through dermal patches, gums, creams, lozenges, nasal sprays or electronic cigarettes to wean them away from smoking.” Ex. 1003 at 1:32-36. Here, Divi expressly refers to (S)-nicotine. *Id.* at 1:21-22; Winkler ¶ 186. A POSITA would have known that electronic cigarette formulations of (S)-nicotine necessarily include “the (S)-nicotine in a solvent with one or more additives.” Winkler ¶ 187; Ex. 1008 at 1:23-26 (disclosing (S)-nicotine in solution with flavors in vaporizers).

13. Claim 13

a. “The process of claim 2,”

Claim 2 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.2.

b. “wherein the reductant is formic acid, sodium cyanoborohydride, or palladium/hydrogen.”

Divi disclosed the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Formic acid is the reductant. Winkler ¶ 190.

14. Claim 14

a. “The process of claim 2,”

Claim 2 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.2.

b. “wherein the reductant is formic acid.”

Divi disclosed the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Formic acid is the reductant. Winkler ¶ 193.

B. Claims 6 and 12 Are Obvious by Divi, Moody, Enzymicals, and Arnold.

1. Claim 6

a. “The process of claim 1,”

Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.1.

b. “wherein the process is carried out without isolation of the (S)-nornicotine formed from step (i).”

A POSITA would have been motivated to reduce unnecessary isolation steps in any reaction sequence involving more than one chemical step. Winkler ¶ 197. In Divi’s nicotine synthesis, a POSITA would have recognized that there are two distinct chemical steps: (1) the reduction of myosmine to nornicotine, and (2) the reductive methylation of nornicotine to nicotine. *Id.* A POSITA would have been motivated to avoid isolating the intermediate nornicotine and isolate only the nicotine at the end if it could lead to comparable purity of the final product or an enhanced overall yield. *Id.* A POSITA would have been motivated to avoid that isolation step because it could have reduced costs and there would be a reasonable expectation that the overall yield would be higher. *Id.* It would have been obvious to a POSITA to try to prepare nicotine using the enzyme-catalyzed reaction without isolating the nornicotine intermediate but simply proceeding to the reductive

methylation step to reduce costs and solvent waste, and potentially improve the yield. *Id.*

The synthesis of nicotine from the reduction of myosmine to form nornicotine and the methylation of nornicotine to form nicotine without isolating the nornicotine from the reaction mixture was known in the art. *Id.* ¶ 198. Arnold disclosed synthesizing nicotine via the formation of myosmine, the reduction of myosmine to form (R,S)-nornicotine, and the methylation of the (R,S)-nornicotine using formaldehyde and formic acid to form (R,S)-nicotine. Ex. 1008 at 2:28-3:10; Winkler ¶ 198.

Examples 4 and 5 of Arnold disclose forming (R,S)-nicotine without isolating the (R,S)-nornicotine formed from myosmine. Winkler ¶ 199 A POSITA would have known that Examples 4 and 5 teach the formation of myosmine (Ex. 1008 at 7:33-40 and 7:56-65), the reduction of myosmine to (R,S)-nornicotine (*id.* at 7:40-43 and 7:65-8:3), and the N-methylation of the (R,S)-nornicotine to form (R,S)-nicotine (*id.* at 7:43-52 and 8:4-9). Winkler ¶ 199. A POSITA would have understood that Examples 4-5 of Arnold are conducted without isolating the (R,S)-nornicotine from the reaction mixture because other examples specify when and where an isolation step occurs. *Id.*; compare Ex. 1008 at 6:51-7:8 (Example 2) with *id.* at 7:33-52 (Example 4) and 7:56-8:9 (Example 5).

A POSITA would have been motivated to apply the teachings of Arnold because Arnold is in the field of nicotine synthesis, teaches a reaction sequence that reduces myosmine to form nornicotine and methylates nornicotine to form nicotine, and discusses appropriate reaction conditions for such a synthesis of nicotine. Winkler ¶ 200. A POSITA would have had a reasonable expectation of success in applying Arnold's reaction conditions because the Arnold reaction of reducing myosmine to form nornicotine and methylating nornicotine to form nicotine is the same reaction sequence disclosed in Divi. *Id.*

2. Claim 12

- a. **“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.”**

The preamble (“A process for producing a formulation for an electronic cigarette device”) is not limiting. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.1. Thus, the step of “forming (S)-nicotine according to the process of claim 1” is also obvious. Winkler ¶ 202. Divi disclosed including (S)-nicotine in a solvent with one or more additives for an electronic cigarette formation: “Nicotine is given to patients through dermal patches, gums, creams, lozenges, nasal sprays or electronic cigarettes to wean them away from smoking.” Ex. 1003 at 1:32-36. A POSITA would have known, and Arnold discloses, that

electronic cigarette formulations of (S)-nicotine included “the (S)-nicotine in a solvent with one or more additives.” Winkler ¶ 204; Ex. 1008 at 1:23-26 (disclosing (S)-nicotine in solution with flavors in vaporizers).

C. Claims 7-8 Are Obvious By Divi, Moody, Enzymicals, and Sheldon

1. Claim 7

a. “The process of claim 1,”

Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section IX.A.1.

b. “wherein in step (i) the (S)-nornicotine is formed as part of an aqueous solution, and wherein step (ii) comprises methylating the (S)-nornicotine contained within the aqueous solution.”

Sheldon disclosed a synthesis of (S)-nicotine using an imine reductase enzyme. Ex. 1013 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 POSITA 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. Winkler ¶ 209. A POSITA 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. *Id.* A POSITA 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. *Id.* ¶ 210. The '962 Patent admits both that the “field of the invention” is “a process for synthetically producing (S)-nicotine” and that a POSITA was “familiar” with imine reductases. Ex. 1001 at 1:5-7 and 3:31-41. A POSITA 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. Winkler ¶ 210.

Further, Divi disclosed that the methylation of nornicotine to form nicotine was conducted while the nornicotine was present in an aqueous solution. Ex. 1003 at 5:26-29.

2. Claim 8

a. “The process according to claim 7,”

Claim 7 is obvious by Divi, Moody, Enzymicals, and Sheldon. *See* Section IX.C.1.

- b. “wherein in step (ii) the (S)-nornicotine is reductively methylated using formaldehyde introduced as part of an aqueous solution.”

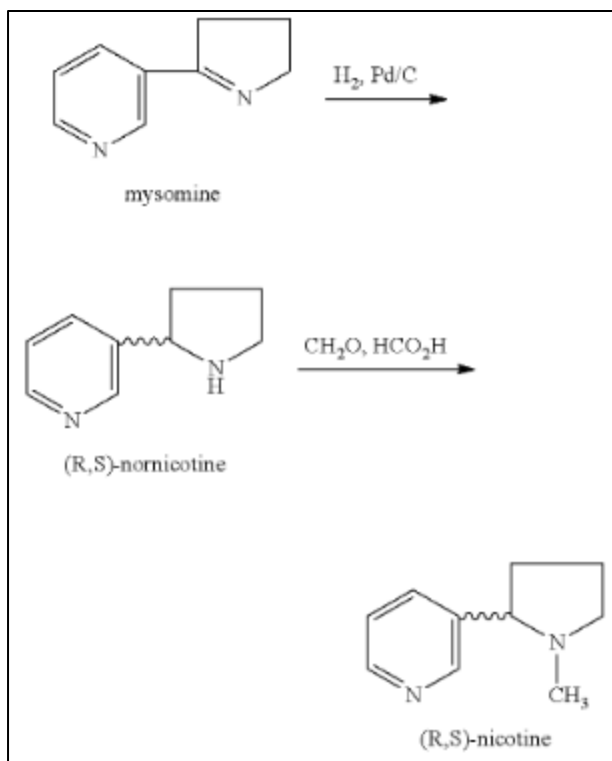
Divi disclosed that the methylation of nornicotine to form nicotine was conducted by introducing formaldehyde as part of an aqueous solution. Ex. 1003 at 5:26-29.

D. Claims 1-14 Are Obvious by Divi, Moody, Velikogne, and Wetzl

1. Claim 1

- a. “A process for making (S)-nicotine comprising the steps of:”

Divi disclosed that syntheses of (S)-nicotine were known in the art, and that using chiral reagents and chiral catalysts were also known but were expensive. Ex. 1003 at 1:64-2:3. Divi’s synthesis of (R,S)-nicotine is depicted as follows:



Id. at 2:35-3:15. Divi disclosed that the synthesized (R,S)-nicotine is followed by a resolution step to separate (S)-nicotine from the “unwanted” (R)-nicotine, which “provides an attractive and economical method for the production of synthetic (S)-nicotine.” *Id.* at 2:8-11, 2:21-25. Accordingly, a POSITA would have looked at the reaction disclosed in Divi as a logical starting point, while recognizing that avoiding a resolution step would further improve the reaction. Winkler ¶¶ 218-219.

b. “(i) reducing myosmine with an enzyme with imine reductase activity to form (S)-nornicotine; and”

- i. Divi disclosed that the reduction of myosmine by reducing the imine bond yields nornicotine.*

Divi teaches that “[t]he most convenient way to prepare (R,S)-nicotine is through myosmine (Scheme 3). Myosmine is hydrogenated to (R,S)-nornicotine, which on N-methylation gives (R,S)-nicotine.” Ex. 1003 at 3:16-19; *see also id.* at 2:8-11, 2:21-25, 2:35-3:16, 4:8-11. Myosmine is reduced when it is “hydrogenated” to nornicotine. Winkler ¶ 221. A POSITA would have recognized that Divi disclosed an achiral reaction and, absent a chiral reagent (such as an enzyme), the reaction results in a racemic product unless resolved. *Id.*

A POSITA would have recognized that the reduction of myosmine to nornicotine in Divi proceeded by reducing the C=N imine bond of myosmine, converting it to the corresponding amine, nornicotine. *Id.* ¶ 222.

- ii. Moody disclosed that enzyme-catalyzed reactions selectively form chiral products and were well-*

established in industrial applications; Wetzl and Velikogne disclosed that enzyme-catalyzed reactions yielded asymmetric, chiral products.

Moody disclosed that the use of biocatalysts in modern chemical production is well-accepted. “The paradigm shift for the acceptance of biocatalysts is persistent and at the forefront of research within the fine chemicals and pharmaceuticals industries.” Ex. 1004 at 12. Moody disclosed that “[b]ioprocessing is now the norm rather than the exception at Almac.” *Id.*

Moody disclosed that “[o]ff-the-shelf and specifically designed enzymes can be accessed within days and weeks respectively. These timelines allow synthetic chemists to include enzyme processing in their synthetic toolbox.” *Id.* According to Moody, not only was biocatalysis accepted in synthetic chemistry, but “[b]iocatalysis has become the workhorse of the chemists’ toolbox for chiral chemistry.” *Id.* Moody praised incorporating enzyme-catalysts into synthetic reaction pathways, stating that “[e]nzyme processes are now at the epicentre of key drivers in process design, scale-up and economics.” *Id.*

Moody recognized that “[t]he synthetic power of enzymes is their ***unequalled selectivity*** for the chemical reactions they catalyse.”

Similarly, Wetzl and Velikogne each disclosed that biocatalytic reactions yielded asymmetric, chiral products. Ex. 1009 at 1749; Ex. 1011 at 3236.

Accordingly, a POSITA would have known that enzymes were effective in the industrial production of chiral compounds, were available commercially, and were the “workhorse” in the “toolbox for chiral chemistry.” Winkler ¶ 227.

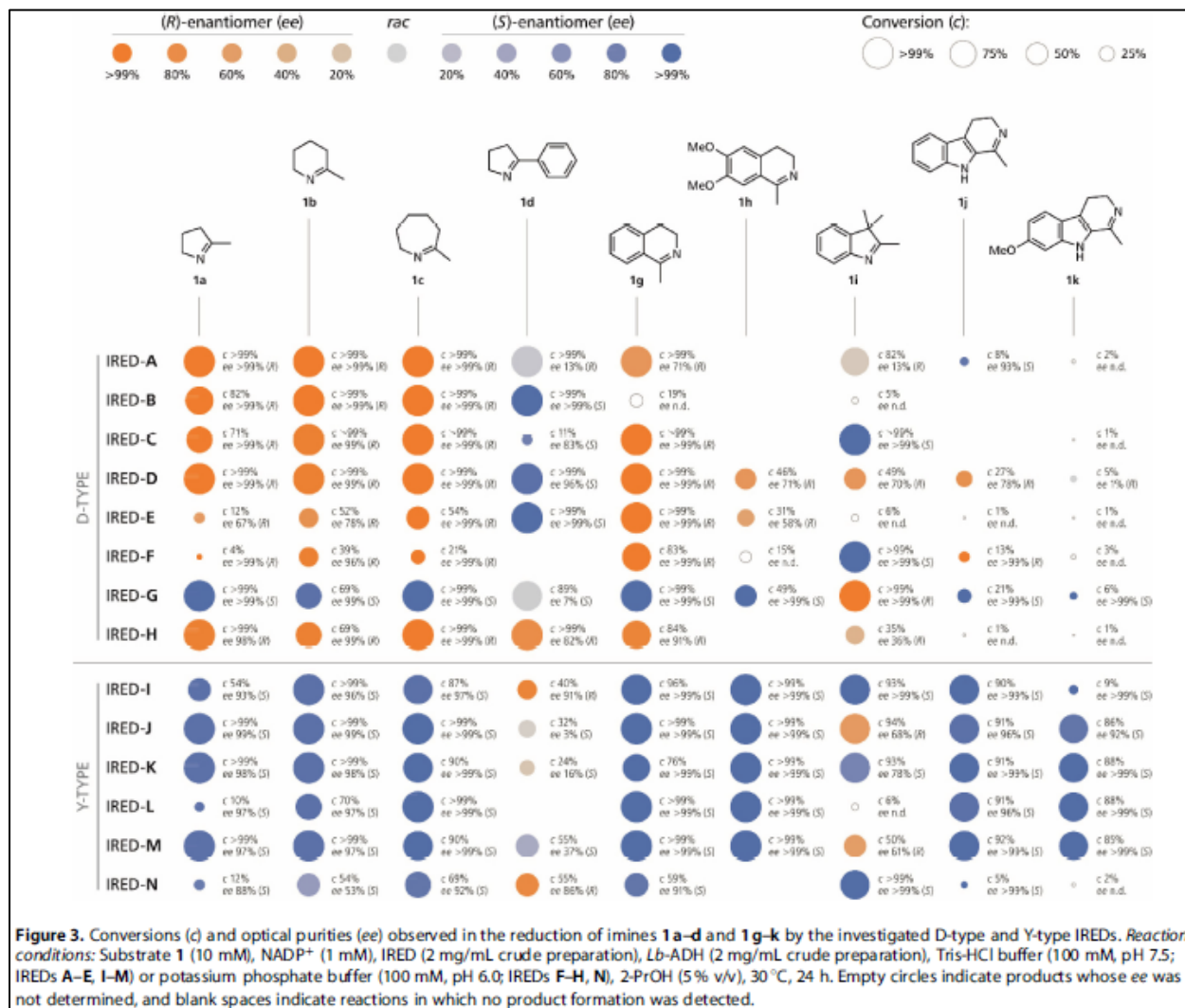
iii. Moody disclosed that imine reductases reduce imines to chiral amines asymmetrically. Velikogne and Wetzl disclosed that imine reductases reduce a broad spectrum of imines to chiral amines asymmetrically.

Moody disclosed that enzymes were the “workhorse of the chemists’ toolbox for chiral chemistry” and that imine reductases enabled “the enantioselective reduction of the imine.” Ex. 1004 at 12 and Fig. 3.

Wetzl disclosed that imine reductases reduced imines to chiral amines across “a broad range of substrates.” Ex. 1009 at 1749. Wetzl disclosed that imine reductases had “utility ... for the asymmetric reduction of a broad panel of cyclic imines producing chiral secondary and tertiary amines.” *Id.* Wetzl screened about 20 imine reductases and found that the “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%.” *Id.* at 1750.

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.” Ex. 1011 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 POSITA would have understood from Velikogne's imine reductase screen that most imine reductases reduce a wide range of imines. Winkler ¶ 231. A POSITA would have understood that, on the relatively small imine reductase screen, every

single screened imine was reduced by at least two imine reductases to the corresponding (S)-amine with at least 99% excess. *Id.*

A POSITA would have known that imine reductases reduced a broad spectrum of imines to chiral amines asymmetrically. *Id.* ¶ 232.

iv. Moody disclosed the commercial availability of custom enzyme screens for a customer's substrates.

Moody described that “[o]ff-the-shelf and specifically designed enzymes can be accessed within days and weeks respectively” and that “enzyme processing” was a part of chemists’ “synthetic toolbox.” Ex. 1004 at 12. Moody disclosed that “Almac can rapidly access specifically built enzyme libraries for specific customer substrates.” *Id.* Moody further stated that “[u]sing this technology, [Almac] can take customer substrates and by performing complex dockings studies can build tailored catalysts for the customer substrate.” *Id.* And Moody disclosed that Almac could build tailored imine reductases designed to reduce a specific customer imine substrate. *Id.*

Accordingly, a POSITA would have known that commercial services were available to screen a given substrate against a panel of different imine reductases to discover the optimal imine reductase for the substrate. Winkler ¶ 234. A POSITA would have understood that these services could specifically design imine reductases for activity against a given imine substrate and had done so successfully. *Id.*

- v. *A POSITA would have been motivated to screen imine reductases using Almac to find an imine reductase catalyzing the asymmetric reduction of myosmine to (S)-nornicotine.*

A POSITA would have recognized that the Divi reaction provided an opportunity for a stereoselective reaction where myosmine is reduced to nornicotine. *Id.* ¶ 235. A POSITA would have understood from the nicotine reaction pathway in Divi that the conversion of myosmine, an imine, to nornicotine, the corresponding amine, requires reducing the imine bond of myosmine. *Id.* The '962 Patent admits that “[t]he skilled person is familiar with” imine reductases. Ex. 1001 at 3:32-41. A POSITA, familiar with imine reductases, would have known that imine reductases reduce imines to their corresponding amines asymmetrically. Winkler ¶ 236. As such, a POSITA would have been motivated to use an imine reductase to catalyze the reduction of myosmine to (S)-nornicotine asymmetrically. *Id.*

Moody disclosed that “[b]iocatalysis has become the workhorse of the chemists’ toolbox for chiral chemistry” and that “[t]he synthetic power of enzymes is their *unequalled selectivity* for the chemical reactions they catalyse.” Ex. 1004 at 12.

The '962 Patent admits that a POSITA would have known about commercially available sources of biocatalysts, including Almac Group. Ex. 1001 at 4:7-14 (disclosing that an imine reductase disclosed to reduce myosmine to (S)-nornicotine was “available from Almac Group”). A POSITA would have known

from Moody that imine reductases were widely available commercially. Winkler ¶ 238. And a POSITA would have been motivated by the disclosures of Moody to use an imine reductase to reduce myosmine to (S)-nornicotine. *Id.* A POSITA would have known from Moody that Almac 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.” Ex. 1004 at 12; Winkler ¶ 238.

Disclosures from Velikogne and Wetzl would have further motivated a POSITA to catalyze the reduction of myosmine to (S)-nornicotine using an imine reductase. Winkler ¶ 239. 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. Ex. 1009 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 “IRED 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 POSITA to use an imine reductase in the Divi reaction to reduce myosmine to (S)-nornicotine. Winkler ¶ 239.

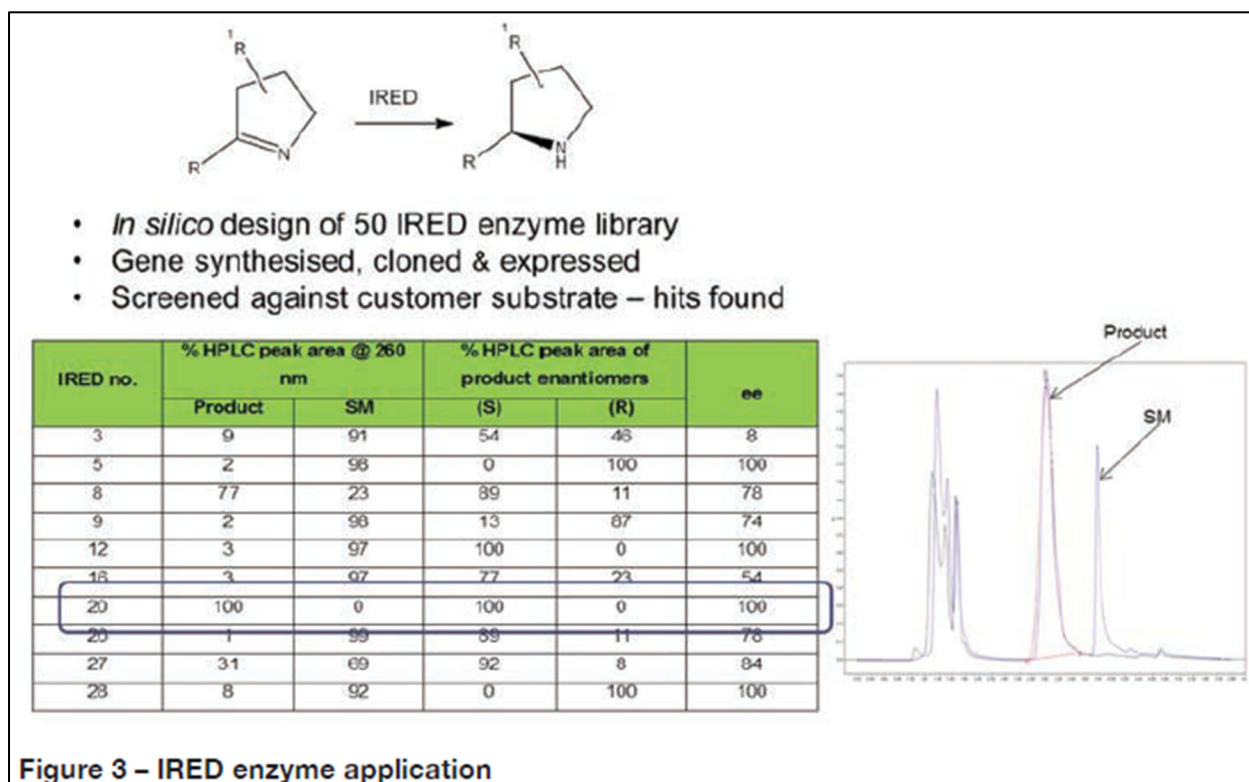
A POSITA, knowing that the Divi reaction could be made stereoselective where myosmine is reduced to nornicotine, would have been motivated to use an imine reductase to reduce myosmine to (S)-nornicotine asymmetrically to improve yield and simplify, if not eliminate, a separation step. *Id.* ¶ 240. A POSITA would have been motivated to use Almac to identify an imine reductase capable of reducing myosmine to (S)-nornicotine and use that imine reductase to catalyze the asymmetric reduction of myosmine to (S)-nornicotine. *Id.*

- vi. *A POSITA would have had a reasonable expectation of success that a screen would identify an imine reductase that would asymmetrically reduce myosmine to (S)-nornicotine.*

A POSITA would have had a reasonable expectation of success that a screen would identify an imine reductase to reduce myosmine to (S)-nornicotine asymmetrically. *Id.* ¶ 241. An enzyme screen was a standard technique to determine whether an enzyme had activity on a given substrate before the '962 Patent. *Id.*

A POSITA would have 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 discover an imine reductase “for the enantioselective reduction of the imine.” Ex. 1004 at 12; Winkler ¶ 242. A POSITA would have had a reasonable expectation of success that Almac’s enzyme screen would identify 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 target imine to the (S)-amine with 100% ee. Winkler ¶ 242; Ex. 1004 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:



Therefore, a POSITA would have had a reasonable expectation of success that an enzyme screen would reveal an imine reductase that reduced myosmine to (S)-nornicotine because Moody described how Almac designed and executed an imine reductase screen to find an imine reductase that reduced a customer-provided imine substrate with high activity and high selectivity. Winkler ¶ 243. As Moody disclosed

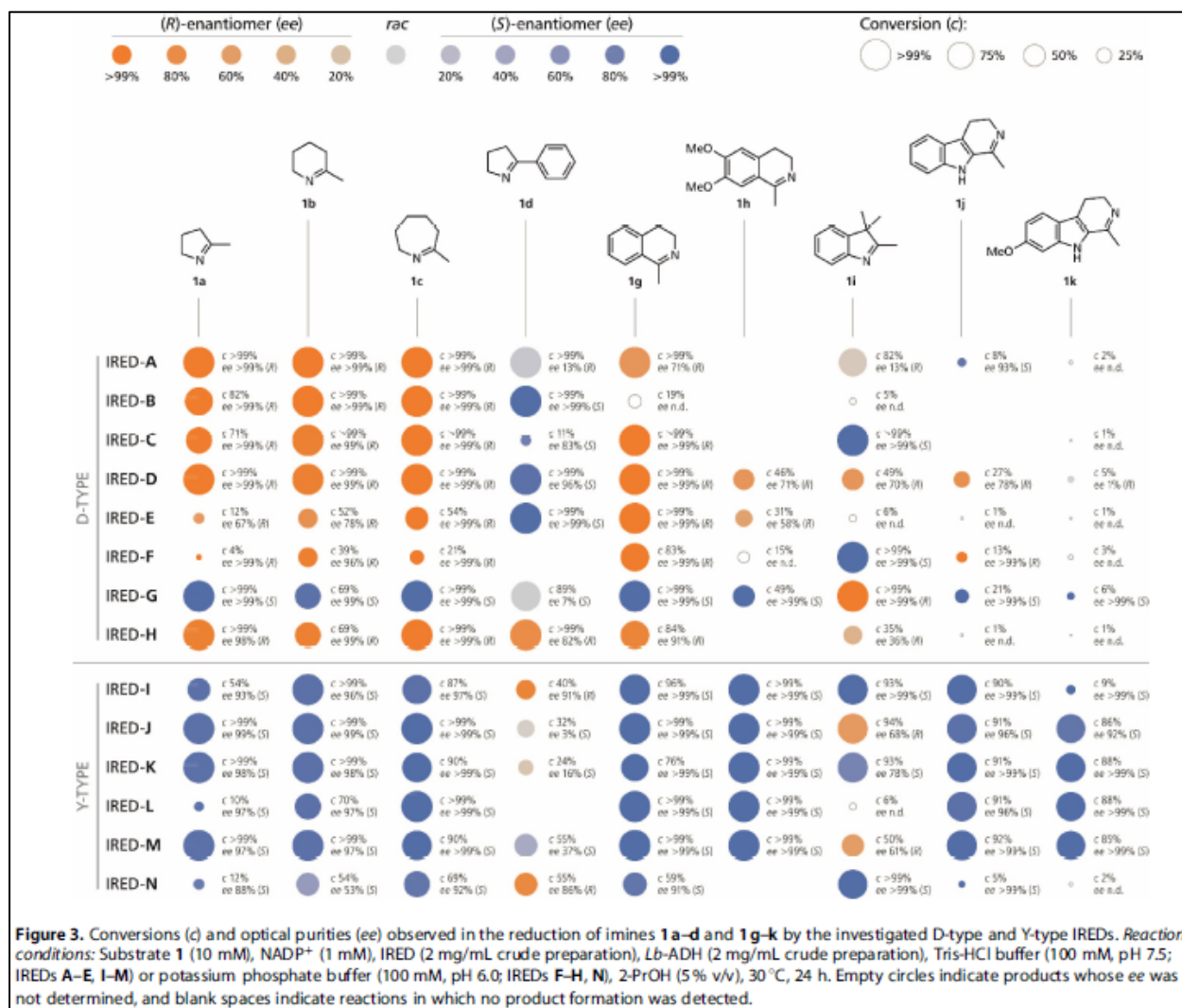
a specific experience in identifying an imine reductase that reduced an imine provided by a customer to the target (S)-amine with 100% ee, a POSITA would have had a reasonable expectation of success that Almac would successfully identify an imine reductase capable of reducing myosmine to (S)-nornicotine asymmetrically. *Id.*

Velikogne demonstrated that by screening a limited, diverse set of imine reductases, a POSITA would likely find an imine reductase that would selectively reduce an imine to the (S)-amine. *Id.* ¶ 244. Velikogne described how a POSITA could create and run a custom enzyme screen to test the activity of numerous imine reductases against an imine substrate. *Id.*

Wetzel 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%.” *Id.* ¶ 245. Wetzel disclosed and characterized (IR_11 in Wetzel) one of the exact imine reductases (IRED_A in the ’962 Patent) that the ’962 Patent states is a working example of an imine reductase capable of reducing myosmine to (S)-nornicotine. A POSITA replicating Wetzel’s *exact panel* of imine reductases would have discovered a working imine reductase.

A POSITA would have known that imine reductases reduced prochiral imines like myosmine to chiral amines across a broad range of substrates. Ex. 1009 at 1749;

Ex. 1011 at 3240; Winkler ¶ 246. 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. *Id.* ¶ 247. A POSITA following Velikogne's teachings would have had a reasonable expectation of success of finding at least one enzyme reducing myosmine to (S)-nornicotine selectively. *Id.*

Therefore, a POSITA would have had a reasonable expectation of success that an enzyme screen would identify an appropriate imine reductase to reduce myosmine to (S)-nornicotine asymmetrically. *Id.* ¶ 248.

c. “(ii) methylating the (S)-nornicotine formed from step (i) to form (S)-nicotine;”

Divi disclosed methylating (R,S)-nornicotine to form (R,S)-nicotine. Ex. 1003 at 3:16-19, 4:8-11, 6:42-45; Winkler ¶ 249. A POSITA would have understood that the N-methylation step in Divi does not impart or change the chirality of the molecule. Winkler ¶ 250. The application of Divi’s N-methylation step to (S)-nornicotine would generate (S)-nicotine, in analogy to Divi’s conversion of (R,S)-nornicotine to (R,S)-nicotine. *Id.* A POSITA would have known that the chirality of nicotine is determined by the chirality of the nornicotine entering the N-methylation step. *Id.*

d. “wherein step (ii) is carried out by way of reductive methylation; and”

Divi disclosed methylating nornicotine to form nicotine by reductive methylation. *See* Section IX.A.1.c. The methylation disclosed in Divi is a reductive methylation using formaldehyde and formic acid. Winkler ¶ 251; Ex. 1003 at 4:8-11.

- e. **“wherein in step (ii) the (S)-nornicotine is reductively methylated, using formaldehyde or a formaldehyde-based compound in the presence of a reductant.”**

Divi disclosed reductively methylating nornicotine using formaldehyde in the presence of a reductant. *See* Section IX.A.1.d; Winkler ¶ 252. Divi disclosed methylating nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Formic acid is the reductant. Winkler ¶ 252.

2. Claim 2

- a. **“The process of claim 1”**

Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.1.

- b. **“wherein formaldehyde is introduced as part of an aqueous solution.”**

Divi disclosed introducing formaldehyde as part of an aqueous solution. Winkler ¶ 255. Divi disclosed: “To a solution of nornicotine (50 g 0.338 mol) in 100 ml water a mixture of 37% formaldehyde (49.7g, 1.656 mol) and 85% formic acid (37.26g 0.81 moles) was added and stirred at 85oC for 20 hrs.” *Id.* at 5:26-29; *id.* at 4:8-11. A POSITA would have understood that when Divi added the formaldehyde/formic acid, it was introduced as an aqueous solution. Winkler ¶ 255.

3. Claim 3

a. “The process of claim 1”

Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.1.

b. “wherein the formaldehyde-based compound is a dimer of formaldehyde, a polymer of formaldehyde, or an acetal of formaldehyde.”

Divi disclosed that “the formaldehyde-based compound is a dimer of formaldehyde, a polymer of formaldehyde, or an acetal of formaldehyde.” Winkler ¶ 258. A “formaldehyde-based compound” is any compound capable of generating formaldehyde in-situ, and the '962 Patent states that a formaldehyde-based compound is “preferably” a polymer of formaldehyde. Ex. 1001 at 5:58-6:14. A POSITA would have known that formaldehyde naturally forms polymers in aqueous solution. Winkler ¶ 258; Ex. 1016 at 401; Ex. 1017. Divi’s disclosure of formaldehyde solution thus inherently discloses a polymer of formaldehyde. Winkler ¶ 258.

4. Claim 4

a. “The process of claim 1,”

Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.1.

- b. “wherein the reductant is formic acid, sodium cyanoborohydride, or palladium/hydrogen.”**

Divi disclosed the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Formic acid is the reductant. Winkler ¶ 261.

5. Claim 5

- a. “The process of claim 1,”**

Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.1.

- b. “wherein the reductant is formic acid.”**

Divi disclosed the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Formic acid is the reductant. Winkler ¶ 264.

6. Claim 6

- a. “The process of claim 1,”**

Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.1.

- b. “wherein the process is carried out without isolation of the (S)-nornicotine formed from step (i).”**

A POSITA would have been motivated to reduce unnecessary isolation steps in any reaction sequence involving more than one chemical step. Winkler ¶ 267. In Divi’s nicotine synthesis, a POSITA would have recognized that there are two distinct chemical steps: (1) the reduction of myosmine to nornicotine, and (2) the reductive methylation of nornicotine to nicotine. *Id.* A POSITA would have been

motivated to avoid isolating nornicotine and isolate only the nicotine at the end of the sequence if it could lead to comparable purity of the final product or an enhanced overall yield. *Id.* A POSITA would have been motivated to avoid that isolation step because it could have reduced costs and there would be a reasonable expectation that the overall yield would be higher. *Id.* It would have been obvious to a POSITA to try to prepare nicotine using the enzyme-catalyzed reaction without isolating the nornicotine intermediate but simply to proceed to the reductive methylation step to reduce costs and solvent waste, and potentially improve the yield and efficiency of the process. *Id.*

Additionally, there are only two ways to run the reaction sequence from myosmine to nicotine: with isolation of the nornicotine, and without isolation of nornicotine. *Id.* ¶ 268. It would have been obvious to try the reaction without isolation of the (S)-nornicotine from step (i), as there were only two options and successfully completing the reaction without isolating the (S)-nornicotine would reduce costs and solvent waste, and potentially improve the yield and efficiency of the process. *Id.*

7. Claim 7

a. “The process of claim 1,”

Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.1.

- b. “wherein in step (i) the (S)-nornicotine is formed as part of an aqueous solution, and wherein step (ii) comprises methylating the (S)-nornicotine contained within the aqueous solution.”**

It would have been obvious to a POSITA that when using a biocatalyst to reduce myosmine to nornicotine, the reduction of myosmine would take place in aqueous solution because enzymes naturally function in aqueous solutions. Winkler ¶ 271. Velikogne described conditions of enzymatic reductions when screening for imine reductase activity. Ex. 1011 at 3243-3244. Velikogne disclosed a substrate stock solution of imine substrate in 2-propanol and a second, aqueous stock solution containing alcohol dehydrogenase, enzyme cofactor NADP⁺, and buffer. *Id.*; Winkler ¶ 271. Both disclosed buffers are aqueous solutions that maintain a steady pH. Winkler ¶ 271. The imine reductase screens took place by adding 25 microliters of substrate stock and 475 microliters of the second aqueous stock to a tube containing the imine reductase. Ex. 1011 at 3244. Velikogne’s imine reductase reductions thus took place in an aqueous solution. Winkler ¶ 271. Accordingly, a POSITA would run the biocatalyzed reaction of myosmine to (S)-nornicotine in aqueous solution so that the imine reductase functioned optimally. *Id.*

Further, Divi disclosed that the methylation of nornicotine to form nicotine was conducted while the nornicotine was present in an aqueous solution. Ex. 1003 at 5:26-29.

8. Claim 8

a. “The process according to claim 7,”

Claim 7 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.7.

b. “wherein in step (ii) the (S)-nornicotine is reductively methylated using formaldehyde introduced as part of an aqueous solution.”

Divi disclosed that the methylation of nornicotine to form nicotine was conducted by introducing formaldehyde as part of an aqueous solution. Ex. 1003 at 5:26-29.

9. Claim 9

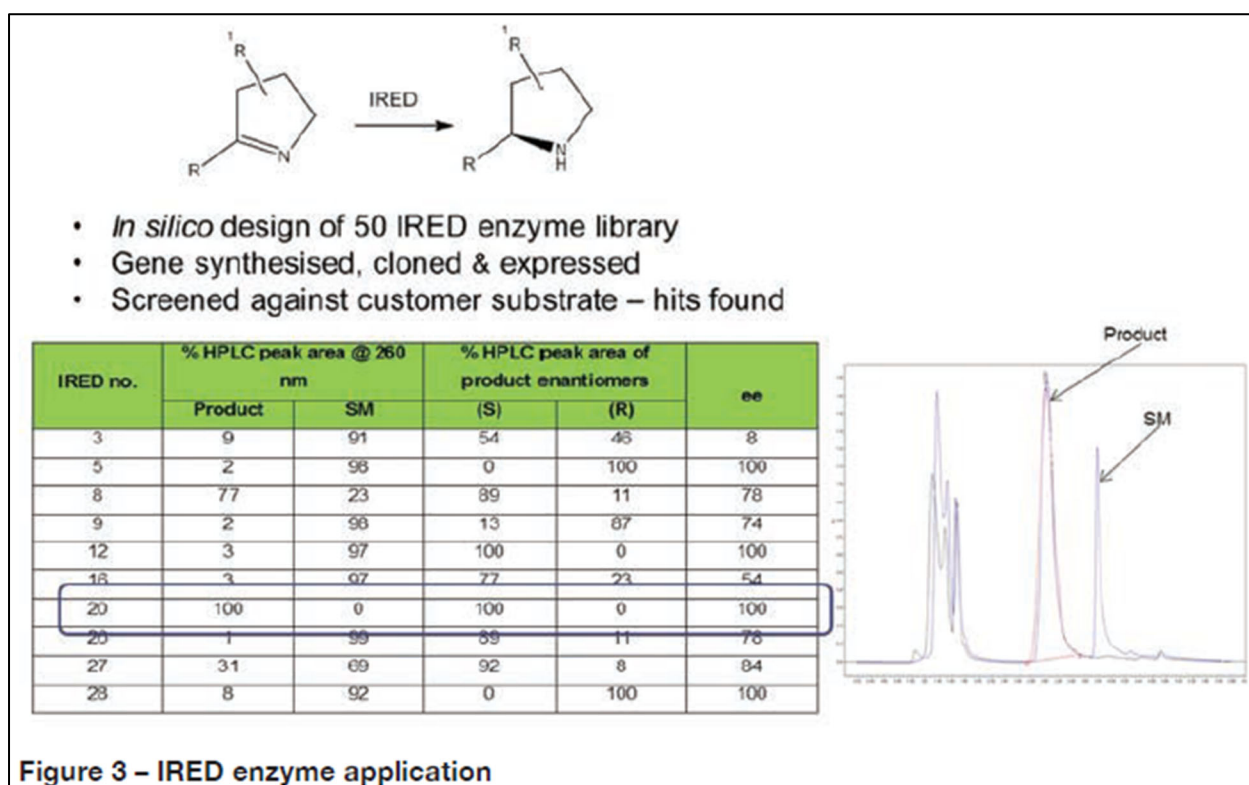
a. “The process of claim 1,”

Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.1.

b. “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%.”

As presented in Section IX.D.1., a POSITA would have been motivated to improve the myosmine-nornicotine-nicotine reaction disclosed in Divi by using an imine reductase biocatalyst as taught by Moody, Velikogne, and Wetzl and would have had a reasonable expectation of success in doing so. Winkler ¶ 278.

Moody disclosed an enzyme screen of imine reductases for a customer-provided imine substrate, which “result[ed] in the identification of an active and selective IRED catalyst.” Ex. 1004 at 12-13. The imine reductase identified from the enzyme screen converted the customer-provided imine substrate to the (S)-amine product with an enantiomeric excess of 100%—all of the amine obtained was the (S)-enantiomer:

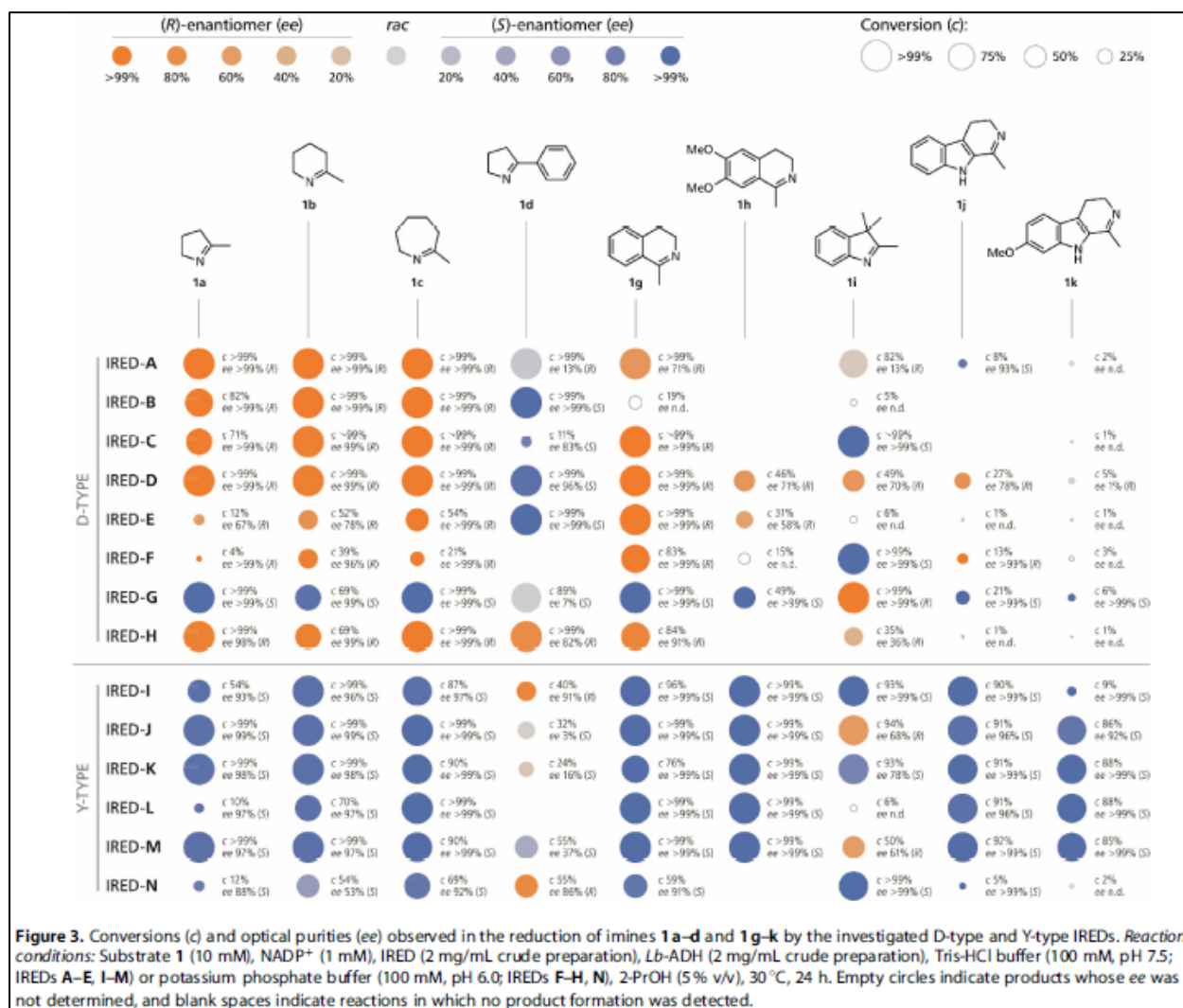


Winkler ¶ 279.

Wetzel screened imine reductases and found that the “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%.” Ex. 1009 at 1750. A POSITA would have had a reasonable expectation of success that an imine reductase would reduce myosmine to (S)-nornicotine with an enantiomeric excess of at least 90%. Winkler ¶ 280.

Velikogne screened numerous imine reductases against numerous substrates. Ex. 1011 at 3240. Velikogne’s Figure 3 illustrates the activities and stereoselectivities of the 14 imine reductases across the 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. Winkler ¶ 282. A POSITA following Velikogne would have had a reasonable expectation of success of finding at least one enzyme reducing myosmine to (S)-nornicotine selectively. *Id.*

A POSITA would have understood that the enantiomeric excess of (S)-nicotine would depend on the enantiomeric excess resulting from the reduction of myosmine to (S)-nornicotine, as the N-methylation of nornicotine would not change the chirality of the molecule. *Id.* ¶ 283. Thus, the proportion of (S)-nicotine to (R)-nicotine following methylation would be the same as the proportion of (S)-nornicotine to (R)-nornicotine. *Id.* Because a POSITA would have had a reasonable expectation of success that reducing myosmine to (S)-nornicotine using an imine reductase would result in an enantiomeric excess of (S)-nornicotine of at least 90% (and as high as 100%), the POSITA would expect to achieve (S)-nicotine in the same enantiomeric excess—at least 90%. *Id.*

10. Claim 10

- a. “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.”**

The preamble (“A process for producing a pharmaceutical composition”) is not limiting. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.1. Thus, the step of “forming (S)-nicotine according to the process of claim 1” is also obvious. Winkler ¶ 285. Divi disclosed including (S)-nicotine in a pharmaceutical composition together with one or more pharmaceutical excipients. *Id.* ¶ 286. Divi disclosed that “[t]reating nicotine dependence requires therapeutic use of nicotine. Nicotine is given to patients through dermal patches, gums, creams, lozenges, nasal sprays or electronic cigarettes to wean them away from smoking.” Ex. 1003 at 1:32-36. Here, Divi expressly refers to (S)-nicotine. *Id.* at 1:21-22. A POSITA would have understood that the pharmaceutical compositions in Divi, such as gum, cream, and lozenges, inherently include pharmaceutical excipients. Winkler ¶ 286; Ex. 1018. Here, (S)-nicotine is the active drug, and things like gum base, flavors, emollients, emulsifiers, preservatives, solvents, and the like are examples of inert substances to prepare an agreeable or convenient dosage form.

11. Claim 11

a. “The process of claim 10,”

Claim 10 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.10.

b. “wherein the pharmaceutical composition is a transdermal patch, a lozenge, or an inhalation formulation.”

Divi disclosed (S)-nicotine in a pharmaceutical composition in each of a transdermal patch, a lozenge, and an inhalation formulation. Ex. 1003 at 1:32-36; Winkler ¶ 290.

12. Claim 12

a. “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.”

The preamble (“A process for producing a formulation for an electronic cigarette device”) is not limiting. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.1. Thus, the step of “forming (S)-nicotine according to the process of claim 1” is also obvious. Winkler ¶ 292. Divi disclosed including (S)-nicotine in a solvent with one or more additives. Divi disclosed that “[n]icotine is given to patients through dermal patches, gums, creams, lozenges, nasal sprays or electronic cigarettes to wean them away from smoking.” Ex. 1003 at 1:32-36. Here, Divi expressly refers to (S)-nicotine. *Id.* at 1:21-22; Winkler ¶ 293. A POSITA

would have known that the electronic cigarette formulations of (S)-nicotine necessarily include “the (S)-nicotine in a solvent with one or more additives.” Winkler ¶ 294; Ex. 1008 at 1:23-26 (disclosing (S)-nicotine in solution with flavors in vaporizers).

13. Claim 13

a. “The process of claim 2,”

Claim 2 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.2.

b. “wherein the reductant is formic acid, sodium cyanoborohydride, or palladium/hydrogen.”

Divi disclosed the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Formic acid is the reductant. Winkler ¶ 297.

14. Claim 14

a. “The process of claim 2,”

Claim 2 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.2.

b. “wherein the reductant is formic acid.”

Divi disclosed the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Formic acid is the reductant. Winkler ¶ 300.

E. Claims 6 and 12 Are Obvious by Divi, Moody, Velikogne, Wetzl, and Arnold.

1. Claim 6

a. The process of claim 1,”

Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.1.

b. “wherein the process is carried out without isolation of the (S)-nornicotine formed from step (i).”

A POSITA would have been motivated to reduce unnecessary isolation steps in any reaction sequence involving more than one chemical step. Winkler ¶ 304. In Divi’s nicotine synthesis, a POSITA would have recognized that there are two distinct chemical steps: (1) the reduction of myosmine to nornicotine, and (2) the reductive methylation of nornicotine to give nicotine. *Id.* A POSITA would have been motivated to avoid isolating the intermediate nornicotine and isolate only the nicotine at the end of the sequence if it could lead to comparable purity or an enhanced overall yield. *Id.* A POSITA would have been motivated to avoid that isolation step because it could have reduced costs and there would be a reasonable expectation that the overall yield would be higher. *Id.* It would have been obvious to a POSITA to try to prepare nicotine using the enzyme-catalyzed reaction without isolating the nornicotine intermediate but simply proceeding to the reductive methylation step to reduce costs and solvent waste, and potentially improve the yield. *Id.*

The synthesis of nicotine from the reduction of myosmine to form nornicotine and the methylation of nornicotine to form nicotine without isolating the nornicotine from the reaction mixture was known. *Id.* ¶ 305. Arnold disclosed synthesizing nicotine via the formation of myosmine, the reduction of myosmine to form (R,S)-nornicotine, and the methylation of the (R,S)-nornicotine using formaldehyde and formic acid to form (R,S)-nicotine. Ex. 1008 at 2:28-3:10; Winkler ¶ 305.

Examples 4 and 5 of Arnold disclose forming (R,S)-nicotine without isolating the (R,S)-nornicotine formed from myosmine. Winkler ¶ 306. A POSITA would have known that Examples 4 and 5 teach the formation of myosmine (Ex. 1008 at 7:33-40 and 7:56-65), the reduction of myosmine to (R,S)-nornicotine (*id.* at 7:40-43 and 7:65-8:3), and the N-methylation of the (R,S)-nornicotine to form (R,S)-nicotine (*id.* at 7:43-52 and 8:4-9). Winkler ¶ 306. A POSITA would have understood that Examples 4-5 of Arnold are conducted without isolating the (R,S)-nornicotine from the reaction mixture because other examples specify when and where an isolation step occurs. *Id.*; compare Ex. 1008 at 6:51-7:8 (Example 2) with *id.* at 7:33-52 (Example 4) and 7:56-8:9 (Example 5).

A POSITA would have been motivated to apply the teachings of Arnold because Arnold is in the field of nicotine synthesis, teaches a reaction sequence that reduces myosmine to form nornicotine and methylates nornicotine to form nicotine, and discusses appropriate reaction conditions for such a synthesis of nicotine.

Winkler ¶ 307. A POSITA would have had a reasonable expectation of success in applying Arnold’s reaction conditions because the Arnold reaction of reducing myosmine to form nornicotine and methylating nornicotine to form nicotine is the same reaction sequence disclosed in Divi. *Id.*

2. Claim 12

- a. **“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.”**

The preamble (“A process for producing a formulation for an electronic cigarette device”) is not limiting. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.1. Thus, the step of “forming (S)-nicotine according to the process of claim 1” is also obvious. Winkler ¶ 309. Divi disclosed including (S)-nicotine in a solvent with one or more additives for an electronic cigarette formation: “Nicotine is given to patients through dermal patches, gums, creams, lozenges, nasal sprays or electronic cigarettes to wean them away from smoking.” Ex. 1003 at 1:32-36. A POSITA would have known, and Arnold discloses, that electronic cigarette formulations of (S)-nicotine included “the (S)-nicotine in a solvent with one or more additives.” Winkler ¶¶ 310-311; Ex. 1008 at 1:23-26 (disclosing (S)-nicotine in solution with flavors in vaporizers).

F. Claims 7-8 Are Obvious by Divi, Moody, Velikogne, Wetzl, and Sheldon.

1. Claim 7

a. “The process of claim 1,”

Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section IX.D.1.

b. “wherein in step (i) the (S)-nornicotine is formed as part of an aqueous solution, and wherein step (ii) comprises methylating the (S)-nornicotine contained within the aqueous solution.”

Sheldon disclosed a synthesis of (S)-nicotine using an imine reductase enzyme. Ex. 1013 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 POSITA 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. Winkler ¶ 316. A POSITA looking to catalyze 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. *Id.* A POSITA would have been motivated to look to Sheldon and apply

the teachings of Sheldon because Sheldon is in the field of nicotine synthesis as well as the field of biocatalytic synthesis and discloses employing imine reductases in the synthesis of nicotine. *Id.* ¶ 317. The '962 Patent admits both that the “field of the invention” is “a process for synthetically producing (S)-nicotine” and that a POSITA was “familiar” with imine reductases. Ex. 1001 at 1:5-7 and 3:31-41. A POSITA 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. Winkler ¶ 317.

Further, Divi disclosed that the methylation of nornicotine to form nicotine was conducted while the nornicotine was present in an aqueous solution. Ex. 1003 at 5:26-29.

2. Claim 8

a. “The process according to claim 7,”

Claim 7 is obvious by Divi, Moody, Velikogne, Wetzl, and Sheldon. *See* Section IX.F.1.

- b. “wherein in step (ii) the (S)-nornicotine is reductively methylated using formaldehyde introduced as part of an aqueous solution.”**

Divi disclosed that the methylation of nornicotine to form nicotine was conducted by introducing formaldehyde as part of an aqueous solution. Ex. 1003 at 5:26-29.

X. THERE IS NO SOUND BASIS FOR A DISCRETIONARY DENIAL

The Board should not decline institution under 35 U.S.C. § 325. Only Arnold was expressly considered by the Examiner during prosecution; there is no evidence that the Examiner considered Divi or Sheldon, and none of Moody, Enzymicals, Velikogne, or Wetzl was before the Office.

The Examiner rejected the claims just once, issuing an enablement rejection under 35 U.S.C. § 112(a) and an obviousness rejection over Arnold and another reference called Flora. Ex. 1019. Patent Owner added a limitation specifying “that the methylation is carried out by way of reductive methylation, using formaldehyde or a formaldehyde-based compound in the presence of a reductant” in response to the enablement rejection. Ex. 1014. To traverse the obviousness rejection, Patent Owner emphasized that the claims recite a “stereoselective synthesis” and that “Arnold at least fails to disclose or suggest step (i) of claim 1, that is, reduction of myosmine using an enzyme with imine reductase activity.” *Id.*

The Examiner allowed the claims. Most references applied in this Petition—Moody, Enzymicals, Velikogne, and Wetzl—are directed to the “enzyme with imine reductase activity” limitation on which Patent Owner for patentability. The grounds presented in this Petition are new and unrepeatitive over what the Office considered. The grounds here are directed at the alleged point of inventiveness. The art thus presents a stronger invalidity case than previously considered.

Neither should the Board decline institution under 35 U.S.C. § 314(a). The District Court Litigation is in its infancy. The parties are in a claim construction phase and have not yet exchanged substantive discovery. *Amazon.com, Inc. v. CustomPlay, LLC*, IPR2018-01496, Paper 12, 7-8 (P.T.A.B. Sept. 6, 2019) (granting institution despite completion of discovery in parallel district court proceeding). The Court has not set a final trial date; rather, the week of January 29, 2024, “or at the Court’s convenience” is the trial date in the schedule. The median time to trial in the Western District of Texas is over 28 months from filing. Ex. 1020.

Instituting IPR will serve the interest of the patent system by ensuring that the patentability of the ’962 Patent is adjudicated against the stronger art presented in the Petition in an expedited proceeding.

XI. CONCLUSION

For the foregoing reasons, Hangsen respectfully requests that the Board institute IPR and cancel all Challenged Claims.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This Petition complies with the word count limitation of 37 C.F.R. § 42.24(a)(1) because, according to the word processing system used to prepare this document, the Petition contains 13,924 words, excluding the cover page, signature block, the exhibit list, and the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Date: January 24, 2023

By: /Kevin W. Kirsch/
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CERTIFICATE OF SERVICE

Under 37 C.F.R. §§ 42.105, 42.6(e), the undersigned hereby certifies that a copy of the Petition and supporting exhibits were served on January 24, 2023 via Priority Mail Express® directed to the Patent Owner at the correspondence address of record:

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