PETITION FOR INTER PARTES REVIEW
OF U.S. PATENT 8,324,283 UNDER
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Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Apotex, Inc. and Mylan Pharmaceuticals Inc. ("Petitioners") petition for Inter Partes Review ("IPR") of claims 1 through 32 of U.S. Patent 8,324,283 to Oomura et al., titled "Solid Pharmaceutical Composition Comprising a S1P Receptor Agonist and a Sugar Alcohol" ("the '283 patent," Ex. 1001). Concurrently filed herewith are Powers of Attorney pursuant to 37 C.F.R § 42.10(b). Pursuant to 37 C.F.R. § 42.103, the fee set forth in § 42.15(a) accompanies this petition. Petitioner Apotex authorizes the Patent and Trademark Office to charge any additional fees or fee deficiencies to Deposit Acct. No. 05-1323 (Ref. No. 002928.0000011).

I. MANDATORY NOTICES

A. Real Parties-In-Interest (37 C.F.R. § 42.8(b)(1))

The real parties-in-interest for Petitioners are Apotex Inc., Apotex Corp., Apotex Holdings, Inc., Mylan Pharmaceuticals Inc. and Mylan Inc.

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

*Inter partes* review of claims 1 – 32 of the '283 Patent was instituted on December 1, 2014 and assigned case number IPR2014-00784. Petitioners are not a party to, or aware of, any prior or pending litigation regarding infringement or invalidity of the '283 patent.
C. Identification of Counsel (37 C.F.R. § 42.8(b)(3))

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D. Service Information (37 C.F.R. § 42.8(b)(4))

Please direct all correspondence to lead counsel and back-up counsels at the contact information above. Petitioners consent to service by electronic mail at the email addresses set forth above.

II. GROUNDS FOR STANDING AND PROCEDURAL STATEMENT

As required by 37 C.F.R. § 42.104(a), Petitioners certify that the ’283 patent is available for IPR and that the Petitioners are not barred or estopped from requesting IPR on the grounds identified herein.
III. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED

Petitioners request *inter partes* review and cancellation of claims 1 through 32 of the ’283 patent under 35 U.S.C. § 103, as set forth herein. The ’283 patent is to be reviewed under pre-AIA § 103. Petitioners’ detailed statement of the reasons for the relief requested is set forth below in the section titled “Statement of Reasons for Relief Requested.” In accordance with 37 C.F.R. § 42.6(c), copies of the exhibits are filed herewith. In addition, this Petition is accompanied by the Declaration of Arthur Kibbe, Ph.D., Ex. 1004.

IV. THRESHOLD REQUIREMENT FOR INTER PARTES REVIEW

A petition for *inter partes* review must demonstrate “a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). This Petition meets this threshold. As explained below, there is a reasonable likelihood that Petitioners will prevail with respect to at least one of the challenged claims.

V. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

The challenged claims of the ’283 patent are generally directed to pharmaceutical compositions, comprising S1P receptor agonists and a sugar alcohol, and, in particular, solid compositions combining the compound FTY720 (fingolimod) with mannitol. Claims 1-32 of the ’283 patent are unpatentable as being obvious under 35 U.S.C. § 103 over Chiba in view of Aulton.
A. Prosecution Background and Summary of the Argument

During prosecution of the ’283 patent, claims directed to solid pharmaceutical compositions suitable for oral administration comprising an S1P receptor agonist and a sugar alcohol were rejected for obviousness. Ex. 1003 at 001233-1237. Included among the rejected claims was then-pending claim 15, which required that the sugar alcohol be mannitol. Id. at 001198. The rejections of all claims were based on the prior art’s disclosure of FTY720, or 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, and the use of mannitol as an excipient for other S1P receptor agonists. Id. at 001234-37.

In a subsequent Amendment, Applicants added new claim 32 (later issuing as claim 19 of the ’283 patent) directed specifically to a solid pharmaceutical composition suitable for oral administration comprising mannitol and 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, or its salt. Id. at 001266. In support of the patentability of all claims, including those rejected for obviousness, Applicants submitted the declaration of Supriya Rane, M.S. Id. at 0012373-77 (“the Rane declaration” or “the Rane testing”). In the Rane declaration, the results of elevated temperature binary mixture compatibility testing were presented for mixtures combining drug substance FTY720 with, respectively, four different excipients: mannitol, microcrystalline cellulose, lactose, and starch. Id. Ms. Rane concluded that, from the perspective of the formulation chemist possessing the average level
of skill in the art, the degree to which mannitol exhibited superior results over the other excipients was surprising. Ex. 1003 at 001275. Ms. Rane never concluded that an ordinarily skilled formulator would have been surprised that mannitol itself demonstrated good compatibility with FTY720 under the testing conditions. Id.

Thereafter, despite an indefiniteness rejection that addressed, among others, claim 15, a number of claims were found to constitute allowable subject matter, including claim 32 (again, now claim 19 in the patent). Id. at 001305-06. The claims were allowed “based on the Rane declaration, which demonstrates the unexpected stability between FTY720 and mannitol, compared to the combination of FTY720 with other excipients disclosed in the prior art.” Id. at 001305.

The alleged “unexpected results” that led to allowance of the subject patent claims are not probative of nonobviousness because the ordinarily-skilled artisan would have maintained more than a reasonable expectation that mannitol would have been compatible in a solid phase binary mixture with FTY720, and a reasonable expectation that lactose and FTY720 would be susceptible to incompatibility because of the known propensity of lactose to react with compounds having a primary amine (like FTY720). The percentage differences asserted to demonstrate unexpected results represent only differences in degree, with no evident practical significance. The asserted evidence of unexpected results is also not commensurate with the full scope of the claims and contains no
comparison to FTY720-mannitol compositions disclosed in what should be regarded as the closest prior art. The asserted evidence also contradicts FTY720-excipient testing disclosed in another Novartis patent, U.S. 8,673,918.

Petitioners submit that the subject matter of all of the claims of the ’283 patent would have been arrived at by following the teachings and suggestions of the prior art which would have motivated a person ordinarily skilled in the art to develop solid oral dosage forms by choosing common pharmaceutical excipients and optimizing the prospective formulation by selecting a best or satisfactory excipient identified from routine drug-excipient compatibility testing. In the present case, the ordinarily-skilled artisan would have harbored more than a reasonable expectation that the conventional solid dosage diluent mannitol would have been compatible with FTY720 in the solid phase.

B. Level of Ordinary Skill in the Art

A person of ordinary skill in the art at the time of the alleged invention of the ’283 patent would have had a Pharm. D. or a Ph.D. in pharmacy, chemical engineering, chemistry, or related discipline, and at least two years of formulation development work or research experience in the area of formulating oral dosage forms, which would include tablets and capsules, or an M.S. and at least five years additional commensurate experience. The individual would have a substantive understanding of other dosage forms such as topically administered products and
injectable or parenteral products. A person of ordinary skill in the art would collaborate with others having expertise in, *e.g.*, (i) methods of treating disease and administering medicines and (ii) analytical chemistry. Kibbe Decl., Ex. 1004 at ¶ 22.

**C. Claim Construction**

The claims of the ’283 patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable interpretation of the claim language. Petitioners do not believe that the Applicant attributed any special meanings to the claim terms in the ’283 patent when the broadest reasonable interpretation standard is applied.

For example, when the broadest reasonable interpretation is applied to the claims of the ’283 patent, one of ordinary skill in the art would understand the following claim terms to have the following meanings:

- “solid pharmaceutical composition suitable for oral administration,” appearing in claims 1 and 19, means “a non-liquid composition that can be ingested via the mouth.” One of ordinary skill in the art would understand this term to embrace tablets, capsules, or powders, as well as lyophilized product. *See* Ex. 1004 at ¶ 142; Ex. 1001 at col 10, 11. 59-63 (“The composition may be in the form of a powder, granule or
pellets, or a unit dosage form, for example as a tablet or capsule.”

- “2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol,” appearing in claims 1, 19, 22, and 32, means “FTY720,” which is synonymous with “fingolimod.” See Ex. 1004 at ¶ 143; Ex. 1001 at col. 8, ll. 22-27; Ex. 1003 at 001275. One of ordinary skill in the art would further understand FTY720 to have the following chemical structure:

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     HO
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H2N—|—OH
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- “pre-screened with a 400-500 μm mesh screen,” appearing in claim 14, means “passed through a screen with 400-500 μm mesh screen size or opening before mixing to produce a product that only has particle sizes the size of the opening or smaller.” See Ex. 1004 at ¶ 145; Ex. 1001 col. 11, ll. 33-36.

- “mean particle size,” appearing in claims 27 and 28, means “average diameter of the particles.” See Ex. 1004 at ¶ 146.

- “bulk density,” appearing in claims 29 and 30, means “density of loosely packed powder before combining into a formulation composition.” See Ex. 1004 at ¶ 147.
“single point surface area,” appearing in claim 31, means “surface area of the powder, calculated by the single point BET method.” See Ex. 1004 at ¶ 148.

“by weight,” appearing in claims 7-12, means “by weight based on total weight of the composition.” See Ex. 1004 at ¶ 149; Ex. 1001 at col. 9, ll. 49-52.

Petitioners’ positions regarding the scope of the claims should not be construed as an assertion regarding the appropriate claim scope in other adjudicative forums, where a different claim interpretation standard may apply.

D. **Printed Publications Relied On**

Petitioners rely on the following patents and publications:

1. **Chiba (Ex. 1006)**

U.S. Patent 6,004,565, titled, “Compositions and Methods of Using Compositions with Accelerated Lymphocyte Homing Immunosuppressive Properties (“Chiba,” Ex. 1006) issued on December 21, 1999. Chiba is prior art to the ’283 patent under 35 U.S.C. § 102(b). Chiba discloses the use of a general class of immunosuppressive compounds, with FTY720 (2-amino-2-[2-(4-octylpheny)ethyl]propane-1,3-diol hydrochloride) as the preferred species. Ex. 1006 at col. 4, l. 64 – col. 5, l. 5; see also, Ex. 1004 at ¶¶ 89-93. Each of the nine
examples included in the specification are directed to FTY720 activity in various assays and rat or dog models. Ex. 1006 at cols. 12-21.

The claims in Chiba are directed toward the use of FTY720. Id. at col. 24, l. 60 – col. 26, l. 9. The specification explains that compounds in the disclosed class are useful in treating autoimmune diseases such as multiple sclerosis. Id. at col. 6, ll. 26-49. The specification states that the disclosed compounds can be formulated for pharmaceutical use, whereupon they are “generally admixed with carrier, excipient, diluent and so on and formulated into powders, capsules, tablets, injections, topical administration preparations, or the like, for administering to patients.” Id. at col. 8, ll. 19-26. Chiba also contemplates that a lyophilized preparation may be produced by a method known in the art. Id. at col. 8, ll. 26-28. Chiba discloses that the compounds may be administered orally, and that appropriate formulations can be prepared from known excipients:

   In many cases, these compositions can be administered orally. The examples below detail the use of FTY720 by oral administration. One skilled in the art is familiar with numerous methods and tests for determining the effectiveness of a selected route of administration. Furthermore, pharmaceutically or physiologically acceptable carriers or excipients for use with the 2-aminopropane-1,3-diol compounds or benzene compound noted herein are known in the art or can be readily found
by methods and tests known in the art. And, pharmaceutically and physiologically acceptable salts of these compounds can also be determined and used by one skilled in the art.

*Id.* at col. 11, ll. 20-31.

2. **Aulton (Ex. 1021)**

*Pharmaceutics: The Science of Dosage Form Design* (“Aulton,” Ex. 1021), a book edited and compiled by M.E. Aulton, published in 1988. Aulton is prior art to the ’283 patent under 35 U.S.C. § 102(b). Aulton explains that preformulation studies are essential in formulation development, and include determining “fundamental physical and chemical properties of the drug molecule.” *Ex. 1021 at 000005; see also, Ex. 1004 at ¶¶ 99-103.* In that regard, Aulton teaches that prior to evaluating the drug’s compatibility with various excipients, drug properties such as solubility, melting point, stability in solution and solid phase, and powder properties should be determined. *Ex. 1021 at 000005.* Knowledge of these properties influences choices made in formulation development. *Id.*

Limiting drug degradation is a primary concern to the formulator when designing a new drug formulation. *Id.* at 000023, 30-31. According to Aulton, drugs degrade primarily by hydrolysis, oxidation, photolysis, and trace metal catalysis. *Id.* at 000023. When tasked with formulating a new drug product from a drug substance, formulators consider which excipients are most likely to limit, and
least likely to exacerbate, any drug degradation. *Id.* Starting with a list of commonly used excipients, formulators apply their knowledge of common drug/excipient interactions to choose excipients that may be compatible with the drug substance at issue. Formulators then test the drug substance with each chosen excipient and observe the stability of the resulting drug product. Testing under conditions of elevated temperatures is common. *Id.* at 000032. Formulators use the results of these tests to select the proper excipients to use with the drug substance.

Aulton states that solid oral dosage forms, such as tablets and capsules, are the most common drug products (*Id.* at 000005); Aulton devotes a chapter each to tablets and capsules. In the tablets chapter, Aulton lists the major types of excipients that are commonly added to tablets: diluents, adsorbents, moistening agents, binding agents, glidants, lubricants, and disintegrating agents. *Id.* at 000040-43. For each of these types of excipients, he lists commonly used materials. Mannitol is listed as one of seven commonly used diluents. *Id.* at 000041. Magnesium stearate is listed as the most commonly used lubricant. *Id.* at 000042.

3. **Additional Prior Art Confirming the General Knowledge of the Ordinarily-Skilled Artisan**

In addition to the prior art discussed above, Dr. Kibbe’s declaration addresses additional prior art confirming the general knowledge of a person of ordinary skill in April 2003. See below at section VI for a table summarizing the
disclosure of these additional printed publications. The ordinarily-skilled artisan would have understood that mannitol was one of a small number of commonly-used diluents used in solid oral dosage forms. See, e.g., Ex. 1004 at ¶¶ 101, 109, 117-127. Moreover, the ordinarily-skilled artisan would have known that mannitol has several properties that are advantageous in the formulation of solid oral dosage forms including (i) that it does not undergo Maillard reactions and is thus suitable for use with amine-containing compounds; (ii) that it is not hygroscopic and will not absorb water making it suitable for water-sensitive active agents; (iii) that it has no reported incompatibilities when in the dry state and has been reported to be inert with respect to various mechanisms associated with drug-excipient compatibility; (iv) that it is sweet tasting; and (v) that it has a negative heat of solution, which provides a cooling effect in the mouth. Id. at ¶¶ 121 & 122.

These additional references also confirm that a person of ordinary skill in the art would have understood that reducing sugars like lactose were known to be incompatible with drugs containing primary amines and their salts. Id. at ¶¶ 128-133.

These additional references further confirm that it was routine for persons of ordinary skill in the art to reduce the particle size of drugs, including, e.g., micronizing, and that this reduction in particle size was desirable because it tends to increase the bioavailability of the drug. Id. at ¶¶ 134-136. Additional references
also confirm the prevalent and routine nature of preformulation compatibility testing between drug and prospective excipients. *Id.* at ¶¶ 104-116.

E. Ground 1: The Challenged Claims are Unpatentable as Obvious Over Chiba and Aulton

1. Claim 19 is Obvious Over Chiba and Aulton

Claim 19 is directed to (i) a solid pharmaceutical composition suitable for oral administration, comprising (ii) mannitol and (iii) 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable salt thereof [FTY720].

Chiba (Ex. 1006) discloses FTY720 to be a preferred species of ALH-immunosuppressive compounds that can be formulated for pharmaceutical use when admixed with “carrier, excipient, diluent and so on and formulated into powders, capsules, tablets, injections, topical administration preparations, or the like.” Ex. 1006 at col. 3, ll. 25-43; col. 4, 1. 64 - col. 5, l. 5; col. 8, ll. 19-28; Ex. 1004 at ¶ 90. Chiba discloses that FTY720 can be administrated orally by employing “physiologically acceptable carriers or excipients” known in the art, or that can otherwise be identified by conventional means. *Id.* at col. 11, ll. 20-34; Ex. 1004 at ¶ 91. One of ordinary skill in the art would have therefore understood from Chiba that FTY720 was a preferred pharmaceutically efficacious compound that could be administered orally when formulated in a solid form, such as a powder, tablet or capsule, using known pharmaceutical excipients following methods
known in the art. Ex. 1004 at ¶ 93. One of ordinary skill in the art would have been motivated by Chiba’s disclosure to formulate FTY720 in solid dosage forms suitable for oral administration, such as a powder, tablet or capsule, and would have maintained a reasonable expectation of success that such a formulation could be prepared via conventional methods employing conventional excipients. Ex. 1004 at ¶ 158.

Upon endeavoring to formulate FTY720 in a solid dosage form for oral administration, the ordinarily skilled artisan would have chosen potential excipients from a limited roster of conventionally-employed diluents, binders, carriers, and lubricants. Ex. 1004 at ¶ 159. Although Chiba does not recite specific species of carriers or diluents or other excipients for a solid dosage form containing FTY720, mannitol (or “D-mannitol”) would have been one such excipient reasonably chosen for consideration. Ex. 1004 at ¶ 160. For one, Aulton discloses mannitol to be a commonly used excipient in tableting and would normally be considered for such application. Ex. 1021 at 000041; see also Ex. 1004 at ¶ 159. Indeed, the HANDBOOK OF PHARMACEUTICAL EXCIPIENTS confirms that mannitol was routinely used for solid oral dosage formulation, particularly noting its non-hygroscopicity, its sweet taste and cooling effect in the mouth. Ex. 1014 at 000004-5. During prosecution of the application leading to the ’283 patent, when claims were rejected for obviousness (Ex. 1003 at 001234-37), Applicants did not
dispute that mannitol would be an excipient to be considered for a solid dosage form containing FTY720. Ex. 1003 at 001268-72. Petitioners submit that there is no prior art disclosure “teaching away” from the use of mannitol in a solid dosage form containing FTY720.

Having chosen a number of prospective excipients, the ordinarily skilled artisan would have conducted drug-excipient compatibility testing to assess compatibility under stressed conditions. Ex. 1021 at 000030-32; Ex. 1004 at ¶ 159. During prosecution of the application leading to the ’283 patent, Applicants expressly acknowledged that “a person of ordinary skill in the art, when formulating a solid dosage form comprising an active ingredient would be concerned about compatibility of the active drug substance with the chosen excipients,” and would have conducted testing to determine compatibility. Ex. 1003 at 001270, 001274. The ordinarily-skilled artisan would have thereafter selected those excipients deemed satisfactory from compatibility testing for further formulation development. In other words, the prior art taught the ordinarily-skilled artisan to choose prospective excipients from a finite list of well-known, pharmaceutically-acceptable ones, test them to confirm compatibility with the subject active, and, in an effort to optimize the formulation, select satisfactorily performing excipients for further development. Ex. 1004 at ¶¶ 99-116. In the present case, mannitol would have been one such excipient to employ in a solid
oral dosage form, and the ordinarily-skilled artisan would have maintained a reasonable expectation that mannitol could be successfully paired with FTY720 (fingolimod) to make a dosage form suitable for its intended purpose. Ex. 1004 at ¶ 160.

During prosecution of the ’283 patent, Applicants asserted that the compatibility between active drug substance with an excipient is not predictable. Ex. 1003 at 001270. However, obviousness does not require absolute predictability, but only a reasonable expectation that the beneficial result will be achieved. *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). In the present case, the ordinarily skilled artisan would have maintained more than a reasonable expectation that mannitol would be compatible with FTY720 because, in April 2003, mannitol was a commonly-employed diluent in tablet and capsule applications whose beneficial properties include its own stability in the dry state and aqueous solutions, its non-participation in Maillard reactions, its lack of reported incompatibilities in the dry state, and its non-hygroscopicity (thus making it desirable for use with moisture-sensitive active ingredients). Ex. 1021 at 000040-41; Ex. 1014 at 000005-8; Ex. 1004 at ¶ 160. Furthermore, Sakai (Ex. 1005) reinforced the expectation to the ordinarily-skilled artisan that mannitol would have been compatible with FTY720 because Sakai discloses pharmaceutical injectable compositions containing FTY720 and mannitol in solution, as well as
lyophilized product meant for long-term preservation in vials containing FTY720 and mannitol. Ex. 1005 at col. 3,11. 42-45; Ex. 1004 at ¶ 165.

During prosecution of the ’283 patent, Applicants submitted testing asserted to support not that it was unexpected that mannitol exemplified compatibility with FTY720, but rather that the “degree of superiority” that mannitol demonstrated compared to three other excipients was unexpected and surprising. Ex. 1003 at 001275. The Rane testing is not probative of “unexpected results” sufficient to support the nonobviousness of the claimed subject matter. As a threshold matter, the Rane testing was performed on binary mixtures of FTY720 and excipient, but the claims of the ’283 patent are directed to compositions “comprising” active ingredient and a sugar alcohol (claim 1) or, more specifically, mannitol (claim 19). Ex. 1001 at col. 18, 11. 8-10 and Certificate of Correction. As such, the claims cover compositions containing excipients in addition to the sugar alcohol (mannitol). The ’283 patent expressly contemplates additional excipients, such as a lubricant, carriers, diluents, or binders, and even stabilizers. Id. at col. 10, 11. 18-58. One of ordinary skill in the art would have reasonably expected that the inclusion of additional excipients could change the compatibility results of the binary mixture tested by Rane. Ex. 1004 at ¶ 170. For example, the poor result demonstrated by lactose in the stressed conditions employed by Rane might be very different if a stabilizer is added, or other excipients that collectively might
mitigate the apparent degradative effect lactose had on FTY720 under those conditions in a binary mixture. Petitioners submit that compatibility testing conducted with binary mixtures are not necessarily probative of unexpected results for claims that cover compositions “comprising” additional excipients. A showing of unexpected results must be commensurate in scope with the claims which the evidence is offered to support. *In re Peterson*, 315 F.3d 1325, 1330-31 (Fed. Cir. 2003).

Furthermore, evidence submitted in support of unexpected results must compare the claimed subject matter to the closest prior art. *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). As demonstrated above, the Sakai reference (Ex. 1005) discloses lyophilized product or powders containing FTY720, lecithin and saccharide, which can be mannitol, xylitol, glucose, or even lactose. Ex. 1005 at col. 3, ll. 3-10. The Rane testing did not employ these powders or lyophilized products. Petitioners submit that the Rane declaration is not probative of unexpected results since the testing did not compare the binary mixtures to what is facially closer prior art.

Another reason the Rane testing fails to demonstrate legally sufficient “unexpected results” is that the results show differences in degree, not kind. Unexpected results probative of nonobviousness are those that are “different in kind, and not merely in degree” from some reference point. *Galderma Labs., L.P.*
v. Tolmar, Inc., 737 F.3d 731, 739 (Fed. Cir. 2013) (citation omitted) (holding that a percentage increase in the prevalence of certain side effects with an increased dosage compared to the prior art, while unexpected, was not probative of nonobviousness because it was a difference in degree, not in kind). That the degradation of the FTY720/mannitol mixture was less than the degradation of the FTY720/microcrystalline cellulose and FTY720/lactose mixtures, illustrates mere differences in degree obtained under conditions designed to expedite and magnify the chemical interactions in the respective binary mixtures. Ex. 1004 at ¶ 166 & 167. As evidence that the mere percentage differences in FTY720 loss among the tested excipients are not ultimately substantive and do not distinguish viable excipients from non-viable excipients, it is noted that although starch performed 10.6 times worse than mannitol in one test (30.7% fingolimod loss (starch) vs. 2.9% fingolimod loss (mannitol)) and microcrystalline cellulose performed 4.5 times worse than mannitol in another test (38.2% fingolimod loss (microcrystalline cellulose) vs. 8.5% fingolimod loss (mannitol)) (Ex. 1003 at 001277), those results did not stop Applicants from considering microcrystalline cellulose and starch to be acceptable excipients for the compositions of the claimed subject matter. Ex. 1001 at col. 10, ll. 34-41 (expressly reciting microcrystalline cellulose and starch as further excipients for the compositions); see also Example 23 at col. 14, l. 63 - col. 15, l. 20, disclosing a composition containing FTY720, mannitol, corn starch,
and Avicel (microcrystalline cellulose); Ex. 1004 at ¶ 167 (also citing claim 1 of U.S. 8,673,918 (Ex. 1025) as evidence that microcrystalline cellulose, starch, and lactose are still deemed acceptable excipients for solid oral compositions containing FTY720). Because microcrystalline cellulose and starch are both still identified as acceptable excipients for the claimed compositions, the resulting percentage differences between these excipients and mannitol in the Rane testing do not appear to have any practical significance, a requisite for being indicia of nonobviousness. Ex parte Gelles, 22 USPQ2d 1318, 1219-1320 (B.P.A.I. 1992) (affirming final rejection of obviousness, holding that asserted evidence of unexpected results was not probative of nonobviousness because it failed to meet, among other qualifications, the requirement that the evidence be of “both statistical and practical significance.”)

The alleged superior results attributed to mannitol in the Rane testing must be viewed in light of the reasonable expectations the ordinarily-skilled artisan would have maintained in 2003 when undertaking compatibility testing. For one, the ordinarily-skilled artisan would have maintained more than a reasonable expectation that mannitol would have demonstrated very good compatibility with FTY720 in solid phase mixture, even under stressed conditions, because the artisan was already aware that mannitol was generally regarded as inert, and in particular, as a non-participant in the Maillard reaction, and that FTY720 had been
successfully formulated with mannitol in solution phase compositions. Ex. 1004 at ¶ 165.

Second, the ordinarily skilled artisan would have reasonably expected that under stressed conditions common in drug-excipient compatibility testing, such as those employed by Rane (elevated temperature of 176 °F), different excipients would have shown a continuum of results, with some showing less degradative effect, and some showing comparatively more. Ex. 1004 at ¶ 166. The Rane testing results confirm that expectation. Lastly, one of ordinary skill in the art in 2003 would have maintained a reasonable expectation that lactose would have fared poorly in stressed binary mixture testing with fingolimod. FTY720 (fingolimod) has a primary amine in its chemical structure. Ex. 1004 at ¶ 168. Lactose was well known to react with compounds containing amines in a reaction called the Maillard reaction. Id.; see also Ex. 1018. Accordingly, one of ordinary skill in the art would not have been surprised that lactose demonstrated marked compatibility issues under the conditions of Rane’s testing. Therefore, any conclusion of “unexpected results” would have to take into account the ordinarily-skilled artisan’s reasonable expectation that lactose would likely have been incompatible with FTY720 under stressed conditions in binary mixture. Ex. 1004 at ¶ 168. There is no evidence in the Rane declaration that Rane considered this known interaction.
Petitioners submit that Applicants’ (Novartis’) allegation that one of ordinary skill in the art would have been “surprised” by mannitol’s alleged superior compatibility compared to lactose, microcrystalline cellulose and starch is further belied by Novartis’ own U.S. 8,673,918 (“the ’918 patent,” Ex. 1025) which was pending in May 2012 when the Rane testing was submitted. The ’918 patent, based on a provisional filing in October 2007, and not prior art to the ’283 patent, nonetheless discloses solid oral dosage compositions containing FTY720 and conventional excipients, and consistent with the prior art to the ’283 patent, explains the Maillard reaction and the role lactose (a reducing sugar) plays by reacting with amino groups on chemical compounds. Ex. 1025 at col. 10, ll. 19-33. The ’918 patent also cautions against using lactose with the subject compounds. Id. at col. 11, ll. 39-41. The ’918 patent further discloses allegedly stable binary mixtures of FTY720 and, respectively, lactose anhydrous, Avicel (microcrystalline cellulose) and starch, as evaluated under different testing conditions than those employed by Ms. Rane. Id. at col. 12, ll. 51-67; Examples 1 and 3 in cols. 13-14. Thus, Applicants’ assertion of unexpected results submitted in support of the ’283 patent contradicts Novartis’ (then) co-pending patent application disclosing (1) compatibility testing showing different results from Rane’s testing and (2) a discussion of the Maillard reaction and lactose matching the prior art to the ’283 patent, but absent from both the ’283 patent and Rane’s analysis.
In any event, “unexpected results” do not control the obviousness conclusion where, as here, there is a strong showing of obviousness. *Pfizer v. Apotex*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).

The Federal Circuit’s decision in *Pfizer v. Apotex* is indeed on point. In *Pfizer*, the court held a claim to the besylate salt of the pharmaceutical active amlodipine to be obvious over prior art disclosing a list of appropriate acid addition salts of amlodipine (although not including besylate) and the list of 53 approved acid addition salt forms for any active ingredient, which listing included besylate. *Id.* at 1360-72.

The Court held that an ordinarily-skilled artisan would have been motivated to make known pharmaceutically-acceptable salts for any active ingredient, but would have employed ones from an FDA-approved listing and would have favorably considered besylate because of prior art disclosing the stability-enhancing property of besylate salts of other actives. *Id.* at 1362-63. Similar to the present case, the ordinarily-skilled artisan would have been motivated to formulate FTY720 in a solid dosage form and would have explored using excipients from a limited roster of conventionally-employed excipients used in approved pharmaceutical products, and would have favorably considered mannitol because of its well-known properties and common use in solid dosage forms, and its known compatibility with FTY720 in solution.
The Pfizer court next held that the ordinarily-skilled artisan would have had a reasonable expectation that the besylate salt could be formed and work for its intended purpose. *Id.* at 1364. In so holding, the Court noted that it was in fact unpredictable what a salt’s properties would be, but the law does not require absolute predictability, only a reasonable expectation of success. *Id.* In the present case, the ordinarily skilled artisan would have likewise harbored a reasonable expectation that mannitol would be compatible with FTY720 in a solid dosage form. Ex. 1004 at ¶ 165. In fact, during the prosecution of the ’283 patent, Applicants never disputed that mannitol would have been expected to be compatible with FTY720. Ex. 1003 at 001261-77.

The Pfizer court then held that making the besylate salt was more than obvious-to-try. *Id.* at 1366-1369. The Court noted that choosing an acid addition salt from a list of previously approved salts, coupled with the prior art’s teaching that standard techniques were employed to evaluate and verify the salt’s properties, did not amount to trial and error procedure. *Id.* at 1366-68. The Court analogized selection and testing of different salt forms to “optimization of a range or other variable,” wherein experimentation needed to arrive at amlodipine besylate was nothing more than the routine application of a well-known problem-solving strategy. *Id.* at 1368. The Court stated that “patentability is not imparted where ‘the prior art would have suggested to one of ordinary skill in the art that this process
should be carried out and would have a reasonable likelihood of success.”” Id. at 1369. Identically in the present case, it was more than obvious-to-try the combination of FTY720 and mannitol for a solid dosage formulation because the prior art already disclosed the compatibility of FTY720 and mannitol. Furthermore, the ordinarily skilled artisan had more than a reasonable expectation of success of such compatibility that would have been verified by routine compatibility testing that the prior art taught as a fundamental part of preformulation design.

Finally, the Pfizer court held that Pfizer’s allegations of the besylate salt’s superior properties did not stand as an unexpected result evidencing the nonobviousness of the compound. Id. at 1371-72. The Court noted that the ordinarily skilled artisan, in testing from among the 53 salt anions, would have expected the salts to demonstrate a range of properties, in which some would be superior, and some inferior, to a reference salt. Id. at 1371. The Court noted that Pfizer simply engaged in routine testing to optimize selection of one of several known and clearly suggested salts. Id. at 1371-72. The fact that the besylate salt was the best performer of the ones actually tested proved nothing more than routine optimization would have been obvious to one of ordinary skill in the art. Id. The same is true in the present case: unexpected results are not supported by the routine compatibility testing that identified mannitol as the best performer among
four excipients tested, especially since the prior art already instructed the artisan to undertake routine compatibility testing as part of the formulation design process, which necessarily evaluated the compatibility of the subject active ingredient with a number of different excipients.

The above establishes a strong case of obviousness, and refutes the only evidence of secondary considerations submitted by Applicants during prosecution in support of nonobviousness (alleged “unexpected results.”) Although any secondary considerations must be taken into account, they do not control the analysis where, as here, there is a strong *prima facie* case. *Pfizer*, 480 F.3d at 1372.

In his accompanying declaration, Dr. Kibbe addresses other secondary considerations tending to show nonobviousness. Ex. 1004 at ¶ 171 & 172. As to commercial success, Dr. Kibbe is unaware of any evidence attributing commercial success of Gilenya®, an approved product containing fingolimod and mannitol in capsule form, to the presence of mannitol in the formulation (Ex. 1004 at ¶ 171, further citing U.S. 8,673,918 (Ex. 1025) as evidence that mannitol (and sugar alcohol) is not needed to make a stable oral dosage composition containing FTY720), and he points out the existence of another patent (U.S. Patent 5,604,229, Ex. 1007) covering the active ingredient itself. *See Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364, 1376-77 (Fed. Cir. 2005) (holding that evidence of commercial success is “weak” and not sufficient to overcome a *prima
facie showing of obviousness when market entry by competitors was blocked by a patent). Ex. 1004 at ¶ 171.

2. **Claims 1 and 32 are Obvious Over Chiba and Aulton**

Claim 1 is directed to a solid oral dosage form comprising a sugar alcohol and one of four S1P receptor agonists, one of which is FTY720, or a pharmaceutically acceptable salt or phosphate thereof. Claim 32 depends from claim 1 and limits the claim 1 composition by expressly reciting FTY720 as the S1P receptor agonist. Mannitol, recited in claim 19, is a sugar alcohol. The ’283 patent identifies mannitol to be a sugar alcohol. Ex. 1001 at col. 9, ll. 53-59; see also Ex. 1014 at 000005. Claims 1 and 32 both embrace, therefore, the same subject matter as claim 19, but are broader in scope. Claims 1 and 32 are therefore obvious for the same reasons discussed above with respect to claim 19. See Ex. 1004 at ¶ 174.

3. **Claim 2 is Obvious Over Chiba and Aulton**

Claim 2 depends from claim 1 and further requires that the S1P receptor agonist be in the hydrochloride salt form. Chiba discloses the hydrochloride salt of FTY720 as a preferred embodiment. Ex. 1006 at col. 4, ll. 63-68. Therefore, claim 2 is obvious for the same reasons discussed above with respect to claims 1 and 19. Ex. 1004 at ¶ 175.

4. **Claims 3 and 4 are Obvious Over Chiba and Aulton**
Claims 3 and 4 depend from claim 1 and further require that the sugar alcohol of the claim 1 composition be non-hygroscopic (claim 3) and that it be mannitol (claim 4). Since mannitol is a non-hygroscopic sugar alcohol (Ex. 1001 at col. 9, ll. 53-59; Ex. 1014 at 000005), these claims embrace the same subject matter as claim 19, although they are broader in scope. Claims 3 and 4 are therefore obvious for the same reasons discussed above with respect to claims 1 and 19. Ex. 1004 at ¶ 176.

* * *

Before addressing remaining dependent composition claims 5-16 and 20-31, as well as method of treatment claims 17 and 18, Petitioner notes that during prosecution of the application that became the ’283 patent, pending claims directed to solid pharmaceutical compositions suitable for oral administration, including dependent claims 13-27 (which later issued as claims 2-16 of the ’283 patent), were rejected for obviousness. (Ex. 1003 at 001233-37). In support of the patentability of those dependent claims, as well as newly presented dependent claims 33-39 (later issuing as claims 20-26), Applicants offered declaration evidence in support of the patentability of claims covering the combination of FTY720 and mannitol, without asserting the separate patentability of any dependent claim. Id. at 001261-72. In essence, Applicants treated the dependent claims as if they rose and fell together with the independent claims from which
they ultimately depended (then-pending claims 11 and 32). Indeed, the compatibility testing presented in the Rane declaration (Ex. 1003 at 1273-77), which was the Examiner’s basis for allowable subject matter (Id. at 001305-06), did not even report information recited by most of the dependent claims, such as inclusion of a second excipient (lubricant), the lubricant’s compositional percentage, or the properties of mannitol employed (including mean particle size, bulk density, and single point surface area). Id. at 1273-77. The testing did not employ compositions in the tablet or capsule form, nor did the testing bear on whether FTY720 was micronized or prescreened with a particular mesh size screen because FTY720 was dispensed in solution, and not in particulate form. Id. As will be explained in more detail below, the remaining dependent claims do not impart patentably distinguishing elements to the claim 1 or claim 19 compositions, and instead recite features disclosed in the prior art, or recite aspects of formulation design resulting from the routine optimizing work of the ordinarily skilled artisan. And in no case was the criticality of any element of the remaining dependent claims asserted to distinguish the prior art. Ex. 1003 at 001268-76; 001316. See Purdue Pharma Prods. L.P. v. Par Pharmaceutical, Inc., 377 Fed. Appx. 978, 982-83 (Fed. Cir. 2010) (affirming district court’s holding that claims to a controlled release tramadol formulation for once-daily dosing, including dependent claims reciting particular dissolution rates and drug plasma profiles, were obvious over
prior art expressly disclosing the limitations in the asserted claims or wherein the differences between the prior art and claims would have been established through routine experimentation).

5. **Claims 5, 6, 20 and 21 are Obvious Over Chiba and Aulton**

Claims 5 and 20 depend from claims 1 and 19, respectively, and further require the inclusion of a lubricant in the composition. Claims 6 and 21 depend from claims 5 and 20, respectively, and further require that the lubricant be magnesium stearate. One of skill in the art would have included a lubricant in the oral dosage form as a matter of routine optimization, with a high expectation of success, as lubricants were commonly used in solid formulations. Ex. 1021 at 000042, listing lubricants as a commonly employed excipient type. Magnesium stearate was a commonly-used lubricant. *Id.* at 000042. Further, neither the prosecution history nor the specification indicate that there is any criticality assigned to the use of any lubricant. The Rane testing did not test compatibility in the presence of a second excipient acting as a lubricant. Therefore, claims 5, 6, 20, and 21 are obvious for the same reasons discussed above with respect to claims 1 and 19. Ex. 1004 at ¶¶ 180-182.

6. **Claims 7, 8 and 22 are Obvious Over Chiba and Aulton**

Claims 7, 8, and 22 depend, directly and indirectly, from claims 1 and 19, and impose further limitations on the amount of the S1P receptor agonist (claims 7
and 8) or FTY720 (claim 22) that is included in the solid oral dosage form. Claim 7 requires an amount of 0.01 to 20% by weight, and claims 8 and 22 require an amount of 0.5 to 5% by weight, all understood as “by weight of the composition.” See supra, section V(C). Selecting constituent amounts in a formulation is the result of routine optimization (Ex. 1004 at ¶ 177), and thus constituent amounts are not patentably distinguishing claim elements. Further, neither the prosecution history nor the specification indicate that there is any criticality assigned to the claimed weight percentages. The Rane testing, in fact, only addressed 0.25 weight % FTY720 in each binary mixture evaluated, which is outside the ranges of claims 8 and 22. Id. Therefore, claims 7, 8, and 22 are obvious for the same reasons discussed above with respect to claims 1 and 19. Id.

7. Claims 9, 10 and 23 are Obvious Over Chiba and Aulton

Claims 9, 10, and 23 depend, directly and indirectly, from claims 1 and 19, and impose further limitations on the amount of sugar alcohol (claims 9 and 10) or mannitol (claim 23) that is included in the solid oral dosage form. Claim 9 requires an amount of 75 to 99.99% by weight, and claims 10 and 23 require an amount of 90 to 99.5% by weight, all understood as “by weight of the composition.” See supra, section V(C). Selecting constituent amounts in a formulation is the result of routine optimization (Ex. 1004 at ¶ 184), and thus constituent amounts are not patentably distinguishing claim elements. The recited ranges are within the typical
diluent amounts of from 10% to 90% by weight. *Id.*; Ex. 1014 at 000005. Further, neither the prosecution history nor the specification indicate that there is any criticality to the claimed weight percentages. Therefore, claims 9, 10, and 23 are obvious for the same reasons discussed above with respect to claims 1 and 19. Ex. 1004 at ¶ 184.

8. **Claims 11, 12 and 24 are Obvious Over Chiba and Aulton**

Claims 11, 12, and 24 depend, directly and indirectly, from claims 1 and 19, and impose further limitations on the amount of lubricant that is included in the solid oral dosage form. Claim 11 requires an amount of 0.01 to 5% by weight, and claims 12 and 24 require an amount of 1.5 to 2.5% by weight, all understood as “by weight of the composition.” Selecting constituent amounts in a formulation is the result of routine optimization, Ex. 1004 at ¶ 183, and thus constituent amounts are not patentably distinguishing claim elements. Further, neither the prosecution history nor the specification indicates that there is anything critical to the claimed weight percentages. Therefore, claims 11, 12, and 24 are obvious for the same reasons discussed above with respect to claims 1 and 19. Ex. 1004 at ¶ 183.

9. **Claim 13 is Obvious Over Chiba and Aulton**

Claim 13 depends from claim 1 and requires that the S1P receptor agonist be micronized. The “micronized” element of claim 13 should be interpreted as constituting a process limitation in a claim otherwise directed to a composition.
Claim 13 should therefore be construed as a product-by-process claim. The patentability of a product-by-process claim focuses on the product, not the process for making it. See Amgen Inc. v. F. Hoffman-LaRoche Ltd, 580 F.3d 1340, 1369-1370 and n. 14 (Fed. Cir. 2009). Accordingly, by its plain language and as a matter of law, claim 13 does not add a patentably distinguishing element to the claim composition from which it depends, and claim 13 is unpatentable for the same reasons as claim 1. During prosecution of the ’283 patent, the Examiner treated claim 13 (then-pending claim 24) as reciting product-by-process limitations and accorded no patentable weight thereto. Ex. 1003 at 1236, 1237. Applicants did not dispute that characterization. Ex. 1003 at 1261-1272.

In any event, a person of skill in the art in April 2003 would have turned to the conventional technique of micronizing in designing the claimed solid oral dosage form as a matter of routine optimization to aid in the quick dissolution of pharmaceutically active substance. Ex. 1004 at ¶ 179; Ex. 1015 at 000004; Ex. 1009 at 000053. Further, neither the prosecution history nor the specification indicate that there is any criticality to the micronization of the S1P receptor agonist. The Rane testing employed FTY720 in solution, rendering particle size limitations outside the scope of such testing. Therefore, claim 13 is obvious for the same reasons discussed above with respect to claim 1. Ex. 1004 at ¶ 179.

10. Claim 14 is Obvious Over Chiba and Aulton
Claim 14 depends from claim 1 and requires that the S1P receptor agonist be pre-screened with a 400 to 500 μm mesh screen. The “pre-screened” element of claim 14 should be interpreted as constituting a process limitation in a claim otherwise directed to a composition. Claim 14 should therefore be construed as a product-by-process claim. The patentability of a product-by-process claim focuses on the product, not the process for making it. See Amgen Inc., 580 F.3d at 1369-1370 and n.14. Accordingly, by its plain language and as a matter of law, claim 14 does not add a patentably distinguishing element to the claim 1 composition from which it depends, and claim 14 is unpatentable for the same reasons as claim 1.

During prosecution of the ’283 patent, the Examiner treated claim 14 (then-pending claim 25) as reciting product-by-process limitations and accorded no patentable weight thereto. Ex. 1003 at 1236, 1237. Applicants did not dispute that characterization. Ex. 1003 at 1261-1272.

In any event, a person of skill in the art in April 2003 would have turned to the conventional technique of pre-screening in designing the claimed solid oral dosage form as a matter of routine optimization to control the desired particle size distribution. (Ex. 1016 at 000012.) Further, neither the prosecution history nor the specification indicate that there is any criticality to the pre-screening of the S1P receptor agonist. The Rane testing employed FTY720 in solution, rendering particle size limitations outside the scope of such testing. Therefore, claim 14 is
obvious for the same reasons discussed above with respect to claim 1. (Ex. 1004 at ¶ 179.)

11. **Claims 15, 16, 25 and 26 are Obvious Over Chiba and Aulton**

Claims 15 and 16 depend from claim 1 and further require that the dosage form be a tablet and a capsule, respectively. Similarly, claims 25 and 26 depend from claim 19 and further require that the dosage form be a tablet and capsule, respectively. Both tablets and capsules were conventional dosage forms in April 2003. Ex. 1021 at 000005. Further, neither the prosecution history nor the specification indicate that there is any criticality to the type of solid oral dosage form of the composition. The Rane testing did not test compatibility in a tablet or capsule. Therefore, claims 15, 16, 25, and 26 are obvious for the same reasons discussed above with respect to claims 1 and 19. Ex. 1004 at ¶ 178.

12. **Claims 27 and 28 are Obvious Over Chiba and Aulton**

Claims 27 and 28 depend, directly and indirectly, from claim 19 and further require that the mannitol used in the composition have a mean particle size of 100 to 300 μm (claim 27) and 150 to 250 μm (claim 28). According to the specification, at least one commercially available mannitol product with the claimed characteristics was available in April 2003. Ex. 1001 at col. 10, ll. 10-12. It would have been a matter of routine optimization for an ordinarily skilled artisan to select this commercially available mannitol product. Further, neither the
prosecution history nor the specification indicate that there is any criticality to the mean particle size of the mannitol used in the composition. The Rane testing does not report the particle size of mannitol employed. Therefore, claims 27 and 28 are obvious for the same reasons discussed above with respect to claim 19. Ex. 1004 at ¶¶ 186 & 187.

13. **Claims 29 and 30 are Obvious Over Chiba and Aulton**

Claims 29 and 30 depend, directly and indirectly, from claim 19 and further require that the mannitol used in the composition have a bulk density of 0.4 to 0.6 g/mL and 0.45 to 0.55 g/mL, respectively. According to the specification, at least one commercially available mannitol product with the claimed characteristics was available in April 2003. Ex. 1001 at col. 10, ll. 10-12. It would have been a matter of routine optimization for an ordinarily skilled artisan to select this commercially available mannitol product. Further, neither the prosecution history nor the specification indicate that there is any criticality to the bulk density of the mannitol used in the composition. The Rane testing does not report the bulk density of mannitol employed. Therefore, claims 29 and 30 are obvious for the same reasons discussed above with respect to claim 19. Ex. 1004 at ¶¶ 186 & 187.

14. **Claim 31 is Obvious Over Chiba and Aulton**

Claims 31 depends from claim 19 and further requires that the mannitol used in the composition have a single point surface area of 1m$^2$/g to 7m$^2$/g. According to
the specification, at least one commercially available mannitol product with the
claimed characteristic was available in April 2003. Ex. 1001 at col. 10, ll. 10-12. It
would have been a matter of routine optimization for an ordinarily skilled artisan to
select this commercially available mannitol product. Further, neither the
prosecution history nor the specification indicate that there is any criticality to the
single point surface area of the mannitol used in the composition. The Rane testing
does not report the surface area of the mannitol employed. Therefore, claim 31 is
obvious for the same reasons discussed above with respect to claims 19. Ex. 1004
at ¶¶ 186 & 187.

15. **Claims 17 and 18 are Obvious Over Chiba and Aulton**

Claims 17 and 18 depend, directly and indirectly, from claim 1 and are
drawn to treating a disease, such as an autoimmune disease (claim 17) or multiple
sclerosis (claim 18) with the solid oral dosage form of claim 1. Chiba discloses that
the compounds disclosed therein, including FTY720, are useful in treating
autoimmune diseases, including multiple sclerosis. Ex. 1006 at col. 6, ll. 26-49. It
would have been obvious for the ordinarily skilled artisan to employ the claim 1
and 19 compositions in treating indications for which FTY720 was identified in the
prior art as useful. Ex. 1004 at ¶ 185. Therefore, claims 17 and 18 are obvious for
the same reasons discussed above with respect to claim 1.
VI. TABLE OF ADDITIONAL PRIOR ART

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<tr>
<td>“Akers”</td>
<td>102(b)</td>
<td>Akers demonstrates that it was known in the art how to perform drug/excipient compatibility studies, and that it was important to perform drug/excipient compatibility studies when developing a solid oral dosage forms. Ex. 1004 at ¶ 104.</td>
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<td>Ex. 1010</td>
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<tr>
<td>“Lieberman”</td>
<td>102(b)</td>
<td>Lieberman further demonstrates that an artisan would perform drug/excipient compatibility studies as part of the preformulation studies in development of tablets. Ex. 1004 at ¶¶ 105-108. Lieberman also explains that there is a limited number of excipients—“probably</td>
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less than 25”— that are commonly used in tablets. Ex. 1012 at 000095-96; Ex. 1004 at ¶ 109.
Lieberman states that mannitol is one of a small number of compounds commonly used as a diluent in tablet formulation. Ex. 1004 at ¶ 109.

| “Serajuddin” | 102(b) | Serajuddin describes the selection of excipients for use in solid dosage forms through drug-excipient compatibility testing where water is added to the drug/excipient mixture. Ex. 1004 at ¶¶ 110-113.
Serajuddin also confirms the known incompatibility of lactose with drugs containing a primary amine. Id. at ¶¶ 114 & 115. |

| “A. Serajuddin, A Selection of Solid Dosage Form Composition through Drug-Excipient Compatibility Testing, 88 JOURNAL OF PHARMACEUTICAL SCIENCES 696 (1999). Ex. 1017 | |  |
“Alderborn”
Ex. 1023

102(b)
Alderborn confirms that an artisan in 2002 would have understood that diluents are a class of excipients commonly used in tablets, which includes mannitol among a small number of other commonly-used tablet diluents. Ex. 1004 at ¶¶ 117-120.

“Kibbe - mannitol”
Ex. 1014.

102(b)
Kibbe - mannitol confirms that it is generally known that “[m]annitol is widely used in pharmaceutical formulations” where “it is primarily used as a diluent (10-90% w/w) in tablet formulations.” Ex. 1014 at

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1 Based on the publication dated provided in Ex. 1024, it is Petitioners’ understanding that Alderborn is prior art to the ’283 patent under 35 U.S.C. § 102(b). Due to the year of publication (2002), however, this book chapter is at least prior art under § 102(a).
Kibbe also describes the advantages of mannitol including that it (i) is not hygroscopic so is safe for moisture-sensitive drugs; (ii) granulations of drug with mannitol dry easily; (iii) has a negative heat of solution is sweet and has good mouth feel; (iv) has no reported incompatibilities in the dry state; and (v) does not undergo Maillard reactions. Ex. 1014 at 000005-8; Ex. 1004 at ¶¶ 121 & 122.

When using mannitol in a tablet formulation, recommended concentrations of lubricant are “1% w/w calcium stearate or 1-2% w/w magnesium stearate.” Ex. 1014 at 000008; Ex. 1004 at ¶
| “Ward” | 102(b) | Ward demonstrates that it was generally known that mannitol was generally compatible with drugs because it was inert with respect to several common mechanisms that cause drug-excipient interaction, including reaction of the excipient with an amine in the drug (amine browning). Ex. 1020 at 000007; Ex. 1004 at ¶¶ 124-127. |
|———|———|———|
| “Kibbe — lactose” | 102(b) | Kibbe - lactose confirms that a person of ordinary skill in the art understood that “[a] Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown-colored products.” Ex. 1013 at 000012; |
| “Kibbe — lactose” | 102(b) | Kibbe - lactose confirms that a person of ordinary skill in the art understood that “[a] Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown-colored products.” Ex. 1013 at 000012; |
| “Wirth” | 102(b) | Wirth confirms that it was known that drugs containing primary and secondary amines and their salts were prone to degradation via the Maillard reaction in the presence of reducing sugars like lactose. Ex. 1004 at ¶¶ 130-133. |

| “Lachman” | 102(b) | Lachman confirms that persons of ordinary skill in the art commonly reduced the particle size of drugs because “Mew materials used in pharmaceuticals exist in the optimum size.” Ex. 1015 at 000004; Ex. 1004 at ¶ 134. Lachman explains that equipment used to reduce the particle size of drugs often includes a screen to control the size of the resulting |
| **“O’Connor”** | 102(b) | O’Connor confirms that persons of ordinary skill in the art commonly reduced the particle size of drugs, which included micronizing. Ex. 1016 at 000005; Ex. 1004 at ¶ 137. O’Connor also explains that screening pharmaceutical powders with a mesh of a particular size was a common step in pharmaceutical manufacturing involving powders. Ex. 1016 at 00006; Ex. 1004 at ¶ 138. O’Connor also confirms that a |
person of ordinary skill in the art would consider powders to be a solid dosage form that is suitable for oral administration. Ex. 1016 at 000019; Ex. 1004 at 139 & 140.

VII. CONCLUSION

Claims 1 through 32 of the ’283 patent are unpatentable for the reasons set forth above. Petitioners have established a reasonable likelihood of prevailing on this Ground, and respectfully request that this petition be granted, that Inter Partes Review be instituted, and that claims 1 through 32 of the ’283 patent be found unpatentable and canceled.

Respectfully submitted,

December 31, 2014

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that this “PETITION FOR INTERPARTES REVIEW OF U.S. PATENT 8,324,283 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42,” including its supporting evidence (Exhibits 1001 to 1025), was served in its entirety this 31st day of December 2014 on the Patent Owners, Novartis AG and Mitsubishi Pharma Corp, as well as at the correspondence address of record for the ’283 patent, as follows:

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