IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HORIZON MEDICINES LLC, Plaintiff, v. ALKEM LABORATORIES LTD., Defendant.	Civil Action No. 18-1014-RGA

TRIAL OPINION

Caryn C. Borg-Breen, Esq., Jessica Tyrus Mackay, Esq., Christopher W. Weber, Esq., GREEN GRIFFITH & BORG-BREEN LLP, Chicago, IL; Chad S.C. Stover, Esq., BARNES & THORNBURG LLP, Wilmington, DE.

Attorneys for Plaintiff.

William A. Rakoczy, Esq., Amy D. Brody, Esq., Anuj K. Wadhwa, Esq., Kevin P. Burke, Esq., Melvin W. Gaddy, Esq., RAKOCZY MOLINO MAZZOCHI SIWIK LLP, Chicago, IL; Dominick T. Gattuso, Esq., HEYMAN ENERIO GATTUSO & HIRZEL LLP, Wilmington, DE.

Attorneys for Defendant.

November 30, 2020

/s/ Richard G. Andrews
ANDREWS, U.S. DISTRICT JUDGE:

Horizon Medicines LLC brought this action against Alkem Laboratories Ltd. for infringement of six patents.[1] (D.I. 1). I held a bench trial from September 14 to 16, 2020.[2] By trial the parties had narrowed the case to U.S. Patent No. 8,067,033 ("the '033 patent").[3]

Before the Court are the issues of validity and infringement of the asserted patent claims. Horizon asserts infringement of claims 1, 8, 11, and 14 of the '033 patent. (D.I. 205). I have considered the parties' post-trial briefing. (D.I. 216, 218, 226, 227, 231, 232).

For the following reasons, I find claims 1, 8, 11, and 14 of the '033 patent invalid for obviousness and not infringed. I find claims 1, 8, 11, and 14 of the '033 patent not invalid for indefiniteness.

I. BACKGROUND

Horizon owns New Drug Application No. 022519 for DUEXIS® (ibuprofen and famotidine) tablets, 800 mg / 26.6 mg. (D.I. 189 Ex. 1 ¶¶ 3-4). The Indications and Usage section of the prescribing information for DUEXIS® (Revised July 2019), as currently approved by the FDA (the "DUEXIS® Label"), states in part that DUEXIS® "is indicated for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper gastrointestinal ulcers, which in the clinical trials was defined as a gastric

[1] The Complaint was filed by Plaintiffs Horizon Pharma, Inc. and Horizon Pharma USA. Horizon Medicines LLC (herein, "Horizon") was thereafter substituted for such Plaintiffs as set forth in the parties' Joint Stipulation to Substitute Parties filed on September 18, 2018. (*See* D.I. 12).

[2] Witnesses testified in person, by remote video, and by deposition. I cite to the trial transcript (D.I. 222, 223, 224) as "Tr."

[3] The Complaint alleges infringement of U.S. Patent Nos. 8,309,127 (the "'127 patent"), 8,318,202 (the "'202 patent"), 8,449,910 (the "'910 patent"), and 8,501,228 (the "'228 patent"), also listed in the Orange Book for DUEXIS®. The parties entered into a Stipulation such that those four patents are no longer asserted in this litigation. (See D.I. 44, 49). The complaint also alleges infringement of U.S. Patent No. 8,067,451 B2 (the "'451" patent). In a letter, Horizon informed the Court that Horizon did not plan to present its infringement case concerning the '451 patent at trial. (D.I. 200).

and/or duodenal ulcer, in patients who are taking ibuprofen for those indications." (*Id.* ¶ 8). The asserted patent is listed in the Orange Book for DUEXIS®. (*Id.* ¶ 19). Alkem submitted Abbreviated New Drug Application (ANDA) No. 211890 on March 31, 2018 seeking FDA approval to engage in the commercial manufacture, use, and sale of ibuprofen and famotidine tablets, 800 mg / 26.6 mg ("ANDA Product"). (*Id.* ¶¶ 10, 11). The active pharmaceutical ingredients in Alkem's ANDA Product are Ibuprofen, USP and Famotidine, USP. (*Id.* ¶ 13). On May 29, 2018, Alkem sent a "Notification of Certification of Invalidity, Unenforceability and/or Non-Infringement for U.S. Patent Nos. 8,067,033 B2, 8,067,451 B2, 8,309,127 B2, 8,318,202 B2, 8,449,910 B2 and 8,501,228 B2 Pursuant to § 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act" to Horizon Pharma, Inc. and Horizon Pharma USA, Inc. Alkem indicated that it was seeking FDA approval of its ANDA so that it could engage in the commercial manufacture, use and sale of its ANDA Product before the expiration of, as relevant here, the '033 patent. (*Id.* ¶ 12). Horizon then filed this action alleging infringement by Alkem's ANDA submission. (D.I. 1).

The asserted patent is directed to stable pharmaceutical compositions of famotidine and ibuprofen in a single dosage form, comprising a famotidine core having a reduced or minimal surface area surrounded by a layer of ibuprofen. ('033 pat. at Abstract). Independent claim 1 and dependent claims 8, 11, and 14 of the '033 patent read as follows:

> 1. A pharmaceutical composition comprising a first portion that comprises 800 mg ibuprofen and a second portion that comprises 26.6 mg famotidine, wherein the surface area of direct physical contact between ibuprofen and famotidine does not exceed 130 mm^2, wherein no more than about 1% sulfamide is present when the composition is stored at 40° C. and 75% relative humidity for a period of one month, wherein the composition is formulated so that release of both the ibuprofen and the famotidine occurs rapidly at about the same time, wherein none of the composition, the famotidine, and the ibuprofen is enterically coated or formulated for sustained or delayed release, and wherein the composition is for use according to a TID (three times per day) administration schedule for reducing

the risk of developing ibuprofen-induced ulcers in a human patient requiring ibuprofen for an ibuprofen-responsive condition.

8. The composition of claim 1 wherein the second portion comprises a layer of famotidine and the first portion comprises a layer of ibuprofen and the two layers are separated by a barrier layer.

11. The composition of claim 1 wherein the composition is formulated so that at least about 80% of the famotidine and at least about 80% of the ibuprofen are released from the composition into solution within 30 minutes at a pH of about 6.8 to about 7.4.

14. The composition of claim 1 wherein at least 98% of the ibuprofen and the famotidine are each present when the composition is stored under room temperature storage conditions of 25° C. and 60% relative humidity for a period of nine months.

I have construed the term "a first portion" to mean "an ibuprofen compartment that is not core" and the term "a second portion" to mean "a famotidine compartment that is not shell." (D.I. 89 at 1). I have construed the term "surface area of direct physical contact between ibuprofen and famotidine does not exceed 130 mm^2" to mean "the surface area over which no barrier layer that prevents physical contact is interposed between ibuprofen and famotidine does not exceed 130 mm^2." (*Id.* at 2). I have construed the term "barrier layer" to mean "layer interposed between components or adjacent compartments of the unit dosage form to prevent contact between the components or adjacent compartments." (*Id.*). I also adopted the parties' agreed-upon construction of "direct physical contact" as "the absence of a barrier layer between components or adjacent compartments of a unit dosage form." (*Id.*).

Horizon concedes that Alkem's ANDA Product does not literally infringe the '033 patent. (D.I. 216 at 6). Horizon argues infringement under the doctrine of equivalents. Alkem contends that it does not infringe any of the asserted claims, while conceding that its product meets the claim limitation "wherein the composition is for use according to a TID administration schedule for reducing the risk of developing ibuprofen-induced ulcers in a human patient

requiring ibuprofen for an ibuprofen-responsive condition" of claim 1 of the '033 patent. (D.I. 205). Alkem argues that all the asserted claims are invalid as obvious in view of the prior art. Alkem also contends that the "no more than about 1% sulfamide" limitation in all asserted claims is invalid as indefinite.

II. OBVIOUSNESS

Under the Court's construction (D.I. 89), independent claim 1 of the '033 patent contains multiple limitations directed to an 800 mg ibuprofen compartment that is not a core, a 26.6 mg famotidine compartment that is not shell, as well as certain stability, release, and dosing limitations. The asserted dependent claims contain additional limitations, such as the ibuprofen compartment and the famotidine compartment are in a bilayer, separated by a barrier layer (claim 8), release limitations wherein at least about 80% of the famotidine and at least about 80% of the ibuprofen are released from the composition into solution within 30 minutes at a pH of about 6.8 to about 7.4 (claim 11), and stability limitations wherein at least 98% of the ibuprofen and the famotidine are each present when the composition is stored under room temperature storage conditions of 25° C. and 60% relative humidity for a period of nine months (claim 14).

Alkem argues that all the asserted claims are invalid as obvious over the prior art. (D.I. 218 at 22-30). Specifically, Alkem argues that a person of ordinary skill in the art ("POSA") would have been motivated to combine the prior art teachings of either (1) Taha and/or US 2007/0043096 A1 (the'096 publication), USP, and US 2005/0020671 A1 (the '671 publication) or (2) Taha and/or the '096 publication, USP, and US 2005/0281876 A1 (the '876 publication) to administer the combination of the non-steroidal anti-inflammatory drug (NSAID) ibuprofen and the H2 receptor antagonist (H2RA) famotidine in effective dosages (800 mg TID; 80 mg total daily dose, respectively) to reduce the risk of developing ibuprofen-induced ulcers. (*Id.* at 8, 22-

30). With the exception of the '096 publication, the references on which Alkem relies undisputedly qualify as prior art under 35 U.S.C. § 102(b). (*Id.* at 8-9). Alkem contends that the '096 publication qualifies as prior art under 35 U.S.C. § 102(a) because the invention thereof was "known or used by others in this country" before the invention of the '033 patent. (*Id.* at 9). Horizon contends that the '096 publication cannot be used as prior art to the '033 patent because the subject matter of the '096 publication is not the work of "another" as required by 35 U.S.C. § 102(a). (D.I. 227 at 2).

A. Legal Standard

A patent claim is invalid as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406-07 (2007). The determination of obviousness is a question of law with underlying factual findings. *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012). "The underlying factual inquiries include (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) any relevant secondary considerations … ." *Western Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1369 (Fed. Cir. 2010) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1078-79 (Fed. Cir. 2012). A patentee, however, is not required to present evidence

of secondary considerations. *See Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1101-02 (Fed. Cir. 2015). In this case, there was no evidence concerning secondary considerations, and they therefore have no effect on the obviousness analysis.

A party asserting that a patent is invalid as obvious must "show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Id.* at 1361. That "expectation of success need only be reasonable, not absolute." *Id.* at 1364. "Whether an ordinarily skilled artisan would have reasonably expected success … is measured as of the date of the invention[] … ." *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1362 (Fed. Cir. 2009).

B. Findings of Fact

1. The level of ordinary skill in the art is a person with a background in pharmaceutical science (e.g., a bachelors or advanced degree in chemistry, organic or process chemistry, pharmaceutics, or a related field) and several years of experience in pharmaceutical formulation or as a clinician (e.g., gastroenterologist or rheumatologist) who has several years of experience with dosing and administration of drugs used for the treatment of arthritis and GI disorders.

2. The priority date of the '033 patent is November 30, 2007.

3. The listed inventors of the '033 patent are George Tidmarsh and Jerry Xu. They are the properly-named inventors of the '033 patent.

4. The listed inventors of the '096 publication are George Tidmarsh, Barry Golombik, and Tianshiuan Lii. They are the properly-named inventors of the

’096 publication.

5. Barry Golombik did not contribute to the purported novel aspect of the ’033 patent and therefore is properly not a named inventor of the ’033 patent.

6. The’096 publication is prior art under 35 U.S.C. § 102(a) to the ’033 patent.

7. Taha, USP, the ’671 Publication, and the ’876 Publication are prior art under 35 U.S.C. § 102(b) to the ’033 patent.

8. Each of the asserted claims is obvious over the combination of Taha and/or the ’096 Publication, USP, and the ’671 Publication.

9. Each of the asserted claims is obvious over the combination of Taha and/or the ’096 Publication, USP, and the ’876 Publication.

C. Conclusions of Law

1. Problem to be Solved

The parties do not seem to dispute that the withdrawal of Cox-2 inhibitors from the U.S. market in 2004-2005 created a market void for drug products used to manage pain relief. (DTX 766 at 2-3; Tr. 171:7-173:18, 463:1-464:19, 479:6-480:3, 590:10-591:1). In light of this withdrawal, it was well-recognized that “the number of patients who receive[d] traditional NSAIDs [was] likely to increase substantially,” making the most widely prescribed NSAID, ibuprofen, the obvious choice as replacement of Cox-2 inhibitors. (PTX 496 at S23-24; Tr. 171:23-172:13, 463:16-464:7). Plaintiff does not argue against the selection of ibuprofen as the most-likely NSAID for further use. (*See generally* D.I. 227).

By 2007, ibuprofen was generally regarded as safe, but it was also well-known that ibuprofen and other NSAIDs could cause gastritis, gastric ulceration, and duodenal ulceration.

(DTX 281 at ALKIF0101735, ALKIF0101739; PTX 371 at [0003]; PTX 496 at 1; Tr. 447:25-448:8, 478:18-479:5, 584:4-585:1). To address such gastrointestinal (GI) risks, practitioners co-prescribed gastroprotectants along with an NSAID. (DTX 770 at 142-43; PTX 371 at [0004], [0006]; Tr. 447:25-448:16, 585:2-16, 219:21-220:5).

The parties further do not seem to dispute that patient convenience and compliance would have motivated the skilled person to pursue a combination product by 2007, wherein a gastroprotectant was combined with the NSAID of choice, here ibuprofen, to overcome possible GI problems, such as ulcers, from the use of the NSAID. (Tr. 463:1-464:19; PTX 511 at 1141, 1142, Table 1). A POSA understood that the patient population would typically take additional individual drug products daily, which would have motivated a POSA to consider a combination drug product to reduce pill burden. (Tr. 465:25-466:10, 220:6-9). A prior art study, Sturkenboom, disclosed that 37% of patients were non-adherent in that they did not take the prescribed amount of gastroprotectant in addition to the prescribed NSAID. (PTX 511 at 1141, 1143, Table 2). The rate of non-adherence increased from 9.7% for subjects with one NSAID prescription to 61% for patients with three or more NSAID prescriptions. (PTX 511 at 1141). Sturkenboom's study showed that non-adherence was a more significant issue for patients on chronic therapy. (Tr. 466:19-467:12). In response, by 2007 major pharmaceutical companies had launched or were collaborating to develop fixed dose combinations of NSAIDs (e.g., naproxen) and gastroprotectants for the treatment of pain. (*See* DTX 281 at ALKIF0101744; DTX 769 at ALKIF0103018-19; DTX 998 at HZNDXS0177365; DTX 1004 at HZNDXS0177340; Tr. 453:12-454:4, 463:1-464:19, 479:6-480:3).

2. Level of Person of Ordinary Skill

Defendant asserts a POSA would have a background in pharmaceutical science (e.g., a

bachelors or advanced degree in chemistry, organic or process chemistry, pharmaceutics, or a related field) and several years of experience in pharmaceutical formulation or as a clinician (e.g., gastroenterologist or rheumatologist) who has several years of experience with dosing and administering drugs used for the treatment of arthritis and GI disorders. (D.I. 218 at 8). Plaintiff does not argue for a different understanding of a POSA in its post-trial brief, and its experts testified that their opinions would not change if I were to adopt the opposing expert's definition of a POSA. (Tr. 196:9-12; 260:23-261:2; 702:15-703:3; 752:6-9). Therefore, I adopt Defendant's definition of a POSA. If I were to adopt Plaintiff's definition as offered at trial, no part of the obviousness analysis would change.

3. Scope and Content of the Prior Art

a. Asserted Prior Art References

i. The '096 Publication Qualifies as Prior Art Under 35 U.S.C. § 102(a)

The parties dispute whether the '096 publication is § 102(a) prior art to the '033 patent. The issue arises because the '096 publication published on February 22, 2007, earlier than the November 30, 2007 priority date of the '033 patent, and the '096 publication's listed inventors are Dr. Tidmarsh, Mr. Golombik, and Dr. Lii, while the '033 patent's listed inventors are Dr. Tidmarsh and Dr. Xu. To qualify as prior art under pre-AIA 35 U.S.C. § 102(a), the '096 publication needs to be "known or used by others in this country" before the invention of the '033 patent. (MPEP § 2132). "[O]thers" refers to any entity that is different from the inventive entity; "[t]he entity need only differ by one person to be 'by others.'" (*Id.*). Specifically, the subject matter relied upon in a prior publication must have been conceived by "another," meaning by a different inventive entity. *Riverwood Int'l Corp. v. R.A. Jones & Co.*, 324 F.3d

1346, 1356 (Fed. Cir. 2003).

Plaintiff argues that the common subject matter of the ’096 publication and the ’033 patent — a combination dosage form comprising 800 mg ibuprofen and 26.6 mg famotidine for TID administration to reduce the risk of developing ibuprofen-induced ulceration in a human patient requiring ibuprofen for an ibuprofen-responsive condition — was conceived of by Dr. Tidmarsh, either alone or with Mr. Golombik, and that neither Dr. Lii nor Dr. Xu contributed to the conception of this subject matter. (D.I. 227 at 5). Dr. Lii was a formulation chemist with UPM, a contract research laboratory retained by Horizon, and Dr. Xu was a formulation scientist with Pii, another contract research laboratory retained by Horizon subsequent to the retention of UPM. (Tr. 53:2-5, 82:3-9, 88:13-15, 110:11-14, 233:16-22, 241:24-242:3.) Thus, Plaintiff advocates for two possible scenarios. The first, that “Tidmarsh alone conceived of the overlapping subject matter, because Golombik’s contributions do not rise to the level of conception, and accordingly the ’033 patent is not the work of ‘another.’” (*Id.* at 8). Under this first scenario, Plaintiff states “no change in inventorship is needed, as Golombik is not listed as an inventor of the ’033 patent, and the ’096 publication is only a patent publication, not a granted patent.” (*Id.*). The second, that “Tidmarsh and Golombik together conceived of the overlapping subject matter, in which case Golombik should have been named as a co-inventor on the ’033 patent, and the ’033 patent also is not the work of ‘another.’” (*Id.* at 8-9). Under this second scenario, Plaintiff “respectfully requests that the Court reconsider its denial of Horizon’s request to change the inventorship of the ’033 patent pursuant to 35 U.S.C. § 256.” (*Id.* at 9).

Defendant contends that the ’096 publication is § 102(a) prior art as it is the work of another. (D.I. 218 at 9). Defendant argues that Plaintiff “offered no evidence to corroborate its new-found litigation theory that somehow Dr. Tidmarsh alone invented the subject matter of the

‘096 publication (or any elements thereof), without contribution of Dr. Lii—no corroborating evidence, much less clear and convincing, including documents (e.g., lab notebooks, notes) or testimony from Dr. Lii." (*Id.*). Defendant argues that Plaintiff did not "come close to proving by clear and convincing evidence that Mr. Golombik should be a named inventor on the ‘033 patent." (*Id.* at 10).

Generally, the inventors named on the face of an issued patent are presumed correct. *Scott v. Zimmer, Inc.*, 889 F. Supp. 2d 657, 662 (D. Del. 2012). "Thus, plaintiffs seeking to add … inventors must meet the heavy burden of proving [their] case by clear and convincing evidence." (*Id.*) (internal citations omitted). Misjoinder (including individuals who are not true inventors) and non-joinder (omitting individuals who are true inventors) must be proven by clear and convincing evidence by the party asserting that the inventors named in the patent are incorrect. *Vanderbilt Univ. v. ICOS Corp.*, 601 F.3d 1297, 1305 (Fed. Cir. 2010) ("Our precedent has long required proof of misjoinder or nonjoinder of co-inventors by clear and convincing evidence.")

"Conception is the touchstone to determining inventorship." *Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997). Conception requires corroborating proof of the alleged inventor's specific contribution to some novel element of the invention. *EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc.*, 859 F.3d 1341, 1346-47 (Fed. Cir. 2017); *Scott*, 889 F. Supp. 2d at 663, 668. While the Federal Circuit has "recognized that contemporaneous documentary evidence can serve as ‘the most reliable proof that the inventor's testimony has been corroborated,'" the Federal Circuit has clarified that "[a] number of factors may guide the corroboration assessment, including the time period between the event and trial and the interest of the corroborating witness in the subject matter in suit." *EmeraChem*, 859 F.3d at 1347 (citing

Sandt Tech., Ltd. v. Resco Metal & Plastics Corp., 264 F.3d 1344, 1351 (Fed. Cir. 2001)). "An evaluation of all pertinent evidence must be made so that a sound determination of the credibility of the inventor's story may be reached." *Price v. Symsek*, 988 F.2d 1187, 1195 (Fed. Cir. 1993).

"[W]here an inventor tries to prove prior conception, the 'inventor's testimony, standing alone, is insufficient to prove conception—some form of corroboration must be shown.'" *EmeraChem*, 859 F.3d at 1345-46 (citation omitted). "This concept stems from the concern the 'inventors … would be tempted to remember facts favorable to their case by the lure of protecting their patent . . . .'" *Id.* (citation omitted).

The '096 publication claims an immediate / rapid release oral dose form comprising 800 mg ibuprofen and 26.6 mg famotidine in an admixture for TID dosing for reducing NSAID-induced ulcers. (PTX 371 at Abstract, [0006], [0013], [0097]-[0099], claims 1 and 11; Tr. 88:18-25). The named inventors on the '096 publication are George Tidmarsh, Barry Golombik, and Tianshiuan Lii. (PTX-371). Dr. Tidmarsh and Mr. Golombik testified to working together in an iterative process whereby they debated different NSAID and gastroprotectant choices and different dosing regimens, to come up with the idea for an immediate release, combination pharmaceutical composition containing 800 mg ibuprofen and 26.6 mg famotidine, dosed according to a TID administration schedule to reduce the risk of developing ibuprofen-induced ulcers. (Tr. 112:12-118:14, 225:18-235:23). These discussions were in response to learning that the widely prescribed COX-2 inhibitor, VIOXX®, was being pulled from the market due to safety concerns. (Tr. 47:23-48:18, 225:1-17). They believed that physicians would revert to prescribing non-selective NSAIDs, which were associated with GI toxicity, and they formed Horizon to create a safer NSAID by combining an NSAID with a gastroprotectant. (Tr. 47:23-49:21, 225:1-17).

Dr. Tidmarsh and Mr. Golombik each testified that they are not aware of anyone else contributing to the idea of a combination dosage form comprising 800 mg ibuprofen and 26.6 mg famotidine for three times a day administration to reduce the risk of developing ibuprofen-induced ulceration in a human patient requiring ibuprofen for an ibuprofen-responsive condition. (Tr. 116:19-25; 232:1-8). Dr. Tidmarsh and Mr. Golombik testified that neither Dr. Lii, a named inventor on the '096 publication but not on the '033 patent, nor Dr. Xu, a named inventor on the '033 patent but not on the '096 publication, contributed to the identification of 800 mg ibuprofen and 26.6 mg famotidine, their administration TID, that the combination product would be formulated for immediate release, or that the combination product could be used to reduce the incidence of developing ibuprofen-induced ulcers. (Tr. 120:16-129:2, 233:23-236:14). Dr. Tidmarsh testified that Dr. Lii was named as a co-inventor of the '096 publication because of his contribution to the identification of formulations, excipients, and methods of manufacture for the admixture formulations disclosed in the publication. (Tr. 89:13-20, 127:16-128:15). Similarly, Dr. Tidmarsh testified that Dr. Xu was named as a co-inventor on the '033 patent because Dr. Tidmarsh and Dr. Xu, a formulation scientist, collaborated with respect to developing the claimed stable composition. (Tr. at 110:11-22, 118:25-120:15).

For purposes of the '096 publication, I find that by the time Horizon retained UPM and later Pii, Dr. Tidmarsh and Mr. Golombik had already conceived of a combination dosage form comprising 800 mg ibuprofen and 20 or 26.6 mg famotidine for TID administration to reduce the risk of developing ibuprofen-induced ulceration in a human patient requiring ibuprofen for an ibuprofen-responsive condition. (Tr. 78:2-24, 125:19-129:2; 245:6-11). That someone had conceived of the combination by that time is corroborated by Horizon's March 22, 2005, pre-IND Meeting Request to the FDA, which was prepared by both Dr. Tidmarsh and Mr. Golombik

(Tr. 51:7-52:22; PTX 766 at 1, 3-5), Horizon's May 9, 2005, Background Information submitted to the FDA in advance of a Pre-IND Meeting (Tr. 54:16-57:2; PTX 763 at 1, 3-4), and Horizon's January 24, 2006, original IND submission to the FDA (Tr. 63:1- 66:16; PTX 768 at 1; PTX 771 at 3). No one at trial was trying to prove that Mr. Golombik (whose background as a non-scientist businessman makes him an unlikely candidate to be an inventor on scientific breakthroughs) was not an inventor on the '096 publication, and certainly no one proved by clear and convincing evidence that he was misjoined as an inventor on that publication. Therefore, I find that Dr. Tidmarsh and Mr. Golombik are correctly named inventors on the '096 publication for their conception of a combination dosage form comprising 800 mg ibuprofen and 20 or 26.6 mg famotidine for TID administration to reduce the risk of developing ibuprofen-induced ulceration in a human patient requiring ibuprofen for an ibuprofen-responsive condition. There was no evidence to suggest, let alone prove clearly and convincingly, that Dr. Lii was not correctly named an inventor on the '096 publication for his contributions to formulation. Thus, I find that he was correctly named.

However, I find that Mr. Golombik is correctly not named as an inventor of the '033 patent, and Dr. Tidmarsh and Dr. Xu are correctly named inventors of the '033 patent. The '033 patent asserted claims relate to a stable pharmaceutical composition comprising a separation of a famotidine compartment and an ibuprofen compartment. (PTX 1 at Title and Abstract, 1:59-62; Tr. at 110:15-112:11, 129:25-131:12). The purported novel aspect of the '033 patent claims "no more than about 1% sulfamide is present when the composition is stored at 40° C and 75% relative humidity for a period of one month." (PTX 1 at claim 1). This is the result of "[t]he reduction and/or minimization of the surface area of the core, or of direct physical contact between the incompatible active pharmaceutical ingredients, [] achieved through control of the

geometry of the famotidine compartment of unit dosage forms in accordance with the present invention." (PTX 1 at 6:10-15). The purported novel aspect of the invention being the separation of the famotidine compartment from the ibuprofen compartment, resulting in greater stability, is supported by the prosecution history; Plaintiff overcame a USPTO rejection by amending its claims to include a stability limitation. (D.I. 75-2, J.A. 11 at HZNDXS0002424). Only then did the USPTO allow the claims, stating in its reason for allowance, "The closest prior art teaches the combination of famotidine and ibuprofen in similar proportions but does not teach the presence of no more than 1 % sulfamide when the composition is stored at 40°C and 75% relative humidity for a period of one month; this unexpected result being the result of limiting the contact between the drugs." (D.I. 75-2, J.A. 12 at HZNDXS0002448).

Dr. Tidmarsh testified that he collaborated with Dr. Xu with respect to developing the claimed stable composition by separating the famotidine compartment from the ibuprofen compartment. (Tr. 110:11-22, 118:25-120:15). The evidence supports the formulation work by Dr. Xu played a significant role. ((*See* PTX 1 at Title and Abstract), 1:59-62 (describing need for compositions "that exhibit exceptional stability"); Tr. 90:12-14 (confirming Dr. Tidmarsh did "not identify any potential solutions for the incompatibility in the '096 publication"), 110:11-22, 118:25-119:16). Mr. Golombik testified that "coming up with the idea of a composition where the ibuprofen is in a first portion and famotidine is in a second portion" was Dr. Tidmarsh's contribution and not Mr. Golombik's. (Tr. 238:16-241:7). Mr. Golombik testified to not knowing what Dr. Xu's contributions to that limitation were, but testified that Dr. Xu was involved in developing a formulation with a famotidine core and an ibuprofen outer shell. (*Id.*).

Therefore, Plaintiff has not met its burden of establishing, by clear and convincing evidence, a specific contribution made by Mr. Golombik to the conception of a novel element of

a patent claim of the ’033 patent. *Scott*, 889 F. Supp. 2d at 668. Plaintiff fails in two ways.

First, since Mr. Golombik was not named on the ’033 patent, his purported contribution to it has to be shown by clear and convincing evidence. The testimony at trial failed to meet this standard. There was no corroboration of Mr. Golombik’s contribution. The testimony of both Mr. Golombik and Dr. Tidmarsh as to the contribution was convenient, uncorroborated, and not very credible. It was non-specific, basically being, Dr. Tidmarsh bounced ideas off of Mr. Golombik. The documentary evidence of when the idea was developed, cited above, did nothing to show that Mr. Golombik contributed to it. Thus, there was no proof that Mr. Golombik made even the slightest contribution to the ’033 patent.

Second, even assuming that Mr. Golombik made the contribution Horizon says he made, it would not matter. The conception contribution, which is supposed to be the idea of a combination dosage form comprising 800 mg ibuprofen and 20 or 26.6 mg famotidine for TID administration to reduce the risk of developing ibuprofen-induced ulceration in a human patient requiring ibuprofen for an ibuprofen-responsive condition, is recognized by his inventorship status on the ’096 publication. However, by the filing of the ’033 patent provisional date of November 30, 2007, the ’096 publication had been publicly available since February 22, 2007. The purported invention of the ’033 patent encompassing the separation of the famotidine compartment from the ibuprofen compartment resulting in greater stability, by Dr. Tidmarsh and Dr. Xu, was building on the disclosures directed to ibuprofen and famotidine, dosing, and indications in the ’096 publication by Dr. Tidmarsh, Mr. Golombik, and Dr. Lii. *See Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1362 (Fed. Cir. 2004) (“A contribution of information in the prior art cannot give rise to joint inventorship because it is not a contribution to conception.”). Under Plaintiff’s theory, the inventors of ibuprofen and famotidine would be

properly named inventors of the ’033 patent, as the patent claims build on the prior art by using those two ingredients. Mr. Golombik did not contribute to the purported novel aspect of the ’033 patent, and thus he is properly not named an inventor on the patent. *Levin v. Septodont, Inc.*, 34 F. App’x 65, at 75 (4th Cir. 2002) (rejecting proposed co-inventor based on *Pannu v. Iolab Corp*., 155 F.3d 1344 (Fed. Cir. 1998) where “contributions did not help to make the mouth rinse patentable”).

Both Plaintiff’s trial theory of Mr. Golombik as an inventor on the ’033 patent and its alternate late-stage post-trial theory of Mr. Golombik as not an inventor of the ’096 publication require clear and convincing evidence. *Vanderbilt*, 601 F.3d at 1305. This leaves a wide middle ground for the presumption of the correctness of the naming of the inventors for both the ’033 patent and the ’096 publication. Plaintiff is in that middle ground. Mr. Golombik and Dr. Lii are properly named inventors on the ’096 publication and not on the ’033 patent. Dr. Xu is properly a named inventor on the ’033 patent but not on the ‘096 publication. The ’096 publication subject matter is the work “of another” and therefore § 102(a) prior art to the ’033 patent.

ii. Taha

Taha is a May 1996 reference that discusses treatment with an 80 mg total daily dose of famotidine to reduce the cumulative incidence of both gastric and duodenal ulcers in patients with arthritis receiving long-term NSAID therapy, including ibuprofen. (PTX 262 at 1). The study compared two doses of famotidine, 20 mg twice daily for a total daily dose of 40 mg, and 40 mg twice daily for a total daily dose of 80 mg, with a placebo “to test the hypothesis that famotidine provides protection against NSAID-associated gastric and duodenal ulcers.” (*Id.*). Ibuprofen was administered at the “standard” dose, which Defendant’s expert Dr. Barnett testified is 800 mg TID. (*Id.*; Tr. at 602:5-22 (Barnett direct)). Taha disclosed that high-dose

famotidine was well-tolerated and effective in preventing both gastric and duodenal ulcers in patients receiving long-term NSAID therapy. (*Id.* at 1-2, 4-5).

iii. USP

The USP is the official compendia of pharmaceutical standards. (PTX 559 at 1). The prior art reference is the 2006 edition. (*Id.*). Under federal law, in order to go to market with a drug product, it must comply with the USP standards for individual active ingredients and other dosage forms including stability, impurity, potency, dissolution, and quality. (Tr. 489:1-17). The USP set a limit of no more than 1.5% total famotidine impurities during the expected shelf-life of the product. (PTX 559 at 9).

iv. The ’671 Publication

The ’671 publication was published on January 27, 2005. (DTX 136). It discloses and claims a pharmaceutical composition that comprises a core containing a first API (ranitidine, an H2RA), a shell containing a second API (acetylsalicylic acid or aspirin, an NSAID) that is incompatible with the first API (ranitidine), and a barrier layer that prevents physical contact between the core and the shell. (DTX 136 at Abstract). The barrier layer prevents physical contact and a reaction between the chemically incompatible APIs in the core and the shell. (*Id.* at [0023]). The barrier layer also reduces the transmission of, and preferably is impermeable to, moisture passing between the core and the shell. (*Id.*). The ’671 publication teaches that many pharmaceutical compositions that comprise incompatible APIs may be formulated with this design, as with the ’671 publication invention directed to acetylsalicylic acid and ranitidine. (DTX 136 at [0003]-[0005]).

The ‘671 publication describes a clear chemical incompatibility between ranitidine and acetylsalicylic acid; the two “react chemically with each other to produce degradation products.”

"The reaction becomes manifest in a matter of days and implies a serious stability problem for pharmaceutical compositions containing both active ingredients." (*Id.* at [0006]). To solve that problem, the inventors used tablet-in-tablet dosage forms comprising an 84 mg ranitidine core, an Opadry AMBTM barrier layer applied to the core, and a 500 mg acetylsalicylic acid shell. (*Id.* at [0036]-[0060] (Example 1), [0061]-[0065] (Example 2)). In both examples, the ranitidine core was shown to be stable for at least six months at 40°C / 75% relative humidity, and the acetylsalicylic acid outer shell was stable for at least two months at 40°C / 75% relative humidity. (*Id.* at [00060], [0065]).

v. The '876 Publication

The '876 publication was published on December 22, 2005. (DTX 785). It discloses an oral dosage form that has a core containing an acid-labile API surrounded by a barrier layer that is subsequently coated with a shell layer, which may be combined with a second API. (DTX 785 at Abstract, [0001], [0039], [0082], [0087]-[0088]). Figure 1 shows an embodiment with the acid-labile API in a small core, surrounded by a barrier layer, to which an outer shell containing a second API can be applied. (DTX 785 at [0039], Figure 1; Tr. at 500:12-501:8). Figure 2 shows a different embodiment in the configuration of a bilayer tablet, with the core containing the barrier coated acid-labile API in one layer and the second API in the other layer. (DTX 785 at [0040], Figure 2; Tr. at 501:9-18).

4. Comparing Prior Art and Claimed Subject Matter

a. Claim 1

i. Motivation to Select 800 mg TID Ibuprofen with a Reasonable Expectation of Success

Plaintiff does not argue against the selection of ibuprofen in its post-trial brief. (*See*

generally D.I. 227). However, Plaintiff contends that a POSA would not know what a "standard" dose of ibuprofen is given the disclosures in Taha administering a "standard" dose. Plaintiff argues that even assuming a "standard dose" refers to ibuprofen's FDA-approved "suggested dosages" for treating RA and OA, the approved dosages for ibuprofen ranged from "1200 mg-3200 mg daily," administered using a variety of unit dosages strengths and dosing intervals. (Tr. 583:1-9, 612:2-614:6; 726:6-24; DTX 281 at 11(Motrin® Ibuprofen Tablets (800 mg) Package Insert)). Plaintiff's expert Dr. Gibofsky testified that he treats the majority of his patients with 600 mg ibuprofen TID (1800 mg total daily), consistent with the standard recommended practice of using the "lowest effective dose" of ibuprofen. (Tr. 210:2-13; DTX 281 at 2, 6).

While the FDA-approved "suggested dosages" for treating RA and OA included 800 mg ibuprofen four times a day (QID) for 3200 mg total daily dose, the Motrin® Ibuprofen Tablets (800 mg) Package Insert also stated patients on 3200 mg ibuprofen did not show a better efficacy mean response compared with 2400 mg in well-controlled clinical trials. (DTX 281 at ALKIF0101740). Therefore, a POSA wanting to administer the greatest dose to provide relief for RA and OA while balancing the standard recommended practice of using the "lowest effective dose" of ibuprofen would be motivated to administer 800 mg ibuprofen TID, and to have a reasonable expectation of success in doing so. (Tr. at 582:11-584:3, 591:2-592:7).

ii. Motivation to Select an H2RA as the Gastroprotectant in a Combined NSAID/Gastroprotectant Product with a Reasonable Expectation of Success

In deciding which gastroprotectant to accompany ibuprofen in a combination product, the parties initially dispute whether a POSA would be motivated to select an active ingredient from

the H2RA class or the proton pump inhibitor (PPI) class. Plaintiff argues that a POSA would have selected a PPI, not an H2RA, because "the H2RA famotidine was only approved by the FDA for healing of active ulcers and maintenance therapy of healed ulcers—neither of which relates to preventing NSAID-induced ulcers." (D.I. 227 at 14; Tr. 716:5-717:21). Plaintiff contends that "a POSA would have understood prevention of NSAID-induced ulcers to be much more complicated than treatment or prevention of ulcers generally." (D.I. 227 at 14; Tr. 708:12-710:10, 714:2-24, 716:5-717:21). More specifically, Plaintiff contends that "PPIs had (1) better potency, (2) reduced risk of developing tolerance, and (3) reduced risk of mere symptom masking." (D.I. 227 at 15).

For potency, according to Plaintiff's expert, Dr. Scheiman, H2RAs were known to be less potent in suppressing gastric acid than PPIs, such that H2RAs were infrequently prescribed for any purpose. (Tr. 698:5-12, 720:8-21; DTX 989 at 1). For tolerance, Dr. Scheiman explained that in 2007, it was known that PPIs were not associated with tolerance issues. H2RAs block proteins, called receptors, on the membrane of stomach cells that respond to histamine, preventing acid production. (D.I. 218 at 13-14; DTX 989 at 1, 2; Tr. 598:3-16). Thus, patients taking H2RAs were prone to developing a tolerance because the body would upregulate acid in response to the H2RA blocking one of the receptors. (Tr. 718:16-720:7; DTX 989 at 2, 5; PTX 7-B at 1184). The prior art explains, "Once effective acid suppression has been achieved with a PPI, it can be maintained over the long term without increasing the dosage. In contrast, tolerance to H2RAs develops rapidly within 3-5 days of therapy." (DTX 989 at 2, 5; Tr. 712:23-713:4.) For symptom masking, the prior art discusses that taking a GI medication prophylactically can be "dangerous practice, because these medications may suppress symptoms—potential warning signs—without reducing the risk of serious GI complications." (DTX 114 at 5-6).

Defendant argues that a POSA would be motivated to select H2RAs over PPIs for a number of reasons. First, H2RAs had a faster onset of action than other gastroprotectants such as PPIs, which can be advantageous when administering concurrent high doses of an NSAID, such as ibuprofen. (DTX 989 at 5). The prior art explains that when PPI therapy begins, the degree of acid suppression increases over the first three days until a new steady state for acid secretion is achieved. (*Id.*) Unlike with H2RAs, maximum relief is not achieved with the first PPI dose. (*Id.*) Therefore, PPIs are generally not recommended for immediate symptom relief. (*Id.*) According to Defendant's experts, Dr. Chambliss and Dr. Barnett, the faster onset of action of H2RAs would have been advantageous for treating a patient with an ibuprofen-responsive condition, such as rheumatoid arthritis (RA) or osteoarthritis (OA), when the patient is experiencing an acute flare-up, and for those patients who miss doses or use the drug intermittently. (Tr. 470:25-472:12, 597:22-599:5, 630:10-21, 631:16-632:8). Defendant admits PPIs were known to be more potent than H2RAs. (D.I. 218 at 14). However, Defendant argues a POSA would have been dissuaded to use PPIs because the side effects were prevalent and well-known, including increasing the risk of hip fractures and potential interference with calcium absorption. (*See, e.g.*, DTX 918 at 2947, 2951, 2953; Tr. 470:25-472:14, 596:10-597:20). Thus, a POSA would have viewed famotidine as having a more favorable safety profile than a PPI. (Tr. 596:10-597:12). Defendant argues a financial motivation for a POSA to use H2RAs due to the cost-effectiveness of H2RA therapy over PPIs. (Tr. 595:22-596:9, 173:13-18).

It would not have been clear to a POSA to use PPIs over H2RAs. H2RAs had certain flaws; they were not as potent as PPIs and had the potential for tolerance development. There was some prior art that advised not to administer H2RAs prophylactically because of the potential for symptom masking. However, PPIs were not without their own drawbacks. H2RAs

had a faster onset of action than PPIs. Plaintiff minimizes this benefit "because it would have been inconsequential during chronic treatment, where the sustained efficacy of PPIs would be preferable." (D.I. 227 at 17). Despite this argument, I am persuaded by Defendant's experts who point out the faster onset of H2RAs is beneficial for patients who miss doses or use the drug intermittently, starting and stopping treatment in response to acute flare-ups. (Tr. 470:25-472:12, 597:22-599:5, 630:10-21, 631:16-632:8). The safety profile of H2RAs and their decreased risk of hip fractures and potential interference with calcium absorption compared to PPIs was particularly beneficial for patients with RA and/or OA. The cost considerations also favored H2RAs.

While some prior art advised not to administer H2RAs prophylactically for NSAID-induced ulcers, in light of the asserted prior art references — the '096 publication and Taha — that had already used famotidine effectively with ibuprofen, I find that a POSA would have been motivated to use H2RAs over PPIs. Neither class of gastroprotectants was flawless or a clear choice to a POSA. Considering a POSA would have been further motivated to provide an alternative therapy for reducing the risk of ulcers outside of existing therapies (Tr. 599:6-20) and the benefits that H2RAs demonstrated, a POSA would have had motivation to select this class of gastroprotectants for a combination therapy with ibuprofen. *See In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("a finding that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed by the patent applicant is the preferred, or most desirable, combination.")

iii. Motivation to Combine Famotidine with Ibuprofen with a Reasonable Expectation of Success

Defendant contends a POSA would have been motivated to select famotidine over other

H2RAs, e.g., cimetidine, ranitidine or nizatidine, because the POSA could minimize the dosage form size with the 80 mg daily approved dose. (*See* PTX 511 at 1141, 1143 (Table 2) (reporting 80 mg recommended dose of famotidine, 20 times less than recommended dose of cimetidine (1600 mg) and 7.5 times less than recommended dose for ranitidine and nizatidine (both 600 mg))). Defendant argues this capability "would have been an important consideration to the skilled person because using a higher dose of other approved H2RAs would either have dramatically increased the dosage form size, making it more difficult for the patient to swallow; or have required the administration of more than one tablet to obtain the required dose, increasing the pill burden and eliminating an advantage of a combination product." (D.I. 218 at 17; Tr. at 474:20-475:16). Defendant contends that Taha would have motivated a POSA to use famotidine in a combination therapy with ibuprofen because Taha "teaches that treatment with an 80 mg total daily dose of famotidine significantly reduces the cumulative incidence of both gastric and duodenal ulcers in patients with arthritis receiving long-term NSAID therapy, including ibuprofen." (D.I. 218 at 16; PTX 262 at 1435, 1437).

Plaintiff contends that a POSA in 2007 would have recognized that the Taha study had limitations that would have prevented a POSA from using famotidine in combination with ibuprofen with a reasonable expectation of success in reducing the risk of ibuprofen-induced ulceration. (Tr. 724:2-5, 727:2-17, 748:8-13.) Plaintiff argues that Taha provided minimal results regarding ibuprofen, as Taha reports the incidence of ulcers in each of the patient groups for all NSAIDs, and only 30 of the total 285 patients were taking NSAIDs. (Tr. 724:2-25; PTX 262 at 3.) Therefore, limited information could be gleaned for famotidine reducing the risk of ibuprofen-induced ulceration. (Tr. 725:1-5, 725:12-726:5). Plaintiff points out that Taha only discloses a "standard" dose of ibuprofen, not which specific dose was administered, and

therefore questions a POSA's understanding of famotidine's efficacy when taken with the specific high dose of ibuprofen. (Tr. 726:6-727:10).

Plaintiff criticizes Taha as critically flawed because it used a "convenience" population of patients who displayed risk factors for ulceration; specifically, half of the patients were already infected with *H. pylori*. (D.I. 227 at 19; Tr. at 724:2-15). Plaintiff argues that it was understood in 2007 that famotidine could treat or prevent the reoccurrence of *H. pylori*-induced ulcers. (Tr. 627:16-21; 697:2-7). Plaintiff argues a credible study of famotidine for the prevention of NSAID-induced ulcers would need to exclude *H. pylori* infected patients. (D.I. 227 at 19). Plaintiff cites prior art noting that despite Taha, "the use of H2-receptor antagonists for the prevention of NSAID-associated ulcers cannot be recommended[.]" (PTX 531 at 8; Tr. 734:1-21). Plaintiff contends, "Taha, at best, presented a hypothesis that warranted further evaluation." (D.I. 227 at 21).

Defendant's expert Dr. Barnett counters that not only is the use of real-world patients reliable, but the distribution of *H. pylori* infection was even across all patients and "there would be no reason to suspect that the antacid treatment was treating an *H. pylori* ulcer as compared to an NSAID ulcer." (Tr. 628:5-629:19). I find Dr. Barnett credible. There are multiple prior art references that credit Taha for its finding that the double dose of 40 mg (i.e., 80 mg) daily of famotidine reduced gastric and duodenal ulcers in patients receiving long-term NSAID therapy. (*See* PTX 496 at 3, n.12; DTX 925 at 7, n.40; DTX 928 at 176, n.74; PTX 492 at 8, 14, 39; PTX 511 at 1138, n.9). Despite this finding, some of these articles advise alternatives to H2RAs for the prevention of NSAID-induced ulcers, reasoning that Taha was a single study showing a moderate, though statistically significant, benefit and that there were compliance concerns with twice-daily dosing of famotidine. (PTX 496 at S25; DTX 925 at 7; PTX 531 at 8). None of these

articles criticize the use of patients with *H. pylori* in the study. Further, the '096 publication alleviated concerns with famotidine double dosing by administering the famotine TID.

In light of (1) prior art that credits Taha for its finding that the double dose of 80 mg daily of famotidine reduced gastric and duodenal ulcers in patients receiving long-term NSAID therapy, (2) the disclosures in the '096 publication combining famotidine with the NSAID ibuprofen, and (3) my finding that a POSA would have been motivated to provide alternative therapy for reducing the risk of ulcers outside of existing ones (*see* Tr. 599:6-20, 467:13-468:13), a POSA would have found Taha provided a reasonable expectation of success in using an 80 mg daily dose of famotidine to reduce gastric and duodenal ulcers in patients receiving long-term NSAID therapy, including ibuprofen.

iv. Motivation to Select 26.6 mg TID Famotidine with a Reasonable Expectation of Success

Defendant contends that because Taha taught an 80 mg daily dose of famotidine administered in two portions (i.e., "BID") whereas ibuprofen was administered with a "standard" TID dose (PTX 262 at 1435; Tr. 602:5-22), a POSA would have understood that in a combination drug product the two APIs are administered on the same dosing interval. (D.I. 218 at 16). Therefore, Defendant contends a POSA would have divided the total daily dose of 80 mg of famotidine into thirds (80/3 = 26.6 mg). (*Id.*). Defendant argues a POSA "would have been motivated to develop the pharmaceutical composition comprising 800 mg of ibuprofen and 26.6 mg famotidine because such a composition would have reduced patient pill burden and provided an optimal daily dose of ibuprofen (i.e., 2400 mg) along with an optimal daily dose of famotidine (i.e., 80 mg) for reducing the risk of the patient developing gastric and duodenal ulcers." (*Id.* at 16-17). Defendant argues these are the same doses and regimen taught and claimed by the '096

publication. (*Id.* at 17).

Plaintiff contends that a POSA would neither have been motivated to consider, nor have had a reasonable expectation of success, that administration of 26.6 mg of famotidine TID would effectively reduce the risk of ibuprofen induced ulceration because neither a 26.6 mg dose nor a TID dosing regimen of famotidine was approved by the FDA for any purpose. (Tr. 735:1-14; DTX 120 at 8-9 (Pepcid® Package Insert (June 6, 2002))). Plaintiff argues that a POSA would not have expected that any efficacy associated with a 40 mg dose of famotidine given BID, as reported by Taha, could be extrapolated to a 26.6 mg dose of famotidine given TID. (Tr. 735:7-736:7). Plaintiff argues that a POSA would not have extrapolated the pharmacokinetic (PK) and pharmacodynamics (PD) of 40 mg famotidine BID to 26.6 mg famotidine TID and any such hypothesis would need to be tested for an expectation of success. (D.I. 227 at 22; Tr. 735:1-736:7).

Plaintiff contends the lack of clinical data in the '096 publication would not have offered a POSA any reasonable expectation of success for TID dosing of famotidine. Plaintiff notes the evidence supporting the use of TID dosing in the '096 publication is limited to a single PK model in Example 1. That example studied the differences in gastric pH resulting from TID versus BID famotidine dosing regimens; specifically, the length of time that gastric pH remained greater than 3.5. (PTX 371 at ¶¶ [0179]-[0182]). Plaintiff argues there was no understanding in 2007 that maintaining a gastric pH above a certain value for any particular length of time would actually translate to clinical efficacy for reducing the incidence of NSAID-induced ulcers. (Tr. 709:25-710:10, 736:25-737:7). Plaintiff maintains that the '096 publication also discloses an anticipated clinical study of famotidine dosed TID versus BID in Example 2. Plaintiff asserts the anticipated clinical study discloses only aspirational expectations, rather than any actual results.

(D.I. 227 at 23, citing *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012)).

Taha only discloses 40 mg famotidine BID for a total daily dose of 80 mg to reduce gastric and duodenal ulcers in patients with arthritis receiving long-term NSAID therapy, including ibuprofen. (PTX 262 at 1). However, the disclosures in the '096 publication combine 26.6 mg famotidine TID with ibuprofen for reducing NSAID-induced ulcers. (PTX 371 at Abstract, [0006], [0013], [0097]-[0099]). A POSA would have known that the bioavailability of famotidine was dose independent, and prior art suggested famotidine has linear PK during multiple-dose administration. (DTX 772 at 184-85 ("During repeated oral administration of famotidine 20 mg 3 times daily, C_{max} and trough plasma concentrations (C_{min}) of the drug were largely constant …Thus, there appears to be no firm evidence indicating that the pharmacokinetics of famotidine could be non-linear during a long term dosage regimen.")). Plaintiff criticizes this prior art disclosure because it "discusses the pharmaco*kinetics*—not the pharmaco*dynamics*—of famotidine" and reducing the risk of NSAID-induced ulcers was an unproven pharmacodynamic effect of famotidine. (D.I. 227 at 23-24; Tr. 741:24-742:20). However, Plaintiff offers no evidence or testimony to support the assertion that reducing the risk of NSAID-induced ulcers was an unproven pharmacodynamic effect of famotidine.

Plaintiff cites to *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, but there the Federal Circuit found that the lack of a known PK/PD relationship would prevent a POSA's reasonable expectation that an immediate release and an extended release bioequivalent would produce the same PD effect, and therefore, the same therapeutic effect. *In re Cyclobenzaprine*, 676 F.3d at 1070. Here, there is prior art that suggests a linear PK profile of famotidine (DTX 772 at 184-85), and there is no evidence that reducing the risk of NSAID-

induced ulcers was a PD effect of famotidine. The famotidine label also discloses "plasma levels after multiple doses are similar to those after single doses." (DTX 120 at 2).

Plaintiff notes that the FDA had not approved TID dosing regimen of famotidine. But "dosing frequencies of 1, 2, and 4 times a day had been approved by the FDA." (Tr. 476:21-477:3). I do not think the absence of FDA approval of an intermediate dosing regimen matters. Therefore, a POSA would have had a reasonable expectation of success for three times a day administration.

Regarding Plaintiff's contention of a lack of any reasonable expectation of success because the '096 publication contained model data rather than demonstrated clinical efficacy for reducing the incidence of NSAID-induced ulcers, "[c]onclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) (noting Plaintiff's at-issue patents being challenged as obvious did not themselves contain the relevant clinical data).

I find a POSA would have been motivated to, and would have had a reasonable expectation of success, in dosing 26.6 mg famotidine TID.

v. Motivation to Achieve Stability and Separation of Active Ingredients with a Reasonable Expectation of Success

As an initial matter, Plaintiff alleges that a POSA would not have been motivated to develop a product that was stable for the expected shelf life because the teachings in the '096 publication demonstrate "that ibuprofen and famotidine were extremely incompatible with one another, with ibuprofen causing the rapid and extensive degradation of famotidine in short order

under forced degradation conditions."[4] (D.I. 227 at 24). Therefore, Plaintiff alleges that a POSA would not have chosen ibuprofen in combination with famotidine, especially in dosage amounts of 800 mg and 26.6 mg. (*Id.* at 25-26). However, the art motivated a POSA to separate chemically incompatible active ingredients in a tablet-in-tablet dosage form. (*See* DTX 774 at 229; DTX 775 at 157-59; DTX 779 at 145). The '671 publication specifically "relates to improvements in the formulation of pharmaceutical compositions wherein two or more active ingredients are present in the composition and wherein at least two of the active ingredients are incompatible with one another," thereby disclosing a tablet-in-tablet dosage form with a H2RA ranitidine core surrounded by a NSAID acetylsalicylic acid shell, separated by a barrier layer. (DTX 136 at [0001], [0003], [0007]). Therefore, knowing the great deal of incompatibility between ibuprofen and famotidine that the '096 publication discloses, I find a POSA would have been particularly motivated to overcome this by utilizing a tablet-in-tablet dosage form specifically taught in the art to overcome this sort of incompatibility.

Plaintiff next contends that a POSA would not have had a reasonable expectation of success in achieving the claim limitations (1) no more than about 1% sulfamide when stored at 40° C and 75% relative humidity for one month (*see* claim 1) and (2) at least 98% ibuprofen and at least 98% famotidine when stored at room temperature conditions of 25° C and 60% relative humidity for nine months (*see* claim 14). (D.I. 227 at 26). Plaintiff first argues the USP only offered a POSA an "aspirational goal" for stability — not a reasonable expectation of success that such a goal could actually be achieved. (*Id.*) Plaintiff asserts that because the USP sets forth

[4] Despite arguing that the '096 publication is not available as prior art, Plaintiff alleges its teachings are still relevant to both motivation and reasonable expectation of success. (D.I. 227 at 24 n. 5). *See, e.g., Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd*., 357 F.3d 1319, 1337–38 (Fed. Cir. 2004) ("motivation to combine need not be found in prior art references, but equally can be found in the knowledge generally available to one of ordinary skill in the art"); *AstraZeneca LP v. Breath Ltd*., 88 F. Supp. 3d 326, 350 (D.N.J. 2015). Defendant appears to agree. (D.I. 231 at 7 n. 6). Since I have found the '096 publication is § 102(a) prior art, I may consider its disclosures in connection with motivation and reasonable expectation of success without further consideration of Plaintiff's cited cases.

standards for famotidine and ibuprofen alone and not in combination, the POSA would not understand that those same impurity standards may be achievable for a combination product that contains both active ingredients. (*Id.* at 27; Tr. 763:22-764:19).

Plaintiff then argues the '671 publication would not offer a POSA a reasonable expectation of success that the high level of stability required by the asserted claims could be achieved. (D.I. 227 at 27-28). Plaintiff dismisses the stability disclosures of the '671 publication as conclusory; the disclosures would not provide a POSA a reasonable expectation of success because the publication "does not describe which active ingredient is degrading the other, …the degradants that are formed as a result of the incompatibility of ranitidine and aspirin, … or the mechanism of degradation that is occurring." (*Id.* at 28; Tr. 769:25-770:18). Plaintiff contends "the '671 publication does not include the percentage of degradants that were formed," and "does not provide any comparative stability data that shows just how incompatible ranitidine and aspirin are when in an admixture or multiparticulate dosage form." (D.I. 227 at 28-29; Tr. 767:24-768:3, 770:19-771:1).

Plaintiff's arguments are not convincing. The USP disclosed the allowable limit for four famotidine impurities, including a limit of 0.5% for Famotidine Impurity C, which a POSA would know with reasonable certainty is sulfamide. (PTX 559 at 8; *see infra* 40-45). In addition to the limits of individual famotidine impurities, the USP disclosed no more than 1.5% total impurities. (PTX 559 at 8-9). Plaintiff points to a lack of stability data in the '671 publication and claims that the USP impurity limits were aspirational, but does not offer evidence to substantiate its expert's testimony as to why a POSA would have anticipated difficulty in achieving the 0.5% allowable limit for sulfamide and 1.5% allowable limit for all famotidine impurities disclosed in the USP, using the separation methods of the '671 publication. Plaintiff

simply asserts that a POSA would not have a reasonable expectation of success in achieving the USP stability levels because of how incompatible ibuprofen and famotidine are with one another. (*Id.*). However, the whole purpose of the separation methods of the '671 publication is to achieve greater stability for incompatible NSAIDs, such as ibuprofen, and H2RAs, such as famotidine. (DTX 136 at [0060], [0065]). The '671 publication discloses that through the tablet-in-tablet pharmaceutical formulation, the H2RA core was shown to be stable for at least six months at 40°C / 75% relative humidity, and the NSAID outer shell was stable for at least two months at 40°C / 75% relative humidity. (*Id.*). Plaintiff also does not explain why it would be necessary for a POSA to know which active ingredient is degrading the other, the degradants that are formed from the incompatibility, or the mechanism of degradation, to have a reasonable expectation of success, so long as the POSA knew to separate the two incompatible active ingredients to improve stability, which the '671 publication discloses. (*Id.* at [0001]-[0007], [0060], [0065]).

The USP dissolution standards are for immediate release ibuprofen tablets and immediate release famotidine tablets. (PTX 559 at 883-84, 1102-03). The '671 publication is also directed to immediate release formulations that are not enterically coated or formulated for sustained or delayed release. (DTX 136 at [0036], [0061]; Tr. 504:24-506:8). Plaintiff identifies no reason why a POSA would not have a reasonable expectation that the '671 publication's proffered separation methods could achieve the USP stability goal of 0.5% as the allowable limit for sulfamide and 1.5% as the allowable limit for all famotidine impurities. Therefore, I find that in light of the USP impurity limits, and the separation strategy and stability disclosures of the '671 publication, the '033 patent limitation of "no more than about 1% sulfamide is present when the composition is stored at 40° C. and 75% relative humidity for a period of one month" would

have been obvious to a POSA. Despite Plaintiff's criticism that "a POSA would not know whether the formulation strategy used in the '671 publication could solve the extreme incompatibility of ibuprofen and famotidine to the degree and extent required by the level of stability set forth in claims 1 and 14 of the '033 patent" (D.I. 227 at 29), a POSA need only have a reasonable expectation of success. *See Par Pharm., Inc. v. TWi Pharms., Inc*., 773 F.3d 1186, 1198 (Fed. Cir. 2014) ("The reasonable expectation of success requirement for obviousness does not necessitate an absolute certainty for success.")

Plaintiff similarly contends that the '876 publication would not offer a POSA a reasonable expectation of success in achieving the stability required by the asserted claims because the '876 publication is directed to formulating an acid labile active ingredient that passes through the stomach to release in the small intestine where the pH is higher; it is not directed to solving the incompatibility of two active ingredients. (D.I. 227 at 29; Tr. 772:19-775:19, 777:6-778:19). Plaintiff argues that even if a POSA looked to the '876 publication, a POSA would not arrive at an immediate release formulation because the '876 publication is directed to coordinated release dosage forms, wherein one active ingredient is immediately released while the other active ingredient is formulated for sustained release. (D.I. 227 at 29-30; Tr. 773:11-775:19, 778:19-22; DTX 785 at [0033], [0035]-[0038]).

The '876 publication is directed to a tablet-in-tablet formulation with a core containing an acid-labile active ingredient. (DTX 785 at Abstract). The publication defines "acid labile" ingredients as PPIs, some antibiotics, and some antivirals. (*Id.* at [0044]). The publication does not define H2RAs as "acid labile" but does caution that a POSA "will recognize the above list of acid labile active ingredients is not exhaustive." (*Id.*). Plaintiff's argument — that a "POSA would not have been motivated to use famotidine in place of the acid labile active ingredient"

(D.I. 227 at 30; Tr. 776:17-777:5) — is undermined by the disclosures in the ’876 publication and Plaintiff’s own argument as it relates to indefiniteness. A POSA would have known famotidine could be considered a candidate for the “acid labile” core because the ’876 publication discloses, “Chemical substances that degrade or are inactivated in an acid medium are termed herein acid-labile.” (*Id.* at [0003]). Plaintiff admits, “there can be no reasonable dispute … famotidine is susceptible to acid catalyzed hydrolysis.” (D.I. 227 at 32-33; Tr. 687:7-688:1, 691:8-11).

While the ’876 publication does not list H2RAs or famotidine as “acid labile,” it does disclose H2RAs such as famotidine as a suitable active ingredient for use as the second active ingredient. (*Id.* at [0083], [0085]). Plaintiff contends the ’876 publication does not provide a reasonable expectation of success because it does not disclose a form that contains both ibuprofen and famotidine, but rather describes them both as second active ingredients. (D.I. 227 at 30; Tr. at 777:10-17; DTX 785 at [0043], [0085]-[0090]). However, considering the disclosures for ibuprofen and famotidine as the second active ingredients, the known incompatibility Plaintiff has repeatedly highlighted (D.I. 227 at 24-26), and the disclosures for “a method for the production of a stable dosage form for oral administration, which comprises acid-labile actives as an active ingredient,” the ’876 publication would have provided a POSA with a reasonable expectation of success using famotidine in the core surrounded by a barrier layer, and an ibuprofen as the second active ingredient in the shell. (DTX [0115]; Tr. 501:19 -502:19). A POSA would also have understood that the enteric layer described in the ‘876 publication is not required when the acid labile API in the core is an H2RA, because H2RAs are not unstable in the stomach like PPIs. (DTX 785 at Abstract; Tr. 499:16-500:2). Again, Plaintiff does not offer an explanation as to why the separation strategy of the ’876 publication, when using the H2RA

famotidine and the NSAID ibuprofen, would not have resulted in a reasonable expectation of success of the 0.5% allowable limit for sulfamide and the 1.5% allowable limit for all famotidine impurities disclosed in the USP, which is within the 1% sulfamide limitation of the ’033 patent.

The separation strategies of both the ’671 publication and the ’876 publication teach the use of a barrier layer interposed between the two incompatible active ingredients. (*See e.g.*, DTX 136 at Abstract, [0007], [0022]-[0025], [0036], [0061]; DTX 785 at Abstract, [0032]-[0035], [0039]-[0041], [0092] Fig. 1, Fig, 2; Tr. 497:1-502:19). The barrier layer in these disclosures prevents physical contact between the two incompatible active ingredients. (*Id.*). This results in the surface area of direct physical contact of essentially 0 mm^2. Therefore, the ’033 patent limitation of “surface area of direct physical contact between ibuprofen and famotidine does not exceed 130 mm^2” would have been obvious to a POSA in light of the ’671 publication and the ’876 publication teachings of a barrier layer to prevent physical contact between the two incompatible active ingredients.

Finally, Plaintiff contends that a POSA would not have a reasonable expectation of success in achieving the claimed level of stability when formulating two incompatible active ingredients in view of the US Patent No. 5,593,696 (the ’696 patent), issued January 14, 1997. (D.I. 227 at 30; PTX 376). The ’696 patent relates to improving the stability of compositions containing famotidine and sucralfate. Sucralfate is known to degrade famotidine. The patent discloses coating famotidine particles with a barrier layer. (Tr. 779:11-780:9; PTX 376 at 1:53-56, 1:68-2:3). The ’696 patent discloses degradates for two kinds of separation strategies — bilayer compartmentalized and barrier coated — between famotidine and sucralfate: (1) bilayer compartmentalized tablets and barrier coated famotidine (samples 1, 2); (2) single tablet multiparticulate and barrier coated famotidine (samples 3, 4); (3) bilayer compartmentalized

tablets without barrier coated famotidine (samples A, B); and (4) single tablet multiparticulate without barrier coated famotidine (samples C, D). (PTX 376 at 4:65-5:5, 5:12-14). Samples 1-4 are all barrier coated and samples A-D are all non-barrier coated. (*Id*.). Samples 1, 2, A, and B are all bilayer compartmentalized and samples 3, 4, C, and D are all single tablet multiparticulate. (*Id*.). Plaintiff contends that because sample 2 used a compartmentalized dosage form and a barrier layer but had 2.50% total degradates, while samples 3 and 4 (single tablet multiparticulate and barrier coated famotidine) had a lower amount of total degradates, 0.19% and 0.28%, respectively, a "POSA would not reasonably expect that simply separating two incompatible active ingredients into compartments, either with or without a barrier layer, would be sufficient to achieve the level of stability required by the Asserted Claims." (D. I. 227 at 31).

In viewing all of the degradate data, the '696 patent disclosure would support a reasonable expectation of success in achieving the claimed level of stability when formulating two incompatible active ingredients, one of which was famotidine. Samples 1, 3, and 4 with barrier coated famotidine contained less than 1% total degradants after five weeks of storage at 40°C / 75% relative humidity; both bilayer compartmentalized tablets without barrier coated famotidine (samples A, B), contained less than 1% total degradants after five weeks of storage at 40°C / 75% relative humidity.[5] Single tablet multiparticulate without barrier coated famotidine (samples C, D), which would be most akin to the famotidine / ibuprofen admixture of the '096 publication, contained far more than 1% degradates, with 12.73% and 13.34% respectively. Thus, because the five out of six of the samples that had separated their incompatible APIs, one of which was famotidine, either by a barrier layer or by bilayer compartmentalization (samples

[5] Sample 1 = 0.72%; Sample 2 = 2.50%; Sample 3 = 0.19%; Sample 4 = 0.28%; Sample A = 0.66%; Sample B = 0.74%; Sample C = 12.73%; Sample D = 13.34%. (PTX 376 at Table 1).

A, B, 1, 3 and 4), had less than 1% "total degradants," a POSA would have reasonably expected that separating famotidine from an incompatible API (e.g., ibuprofen) would improve stability. This expectation is underscored by comparison of the success in the separated samples[6] to the high amount of degradates in the admixture (samples C, D) with no incompatible API separation.

b. Claim 8

Dependent claim 8 further recites that "the second portion comprises a layer of famotidine and the first portion comprises a layer of ibuprofen and the two layers are separated by a barrier layer." (PTX 1 at 15:6-9). This is an obvious variation of a tablet-in-tablet that is illustrated in Figure 2 of the '876 publication. In Figure 2, the core containing the acid-labile API is offset into one layer of the bilayer tablet, surrounded by a barrier layer, and then separated from the second active ingredient by a second barrier layer. (DTX 785 at [0040], [0092], Figure 2; Tr. 509:2-16). The '876 publication's disclosure in Figure 2 would have provided motivation and a reasonable expectation of success to a POSA to make and use a bilayer tablet separated by a barrier layer to separate the incompatible famotidine from ibuprofen.

c. Claim 11

Dependent claim 11 further recites that "the composition is formulated so that at least about 80% of the famotidine and at least about 80% of the ibuprofen are released from the composition into solution within 30 minutes at a pH of about 6.8 to 7.4." (PTX 1 at 15:16-20). This is also obvious because it simply further quantifies what is meant by rapidly released at about the same. (Tr. 509:17 – 510:8, 511:3-14). A POSA would have been motivated to formulate the composition to release the ibuprofen and famotidine as fast as possible to give the patient relief. (Tr. 509:22-510:5). A POSA would have been motivated to make an immediate

[6] Sample 2's result would not indicate otherwise. It is clearly out of step with the results of the other five separated samples. It is an outlier.

release pharmaceutical composition comprising ibuprofen and famotidine because that complies with the dissolution standards of the USP, which are for immediate release, and the ’096 publication disclosed concurrent administration of immediate release forms of ibuprofen and famotidine. ((PTX 559 at 883-84, 1102-03; DTX 371 at [0079]). A POSA would have had a reasonable expectation of success because the ’671 publication tablet-in-tablet design was for immediate release pharmaceutical compositions. (DTX 136 at [0036], [0061]). The prior art demonstrates that it would have been routine for a skilled person to optimize the formulation so that at least 80% of the famotidine and at least 80% of the ibuprofen are released within 30 minutes at a pH of about 6.8 to 7.4. (PTX 371 at [0028], [0097]-[0099], [0210]).

d. Claim 14

Dependent claim 14 further recites that “at least 98% of the ibuprofen and the famotidine are each present when the composition is stored under room temperature storage conditions of 25°C and 60% relative humidity for a period of nine months.” (PTX 1 at 16:10-14). A POSA would have been motivated to have the pharmaceutical product as shelf-stable as possible to cover the entire distribution channels from manufacturing to patient dosing. (Tr. at 457:14-458:10, 510:15-511:2). A POSA would have reasonably expected that at least 98% of the ibuprofen and famotidine would be present in the composition after nine months of storage at 25°C / 60% relative humidity because examples 1 and 2 of the ’671 publication disclosed that ranitidine was stable for six months at 40°C / 75% relative humidity in a tablet-in-tablet with this design. (DTX 136 at [0060], [0065]; Tr. 510:15-511:2).

5. Secondary Considerations

During trial, the parties agreed that there are no secondary considerations of nonobviousness relevant to the ’033 patent. (*Id.* at 648:19-24). As there are no relevant

secondary considerations, they play no part in the obviousness analysis.

D. Conclusion

Considering the evidence as a whole, I conclude that Defendant has proven by clear and convincing evidence that claims 1, 8, 11, and 14 of the ’033 patent are invalid as obvious.

III. INDEFINITENESS

Defendant contends that the “no more than about 1% sulfamide” limitation in all the asserted claims does not inform, with reasonable certainty, a POSA about the scope of the invention, and thus is indefinite under 35 U.S.C. § 112. (D.I. 218 at 30).

A. Legal Standard

A patent must “inform those skilled in the art about the scope of the invention with reasonable certainty.” *Nautilus, Inc. v. Biosig Instruments, Inc*., 572 U.S. 898, 910 (2014). To determine indefiniteness, courts examine “the patent record—the claims, specification, and prosecution history—to ascertain if they convey to one of skill in the art with reasonable certainty the scope of the invention claimed.” *Teva Pharms. USA, Inc. v. Sandoz, Inc*., 789 F.3d 1335, 1341 (Fed. Cir. 2015). “[I]f necessary, a court may consult extrinsic evidence to understand the meaning of a term in the relevant art.” *Transcend Med., Inc. v. Glaukos Corp*., 2015 WL 5546988 at *5 (D. Del. Sept. 18, 2015) (citation omitted). Defendant has the burden of proof, which is clear and convincing evidence.

B. Findings of Fact

1. A POSA would understand the “no more than about 1% sulfamide” limitation in all the asserted claims to refer to Famotidine Impurity C.

C. Conclusions of Law

Defendant contends the “no more than about 1% sulfamide” limitation in all the asserted

claims is indefinite because the ’033 patent does not define “sulfamide,” provides no chemical name, structure or specific method of testing for “sulfamide,” does not refer to the USP or Famotidine Impurity C, and does not provide any method for identifying or quantifying “sulfamide” in a composition. (D.I. 218 at 31). Defendant argues that a POSA would not have reasonably concluded that “sulfamide” and “sulfamoyl amide” are synonymous. (*Id.*; D.I. 231 at 17). Therefore, any prior art describing a compound with a functional group as “sulfamoyl amide,” such as Famotidine Impurity C in the USP, would not have informed a POSA that such a compound is “sulfamide.” (D.I. 218 at 31; D.I. 231 at 17). Defendant argues that a POSA would have known “sulfamide” generally is the small molecule $H_2NSO_2NH_2$. (D.I. 218 at 31).

Defendant contends that even if a POSA had turned to the USP, a POSA would not have known “sulfamide” to be Impurity C because Impurity C is not labeled as “sulfamide” and is not identified as a principal degradant of famotidine; further, the USP lists Impurity A as having a higher allowable limit of that impurity. (*Id.* at 32-33). Defendant asserts that because the ’033 specification does not discuss hydrolysis of famotidine as the way in which degradation occurs, “sulfamide” could be referring to Impurity A, which results from the reaction of famotidine with byproducts produced from the oxidation of ibuprofen. (*Id.* at 34). Alternatively, “sulfamide” could be referring to Impurity B, an acid hydrolysis degradant with the same allowable limit of that impurity as the allowable limit of Impurity C in the USP. (*Id.* at 35).

Regarding the ’033 specification’s labelling of sulfamide as “a principal degradant,” Defendant points to prior art to show that there are multiple famotidine degradation products caused by hydrolysis. (PTX 442 at 601-02). Defendant’s expert testified that it “is a cascading reaction that continues to go. So at any point in time, whatever your primary degradant is[,] is going to change over time.” (Tr. at 517:9-18). As such, Defendant argues the principal

degradant will change over time because Impurity C will hydrolyze to Impurity B and generate the small molecule sulfamide, $H_2NSO_2NH_2$, as a byproduct and additional degradant. (Tr. 675:23-676:11, 676:21-677:15; PTX 514 at 1511).

Plaintiff contends that a POSA would understand "sulfamide" in the "no more than about 1% sulfamide" limitation in all the asserted claims to be USP Famotidine Impurity C. (D.I. 227 at 32). Plaintiff's expert, Dr. Little, testified that "sulfamide" and "sulfamoyl amide" are essentially synonyms. (Tr. 284:6-8). Plaintiff argues that while "sulfamide" can either refer to the small molecule sulfamide or a larger molecule that contains a sulfamide functional group, the '033 patent explains that "sulfamide" is "a principal degradant of famotidine formed by the interaction of famotidine and ibuprofen." (*Id.*; PTX 1 at 9:8-10). Therefore, "a POSA would have understood that 'sulfamide' in the '033 patent does not refer to the small molecule sulfamide, but instead means Famotidine Impurity C in the USP because it is the only known principal degradant that contains a sulfamide functional group and that is formed as a result of the acid-catalyzed hydrolysis of famotidine." (D.I. 227 at 32).

Here, Defendant's expert admits that the mechanism by which ibuprofen degrades famotidine is acid-catalyzed hydrolysis. (Tr. 687:7-688:1). A POSA looking up famotidine impurities in the USP would recognize that Famotidine Impurity C is both the only disclosed famotidine degradant there that contains a sulfamoyl amide functional group and the only disclosed famotidine degradant formed as a result of the acid-catalyzed hydrolysis of famotidine. (Tr. 283:15-284:10; 289:3-292:20). While Famotidine Impurity A has a higher allowable limit of that impurity, acid-catalyzed hydrolysis was the mechanism by which ibuprofen was understood to degrade famotidine. (Tr. 292:2-20; 687:7-688:1). Although Defendant contends that Impurity A can result from famotidine interaction with ibuprofen oxidation products,

Defendant's expert Dr. Laird agreed that a POSA would understand that "sulfamide" is produced as a result of the ibuprofen molecule degrading the famotidine molecule. (Tr. 685:13-686:2). The patent specification also discloses sulfamide as the principal degradant produced through the chemical interaction of famotidine and ibuprofen, not through chemical interaction of famotidine with ibuprofen degradants or byproducts. (Tr. 293:20-294:16).

Defendant also puts forth Famotidine Impurity B as a candidate for "sulfamide" as it is formed by acid hydrolysis, but Dr. Laird agreed that "sulfamide" would refer to a compound with a sulfamide moiety, which Famotidine Impurity B does not have. (Tr. 659:10-15). While Defendant contends that "sulfamide" may refer to the small molecule, the specification refers to "sulfamide" as a "principal degradant." (PTX 1 at 9:8-10). Defendant points out that the small molecule sulfamide is produced in the degradation pathways to the larger degradants Famotidine Impurity B and C (PTX 442 at 601-02), but even Defendant describes it "as a byproduct." (D.I. 218 at 35). A POSA would not consider the small molecule sulfamide to be a principal degradant. By process of elimination, a POSA would understand with reasonable certainty that "sulfamide" is Famotidine Impurity C.[7]

Defendant analogizes to *HZNP Meds. LLC v. Actavis Labs. UT, Inc*., where the Federal Circuit affirmed a finding of indefiniteness. 940 F.3d 680, 690-91 (Fed. Cir. 2019). There, Horizon claimed a POSA would understand "impurity A" of its diclofenac sodium topical solution to mean "USP Related Diclofenac Compound A." (*Id.*). However, the facts of that case are different from the present one. There, "impurity A" was an unknown compound. (*Id.*). The specification: (a) did not disclose the chemical name of the impurity; (b) used quotes to refer to "impurity A," suggesting it is not the formal name of a known impurity; and (c) "justifie[d] not

[7] In this way, it is analogous to Sherlock Holmes in "The Adventure of the Beryl Coronet," "[W]hen you have excluded the impossible, whatever remains, however improbable, must be the truth."

conducting additional tests to identify the impurity merely because it occurs in low amounts." (*Id.* at 690). The Federal Circuit also determined that the at-issue patent did not make clear that "impurity A" refers to an impurity of diclofenac sodium, rather than an impurity of the entire formulation. *Id.* The written description for "impurity A" only contained retention times derived from high performance liquid chromatography (HPLC) but was "devoid of other information about the conditions of the HPLC experiment." (*Id.* at 690-91). The district court had found "that Horizon's expert did not explain why a POSITA would know that the HPLC test in Example 6 was undertaken using a pharmacopoeia chromatographic system." (*Id.* at 691.) Ultimately the Federal Circuit saw no clear error in the district court's determination that "a POSITA faced with this specification would not reasonably presume that Example 6 was undertaken using a pharmacopoeia chromatographic system. That outcome undermined Horizon's reliance on the pharmacopoeias to extrapolate meaning into 'impurity A.'" (*Id.*).

Here, the specification recognizes that sulfamide is not an unknown impurity that occurs in low amounts, but rather is a principal degradant produced specifically through the chemical interaction of famotidine and ibuprofen. (PTX 1 at 9:8-10). The specification does not use quotes, suggesting a known impurity. When a POSA looked to the USP to identify the known impurities of famotidine, there would only be one choice with a "sulfamoyl amide" functional group produced from acid-catalyzed hydrolysis, Famotidine Impurity C. *HZNP Medicines*, 940 F.3d at 691 ("To be clear, we do not hold that a reference to an impurity is indefinite in all contexts, only that on this record, the term 'impurity A' is indefinite.").

D. Conclusion

Considering all the evidence, I find that the '033 patent conveys to a POSA with reasonable certainty that "sulfamide" is USP Famotidine Impurity C. Defendant has failed to

provide clear and convincing evidence that claim 1 and the asserted dependent claims of the ’033 patent are invalid under 35 U.S.C. § 112.

IV. INFRINGEMENT

Plaintiff contends Alkem’s ANDA Product infringes the asserted claims. (D.I. 216 at 1).

A. Legal Standard

The application of a patent claim to an accused product is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1332 (Fed. Cir. 2001). Literal infringement is present only when each and every element set forth in the patent claims is found in the accused product. *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575-76 (Fed. Cir. 1995). The patent owner has the burden of proving infringement by a preponderance of the evidence. *Envirotech Corp. v. AI George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984) (citing *Hughes Aircraft Co. v. United States*, 717 F.2d 1351, 1361 (Fed. Cir. 1983)). “Under [35 U.S.C.] § 271(e)(2)(A), a court must determine whether, if the drug were approved based upon the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense.” *Glaxo, Inc. v. Novopharm, Ltd*., 110 F.3d 1562, 1569 (Fed. Cir. 1997).

A product that does not literally infringe a patent claim may still infringe under the doctrine of equivalents (DOE) if the differences between an individual limitation of the claimed invention and an element of the accused product are insubstantial. *See Warner–Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 39–40 (1997). “Insofar as the question under the doctrine of equivalents is whether an accused element is equivalent to a claimed element, the proper time for evaluating equivalency—and thus knowledge of interchangeability between elements—is at the time of infringement, not at the time the patent was issued.” *Id.* at 37. The DOE is “applied to individual elements of the claim, not to the invention as a whole.” *Id.* at 29. Under the DOE,

"the essential inquiry [is whether] the accused product or process contain[s] elements identical or equivalent to each claimed element of the patented invention[.] Different linguistic frameworks may be more suitable to different cases, depending on their particular facts." *Id.* at 40.

A plaintiff may prove infringement under the DOE "by showing on a limitation by limitation basis that the accused product performs substantially the same function in substantially the same way with substantially the same result as each claim limitation of the patented product." *Crown Packaging Tech., Inc. v. Rexam Beverage Can Co.*, 559 F.3d 1308, 1312 (Fed. Cir. 2009). The DOE "is not 'simply the second prong of every infringement charge, regularly available to extend protection beyond the scope of the claims.'" *Amgen Inc. v. Sandoz Inc.*, 923 F.3d 1023, 1029 (Fed. Cir.) (citations omitted), *modified on reh'g*, 776 F. App'x 707 (Fed. Cir. 2019). Moreover, a dependent claim cannot be infringed unless each and every element of the underlying independent claim is also infringed. *See Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1310-11, 1311 n.3 (Fed. Cir. 2001). The patent owner has the burden of proving infringement by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

B. Findings of Fact

1. The invention of the '033 patent teaches stable pharmaceutical compositions of famotidine and ibuprofen in a single unit dosage form.

2. The increased stability taught by the '033 patent is achieved by controlling the surface area over which the famotidine and ibuprofen are in direct physical contact so as not to exceed an area calculated from the use of disclosed Formula (I).

3. Rather than direct physical contact between the famotidine and ibuprofen,

a barrier layer can be used between the two compartments.

4. The barrier layer can be omitted without sacrificing stability, resulting in the barrier layer being optional.

5. The ANDA Product does not infringe any of the asserted claims, either literally or by the DOE.

C. Conclusions of Law

1. Claim 1: "a first portion" (limitation 1) and "a second portion" (limitation 2)

Under the Court's construction of "a first portion" as reciting "an ibuprofen compartment that is not a core" and "a second portion" as reciting "a famotidine compartment that is not a shell" (D.I. 89), Plaintiff concedes that Defendant's ibuprofen core and famotidine shell ANDA Product do not literally infringe. (D.I. 216 at 1-3). Plaintiff argues Defendant's ANDA Product infringes under the DOE. (*Id.*) Plaintiff's DOE theory, under both the function-way-result (FWR) test and the insubstantial differences test, comprises separating and compartmentalizing the two active ingredients to reduce the surface area of direct physical contact between the ibuprofen and the famotidine so as to enable a reduction in famotidine degradation caused by ibuprofen. (*Id.* at 8, 11).

Under both of these tests, plaintiff admittedly applies DOE to more than one claim element — "a first portion" and "a second portion" — at the same time. (*Id.* at 4). Plaintiff was specifically instructed at trial to provide legal support for this, which seemingly contradicts applying DOE on an element-by-element basis, not to the invention as a whole. *Warner-Jenkinson.*, 520 U.S. at 40.

The cases relied on by Plaintiff do not support Plaintiff's desired outcome. *Huawei*

Techs. Co. v. Samsung Elecs. Co., 340 F. Supp. 3d 934, 960 (N.D. Cal. 2018) and *Cadence Pharm. Inc. v. Exela PharmSci Inc*., 780 F.3d 1364, 1370-72 (Fed. Cir. 2015) address method claims that involve certain steps, where a change in the step order was determined to be insubstantial. *Huawei* recognizes "the all limitations rule requires that equivalence be assessed on a limitation-by-limitation basis, as opposed to from the perspective of the invention as a whole." *Huawei*, 340 F. Supp at 960 (specifying in the context of a method claim "when the 'limitation' at issue is the implication that the steps of the claim must be performed in order, it seems appropriate to assess equivalence from the perspective of the invention as a whole."),[8] In *Cadence*, the order of the steps stemmed from the same one claim limitation, "aqueous solution." *Cadence*, 780 F.3d 1370-72. The Court there was not evaluating DOE for two limitations simultaneously. (*Id.*).

Plaintiff's cite to *Pozen Inc. v. Par Pharm., Inc*., 696 F.3d 1151, 1169-72 (Fed. Cir. 2012) is similarly unsupportive of examining two claim elements at once. There, the Federal Circuit considering infringement of two elements, "substantially all of said triptan is in the first layer" and "substantially all of said naproxen is in a second, separate layer," together because both elements had the same "substantially all" limitation. *Pozen*, 696 F.3d at 1170. The Court was determining applicability of DOE to that same "substantially all" limitation in both elements. (*Id.*). The Court was not suggesting DOE can be applied to more than one claim element at a time, and stated, "all claim limitations are not entitled to an equal scope of equivalents. Whether the result of the *All Limitations Rule*, prosecution history estoppel, or the inherent narrowness of the claim language, many limitations warrant little, if any, range of equivalents." (*Id.*) (emphasis

[8] I note two things about *Huawei.* The Court there recognized that it was departing from the usual rule. Further, it did not cite any authority for its decision. Its decision makes sense in the method context, but it cannot have any applicability to the composition claims in this case.

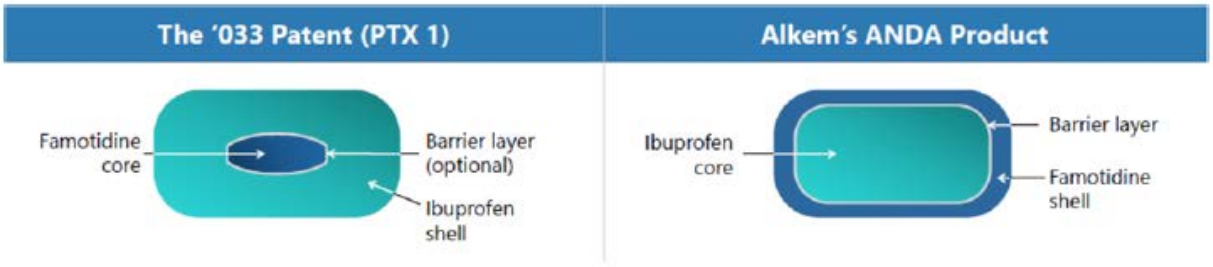
added).

Because Plaintiff violates the "limitation-by-limitation" rule of DOE by applying it to "a first portion" and "a second portion" simultaneously without any legal support, I find DOE is inapplicable here.

In the alternative, I assume that I am wrong that Plaintiff's DOE theory is a non-starter. I assume I can consider multiple limitations at the same time. Nevertheless, Plaintiff still does not show infringement under DOE by a preponderance of the evidence.

a. "Insubstantial Differences" Test

In the chemical arts, the "insubstantial differences" test may be more suitable than the "function-way-result" test for considering DOE. *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858, 869 (Fed. Cir. 2017). Alkem's ANDA Product is a tablet-in-tablet dosage form with a barrier-coated ibuprofen (800 mg) core portion and a famotidine (26.6 mg) shell portion; on the other hand, the claimed composition requires a famotidine (26.6 mg) core and an ibuprofen (800 mg) shell, with an optional barrier layer. (PTX 1 at 4:42-44; 4:60-64; 8:60-62; 9:36-38; 12:17-13:26 (Examples 1-2); DTX 328 at ALKIF085041-44; DTX 236; DTX 237 at ALKIF0100269; Tr 418:3-17; D.I. 189, Ex. 1 ¶ 14). A depiction is shown below. (D.I. 226 at 4).



Conceding that 800 mg ibuprofen in the core rather than 26.6 mg famotidine in the core results in a larger core size (Tr. 344:9-16), Plaintiff contends that this difference is not substantial

in the context of the ’033 patent invention. (D.I. 216 at 12). Plaintiff argues that the ’033 patent explains that a barrier layer can be used to achieve the ’033 patent’s goal of minimizing the surface area of direct contact between ibuprofen and famotidine. (*Id.*). Plaintiff contends that while the sizes of the cores will be different, the use of a barrier layer in Alkem’s ANDA Product still results in minimal, if any, direct physical contact between ibuprofen and famotidine, and thus any differences are insubstantial. (*Id.* at 12-13).

Defendant argues the difference in design is not trivial or merely a difference in appearance stating that Alkem’s ANDA Product is substantially different in at least two important ways – stability and dissolution. (D.I. 226 at 7; Tr. 419:16-23).

In terms of stability, Alkem contends that the asserted claims rely on the geometry of the small famotidine core to reduce and/or minimize “the surface area of the core, or of direct physical contact between the incompatible active pharmaceutical ingredients.” (PTX 1 at 6:6-15; *see also id.* at 8:48-62; Tr. 420:9-23, 421:4-12, 130:16-131:12, 132:24-133:14). Defendant argues a barrier layer is optional due to the design of the invention. (PTX 1 at 8:60-62 (“Moreover, using the design of the present invention, the barrier layer can be omitted without sacrificing stability.”) Defendant contends it does not and cannot take advantage of the invention’s use of geometry; it has to use a barrier layer to separate the first and second portions. (Tr. at 419:24-420:23, 422:16-24). Defendant supports this argument by explaining that the geometry of its ANDA Product requires (i) special packaging (or desiccants) that minimizes the potential for water, since water would destabilize the portions of the ANDA Product, and (ii) control of the manufacturing process to keep water at a minimum during formulation. (D.I. 226 at 8; Tr. 422:16-424:7, 528:25-529:9, 529:13-22).

In terms of dissolution, Defendant argues its ANDA Product is substantially different

from the claims. Defendant's argument is based on evidence of the commercial embodiment of the '033 patent, DUEXIS®.[9] When DUEXIS® is exposed to the dissolution medium, the ibuprofen begins to dissolve from the shell immediately and the famotidine does not begin to significantly dissolve until the dissolution medium further penetrates into the core (i.e., about five minutes later). (D.I. 226 at 10-11; DTX 216 at ALKIF0002697). When Alkem's ANDA Product is exposed to the dissolution medium, the famotidine begins to dissolve from the shell immediately and the ibuprofen does not begin to significantly dissolve until the dissolution medium further penetrates into the core (i.e., about fifteen minutes later). (*Id.*)

Plaintiff contends the specific order and rate of release are not important, so long as the famotidine and ibuprofen are each formulated for immediate release and are released "rapidly at about the same time." (Tr. 345:17-346:18; PTX 1 at 10:42-62, 14:28-31.) Plaintiff argues that "while it is true that the timing of drug release from Alkem's ANDA Product is delayed by about 10-15 minutes relative to Horizon's DUEXIS® Product, and thus is different," this difference is insubstantial because the release of the ibuprofen and the release of the famotidine overlap for at least about fifteen minutes. (D.I. 216 at 12-13). Plaintiff argues the only difference is that this overlap happens in DUEXIS® during the first fifteen minutes, while this overlap happens in Alkem's ANDA Product during the second fifteen minutes. (*Id.*; Tr. 346:19-349:8; PTX 236 at 13). Plaintiff contends that when the overlap happens is not important — rather, what is important is that there is such overlap for an equal duration of time, that is, for fifteen minutes. (*Id.*). Plaintiff also contends that dissolution is not the clinically significant metric, but rather, the absorption and therapeutic effect matter clinically and Alkem's ANDA Product has the same rate and extent of absorption. (D.I. 216 at 13-14; Tr. 202:16- 202:25, 204:15-208:1; PTX 236 at

[9] I understand that infringement involves comparing the accused product to the claims, not to a commercial embodiment. The reference to the commercial product is to illustrate how the claimed composition works.

13; PTX 239 at 14; PTX 240 at 14-5.).

Regarding stability, the inventive aspect of the ’033 patent is a stable pharmaceutical composition of famotidine and ibuprofen in a single unit dosage form comprising a famotidine core, having a reduced or minimal surface area, surrounded by a layer of ibuprofen. The specification repeatedly highlights the increased stability provided by the disclosed geometry. (*See, e.g.*, PTX 1 at 1:65-2:9; 2:21-27; 2:31-39; 2:42-50; 4:30-64;[10] 6:5-15;[11] 8:48-54; 12:17-13:26 (Examples 1-2)). One of the inventors, Dr. Tidmarsh, testified the use of geometry is the essence of the ’033 patent. (Tr. 130:16-131:12, 132:24-133:14). The asserted claims, though, are broader than the scope attributed to geometry. The ’033 patent teaches the use of a barrier layer to reduce the surface area of the two active ingredients *as an option* in addition to the inventive aspect of the reduced surface area design of the patent. (*See, e.g.*, PTX 1 at 4:30-64; [12] 8:60-62; 9:36-38; 12:17-13:26 (Examples 1-2)). Unlike the pharmaceutical composition of the asserted claims, Defendant’s ANDA Product must use a barrier layer and cannot rely on the geometry of a small famotidine core. Therefore, in regard to stability, Defendant’s ANDA Product is substantially different as geometry contributes nothing to stability.

Plaintiff’s argument that Defendant’s use of packaging components to aid in stability may not be required (D.I. 232 at 6) is of no matter. Defendant uses a barrier layer to provide stability, a substantial difference from the ’033 patent disclosures. Plaintiff’s argument that Defendant’s Rule 30(b)(6) witness testified that the barrier layer was to “mak[e] the surface of the tablet

[10] “It has been discovered that by reducing the surface area of direct physical contact between ibuprofen and famotidine, one can attain an unexpectedly profound increase in stability relative to alternative designs (e.g., barrier-coated famotidine multiparticulates in a matrix comprising ibuprofen).” (PTX 1 at 4:37-42).
[11] “The reduction and/or minimization of the surface area of the core, or of direct physical contact between the incompatible active pharmaceutical ingredients, is achieved through control of the geometry of the famotidine compartment of unit dosage forms in accordance with the present invention.” (*Id.* at 6:10-15).
[12] “Moreover, using the design of the present invention, the barrier layer can be omitted without sacrificing stability.” (PTX 1 at 4:42-44).

smooth," and to make "the core tablet that is the ibuprofen . . . harder" is also irrelevant because the witness also testified to telling the FDA that the barrier layer was for stability as well. (Tr. 387:17-388:10, 390:19-392:10.)

Regarding dissolution, Defendant's arguments are not as strong. While there is a discernable difference in the release of the ibuprofen and famotidine in Defendant's ANDA Product occurring about fifteen minutes later than in DUEXIS®, the later release still meets the claim limitation of "release of both the ibuprofen and the famotidine occur[ing] rapidly at about the same time" when "at about the same time" is defined as the '033 patent specification defines it: "release of one API begins before release of the second API is completed." (PTX 1 at 10:49-51, claim 1).

However, Plaintiff's argument regarding absorption as the more clinically significant metric rather than dissolution for therapeutic effect is also unconvincing. Plaintiff points to FDA bioequivalence conclusions to support that Defendant's ANDA Product has the same rate and extent of absorption, without providing any actual data. *See Abbott Labs. v. Sandoz, Inc*., 566 F.3d 1282, 1298 (Fed. Cir. 2009) ("[B]ioequivalency and equivalent infringement are different inquiries."). Even if the bioequivalent ANDA Product meant the same rate and extent of absorption as DUEXIS®, Plaintiff does not offer evidence that the same rate of absorption between DUEXIS® and Alkem's ANDA Product means the same therapeutic effect. The most Plaintiff offered is testimony from its expert Dr. Gibofsky, "[a]bsorption is the uptake of the dissolved substances in their body into the bloodstream where they can then result in therapeutic effect." (Tr. 205:10-12). This does not equate to DUEXIS® and Alkem's ANDA Product having the same therapeutic effect even if absorption between the two products is bioequivalent.

On interchangeability, Plaintiff contends that there was a recognized interchangeability

between (a) an "ibuprofen compartment that is not a core" and a "famotidine compartment that is not a shell" and (b) Alkem's ibuprofen core / famotidine shell configuration, because Alkem did not conduct experimentation or consult literature to determine whether to place the ibuprofen in the core. (D.I. 216 at 16). Plaintiff contends Alkem placed ibuprofen in the core based on prior experience making ibuprofen tablets. (*Id.*; Tr. 386:20-387:4, 389:18-390:6, 396:1-3.) However, that Defendant placed ibuprofen in the core does not equate to interchangeability. It simply was Defendant's starting point based on prior experience.

Plaintiff also argues Horizon's own development work supports interchangeability because the ibuprofen core formulation developed by Horizon met the stability limitation in claim 1 of the '033 patent. (PTX 683 at 6; Tr. 106:17-25). Horizon did not care where the actives were placed in the dosage form, so long as they were in separate compartments that could be made reproducibly and easily. (*Id*.). Plaintiff's theory of interchangeability is undermined by the result that its ibuprofen core / famotidine shell formulation was not pursued "[d]ue to the accelerated stability profile and the significant difficulties obtaining consistent famotidine content uniformity in the spray drying process." (DTX 28 at 37). Stability was specifically cited as a reason the ibuprofen core / famotidine shell formulation, even with barrier coating, was not pursued. (*Id.* at 35).

Accordingly, I find that Horizon has not proven that Defendant's ANDA Product demonstrates insubstantial differences from the asserted claims under a DOE analysis.

b. "Function-Way-Result" Test

A product may infringe under the doctrine of equivalents if it "'performs substantially the same function in substantially the same way to obtain substantially the same result' as the patented invention." *Abraxis Bioscience, Inc. v. Mayne Pharma (USA) Inc.*, 467 F.3d 1370,

1379 (Fed. Cir. 2006) (quoting *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950)).

Plaintiff advocates for applying the "function-way-result" test to determine infringement under DOE for "a first portion" and "a second portion." (D.I. 216 at 8). Plaintiff argues the "function" is to separate the 800 mg of ibuprofen and the 26.6 mg of famotidine from one another, the "way" is to compartmentalize the actives such that all 800 mg of ibuprofen is contained in a single compartment that does not contain any famotidine and all 26.6 mg famotidine is contained in a single compartment that does not contain any ibuprofen, and the "result" is a reduction in famotidine degradation caused by ibuprofen such that it is possible to achieve acceptable shelf stability. (*Id.*; Tr. 337:13-338:7).

Plaintiff contends the '033 patent explains that the reduction in surface area of direct physical contact can be accomplished without the use of a barrier layer if a certain tablet geometry is used, or, alternatively, the '033 patent explains that a barrier layer can be used to essentially eliminate all direct physical contact between the ibuprofen and the famotidine. (Tr. 332:20-333:20; PTX 1 at 4:32-64). Plaintiff contends that defining the "function-way-result" as it proposes is consistent with the '033 patent's goal to improve the stability under forced degradation conditions of single unit dosage forms comprising both ibuprofen and famotidine. (D.I. 216 at 8). Plaintiff argues that the use of the barrier layer differentiates the inventive concept of separation and compartmentalization (i.e., the bilayer and the tablet-in-tablets), and the concept that does not separate and compartmentalize (i.e., the multiparticulate). (*Id*. at 9-10, citing Table 3 of the '033 patent; Tr. 334:2-25).

Defendant argues Plaintiff's analysis is not a limitation-by-limitation analysis; rather, it is merely looking at the product as a whole. (D.I. 226 at 13). Defendant asserts, "Horizon insists

that stability is achieved by placing the active ingredients into separate compartments—again, regardless of location or structure—and either controlling the geometry or using a barrier layer. But this position mischaracterizes the specification, which teaches that by 'using the design of the present invention, the barrier layer can be omitted without sacrificing stability.'" (*Id*. at 15, citing PTX 1 at 8:60-62, 7:8-24 (Table 1), 13:50-67 (Table 3); Tr. 421:13-16, 421:24-422:11, 131:4-12).

I agree with Defendant. The '033 patent specification teaches the use of geometry, with the option of a barrier layer. *See supra* at 52. Despite Plaintiff's contention that the inventive concept is the bilayer and the two tablet-in-tablets (one with a barrier layer and one without) as opposed to the multiparticulate, the specification makes clear that the formulation of the present invention achieves greater stability by using a geometry in which the surface area of famotidine and ibuprofen do not exceed the area disclosed as Formula (I). (*See*, *e.g*., PTX 1 at 4:37-64). "Moreover, using the design of the present invention, the barrier layer can be omitted without sacrificing stability." (PTX 1 at 13:34-40 ("Surprisingly, a tablet-in-tablet formulation in accordance with the present invention exhibited remarkably improved stability, as shown in Table 3 below, as compared to both a multiparticulate formulation and a bilayer formulation, each of which relies on the presence of a barrier between the famotidine and ibuprofen to reduce chemical interaction and degradation of the active pharmaceutical ingredients"). The barrier layer can optionally be used in addition to the geometry to improve stability even further. *See supra* at 52.

Thus, I think Plaintiff's analysis reads the inventive concept of the geometry out of the limitation. With that understanding, the most charitable statement of Plaintiff's "function-way-result" analysis is that the function would be separating the 800 mg of ibuprofen and the 26.6 mg

of famotidine from one another, the way would be using geometry to control the direct physical contact of famotidine and ibuprofen so as that the barrier layer can be omitted without sacrificing stability, and the result would be improved stability caused by a reduction in famotidine degradation from ibuprofen. Plaintiff argues, and is correct, that Formula (I) is an upper limit of the surface area over which the famotidine and ibuprofen are in direct physical contact. (D.I. 232 at 9). However, control of the geometry of famotidine and ibuprofen so that the surface area between them does not exceed this upper limit is the way in which the patent reaches the goal of reduction and/or minimization of the surface area of the core. This understanding of the analysis is consistent with my Markman ruling as well. (D.I. 86 at 81:21-22 ("But basically I think a formula, whatever it is, it's a *way* for getting this upper limit [of surface area of direct physical contact]")). Under this view of the "function-way-result" test, while the function and the result may be substantially the same, the way is not. The way does not use geometry at all. As Alkem's ANDA Product requires a barrier layer as a consequence of its geometrical design, it does not infringe under the "function-way-result" test.

Accordingly, I find that Horizon has not proven that Defendant's ANDA Product functions in substantially the same way under DOE. Consequently, since the "first portion" and "second portion" limitations are in each of the asserted claims, even assuming that they can be considered together for purposes of DOE analysis, Plaintiff's DOE case fails. For the sake of completeness, I analyze the other disputed limitations.

2. Claim 1: "wherein the surface area of direct physical contact between ibuprofen and famotidine does not exceed 130 mm^2" (limitation 3)

The Court has construed this claim term to mean, "the surface area over which no barrier layer that prevents physical contact is interposed between ibuprofen and famotidine does not

exceed 130 mm^2," wherein "barrier layer" is defined as "layer interposed between components or adjacent compartments of the unit dosage form to prevent contact between the components or adjacent compartments." (D.I. 89 at 2.)

Plaintiff contends Defendant's ANDA Product contains a barrier coating between the ibuprofen and famotidine compartments to prevent direct physical contact between the ibuprofen and famotidine, such that the surface area of direct physical contact between ibuprofen and famotidine is essentially zero and, thus, less than 130 mm^2. (Tr. 312:1-16, 326:12-327:20, 398:18-402:1; *see also* D.I. 189 Ex. 1 ¶ 14.) Defendant argues that its ANDA Product does not infringe because its 800 mg ibuprofen core would exceed the upper limit of surface area direct physical contact taught by Formula (I). (D.I. 226 at 19).

Defendant literally infringes this claim limitation by interposing a barrier layer between the ibuprofen and famotidine in its ANDA Product, so that the surface area of direct physical contact between the two active ingredients is essentially zero. Defendant's use of a barrier layer results in the surface area of direct physical contact between the two active ingredients not exceeding 130 mm^2, which is all that is required for literal infringement of this limitation.

Defendant's argument on this point does not follow from its DOE argument on geometry. Under the DOE analysis, the large ibuprofen core is substantially different than a small famotidine core because the ANDA Product can no longer use the inventive geometry taught by the patent to stabilize the pharmaceutical composition. Thus, for DOE, the use of a barrier layer cannot negate the substantial stability differences that arise from a large ibuprofen core compared to a small famotidine core. For literal infringement of a different limitation, though, the barrier layer does cause the surface area of direct physical contact between ibuprofen and famotidine to not exceed 130 mm^2. Thus, there is literal infringement of the third claim

limitation.

3. Claim 1: "wherein no more than about 1% sulfamide is present when the composition is stored at 40° C. and 75% relative humidity for a period of one month" (limitation 4)

Plaintiff contends (similarly to its response to the indefiniteness argument) that a POSA would have understood from the specification that the term "sulfamide" means USP Famotidine Impurity C. (D.I. 216 at 18-21). Plaintiff contends that Alkem's specification indicates that Alkem's ANDA Product must not contain more than 1.5% "Famotidine Related Compound-C" throughout its shelf life, which Plaintiff argues would permit the sale of Alkem's ANDA Product with no more than 1% sulfamide after one month at forced degradation conditions of 40º C and 75% relative humidity. (*Id.*; Tr. 308:8-22). Plaintiff argues Alkem's testing of its ANDA Product demonstrates that, when stored at 40° C and 75% relative humidity for three months, eight of nine exhibit batches contained no more than about 1% "Famotidine Related Compound-C." (Tr. 308:23-309:21; PTX 191 (Alkem stability reports) at 32, 34, 36, 38, 40, 42, 44, 46, 48). While this data provides levels of "Famotidine Related Compound-C" for three months rather than one month, Plaintiff contends one month would necessarily have less "Famotidine Related Compound-C" than the amount present for three months, consistent with the increasing amounts of "Famotidine Related Compound-C" between the initial and six-months readings in the same stability tables. (*Id.*; Tr. 309:22-310:18).

Defendant contends that "1% sulfamide" is indefinite and nothing in the claims or specification provide a POSA with any guidance to reasonably understand what "sulfamide" means in the context of the '033 patent, much less how to determine if a composition includes "not more than about 1% sulfamide." (D.I. 226 at 20-22).

I have found that 1% sulfamide is not indefinite, and the "no more than about 1% sulfamide" limitation in all the asserted claims to refer to Famotidine Impurity C. (*See supra* 40-45). Therefore, based on Alkem's specification and stability data, Alkem's ANDA Product literally infringes this limitation.

4. Claim 1: "wherein the composition is formulated so that release of both the ibuprofen and the famotidine occurs rapidly at about the same time" (limitation 5)

Plaintiff contends the '033 patent defines the term "rapidly" under "neutral pH conditions" (i.e., "a pH of about 6.8 to 7.4, e.g., a pH of 7.2") as "both APIs are significantly released into solution within 20 minutes under in vitro assay conditions," where "significantly released" means that "at least about 60% of the weight of the API in the unit dosage form is dissolved[.]" (Tr. 271:25-272:16, 273:15-274:15, 433:25-437:8; PTX 1 at 10:63-11:10). As Alkem used the same in vitro assay conditions as those disclosed in the patent, Plaintiff contends Alkem's ANDA Product meets the term "rapidly" because average results of Alkem's dissolution testing for 12 tablets from Exhibit Batch Number 7142492 showed 64.08% ibuprofen and 79.58% famotidine were released within 20 minutes. (Tr. 276:9-277:13, 278:11-24; PTX 237 (Alkem ANDA dissolution data) at 6, 12). While conceding certain of Alkem's tablets failed to release at least 60% of the ibuprofen within 20 minutes, Plaintiff argues many tablets within this batch exceeded 60% at 20 minutes. (Tr. 277:14-278:10; 523:4-16; PTX 237 at 6.). Accordingly, Plaintiff contends Alkem's ANDA Product literally infringes this element.

Plaintiff argues the '033 patent provides two alternative definitions of the term "at about the same time": (1) that "release of one API begins within 5 minutes of the beginning of release of the second API," or (2) that "release of one API begins before release of the second API is

completed." (D.I. 216 at 22-23). The second definition, Alkem argues, follows from the '033 patent's statement that "the dosage form is not designed so that one of the APIs is released significantly later than the other." (*Id*. at 23; Tr. 279:25-281:9; PTX 1 at 10:42-53). Plaintiff contends Alkem's ANDA Product meets the second definition because Alkem's dissolution data demonstrates that, in Alkem's exhibit batches, the ibuprofen released from between about fifteen to thirty minutes, while the famotidine released from about five to thirty minutes, so that release of the ibuprofen begins before release of the famotidine is completed. (*Id*. at 23; Tr. 280:6-283:2, 523:17-524:16; PTX 236 at 13). Thus, Plaintiff contends the ANDA Product literally infringes the "at about the same time" limitation.

Defendant contends the dissolution specification for its ANDA Product does not require that any specific amount of ibuprofen and famotidine be released within twenty minutes. (D.I. 226 at 23). Defendant contends that twenty-seven of thirty-six individual tablets tested did not release at least about 60% of the ibuprofen within twenty minutes (*id*.; Tr. 435:6-25, 436:15-437:8; PTX 237 at 6, 8, 10), Exhibit Batch Nos. 7142491 and 7142494 do not infringe (D.I. 226 at 23; PTX 237 at 7, 9), and that four of the twelve individual samples from Exhibit Batch No. 7142492 do not infringe (D.I. 226 at 23; PTX 237 at 6). Thus, Defendant contends Plaintiff has failed to show that it is more likely than not that Defendant's ANDA Product will release at least about 60% of the ibuprofen within 20 minutes.

Regarding the term "at about the same time," Defendant argues the specification definition of "release of one API begins within 5 minutes of the beginning of release of the second API" (PTX 1 at 10:45-49), Defendant does not infringe because in its ANDA Product ibuprofen releases fifteen minutes later than famotidine. (D.I. 226 at 23-24). Defendant argues that by showing that only a very small number of samples may release both APIs within 20

minutes, Plaintiff failed to support its burden on infringement of showing that infringement will be more likely than not. (*Id*.)

Defendant's ANDA Product literally infringes this claim limitation. As Defendant's expert admitted, Defendant's dissolution data demonstrates that certain samples of Defendant's ANDA Product released at least 60% ibuprofen and 60% famotidine within 20 minutes. (Tr. 276:9-277:13, 278:11-24; PTX 237 at 6, 12). Defendant's argument that, because a majority—twenty-seven out of thirty-six—of the tablets did not meet the limitation, Plaintiff has not met its burden to prove infringement of that limitation is unpersuasive. *See, e.g., Forest Labs., LLC v. Sigmapharm Labs., LLC*, 2018 WL 6011697, at *5, *11-12 (D. Del. Nov. 15, 2018) (infringement where seven of twenty-two test runs infringed); *Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc*., 282 F. Supp. 3d 793, 816 (D. Del. 2017) ("[A]t least some of [d]efendant's tablets will meet the claimed dissolution profile. This is all that is required for a finding of infringement."), *rev'd in part on other grounds*, 934 F.3d 1344 (Fed. Cir. 2019), *cert. denied*, 140 S. Ct. 2804 (2020). Under the specification's second definition of "at about the same time" to mean "release of one API begins before release of the second API is completed," Defendant infringes because in its ANDA Product the ibuprofen released from between about fifteen to thirty minutes, while the famotidine released from about five to thirty minutes. Therefore, Defendant's ANDA Product literally infringes the "wherein the composition is formulated so that release of both the ibuprofen and the famotidine occurs rapidly at about the same time" claim limitation.

5. Claim 1: "wherein none of the composition, the famotidine, and the ibuprofen is enterically coated or formulated for sustained or delayed release" (limitation 6)

Plaintiff argues a POSA would have understood that an "enteric coat" provides for "delayed release" where the product passes through the stomach before dissolving, and a "sustained" release coating releases the drug over an extended period of time. (Tr. 266:17-267:8). Plaintiff contends Alkem's Product Development Report describes Alkem's ANDA Product as an "immediate release tablet," rather than enterically coated or formulated for sustained or delayed release. (Tr. 267:9-268:13). Plaintiff contends Alkem's ANDA specifications require dissolution of not less than 80% of the famotidine and ibuprofen each within thirty minutes, which is consistent with the FDA's August 2000 guidance for "Immediate-Release" products. (Tr. 268:14-270:16). Additionally, Dr. Pandey, Alkem's Rule 30(b)(6) witness, testified (i) that each of the "film coatings" in Alkem's ANDA Product is an immediate release coating, (ii) that Alkem's ANDA Product does not contain an enteric, delayed, or sustained release coating, and (iii) that Alkem's ANDA Product is formulated for immediate release. (Tr. 388:11-389:9; *see also* D.I. 189 Ex. 1 ¶ 14.)

Defendant does not argue against infringement of this limitation. Therefore, I find Defendant literally infringes this claim limitation by a preponderance of the evidence.

D. CONCLUSION

Alkem agreed that it will not argue non-infringement of the final claim limitation of claim 1, "wherein the composition is for use according to a TID (three times per day) administration schedule for reducing the risk of developing ibuprofen-induced ulcers in a human patient requiring ibuprofen for an ibuprofen-responsive condition" of claim 1 of the '033 patent. (D.I. 205 at 1-2). Thus, I find that limitation is proved.

Plaintiff has failed to prove that Defendant's ANDA Product infringes claim 1, either literally or under DOE, by a preponderance of the evidence. Because a dependent claim cannot

be infringed unless each and every element of the underlying independent claim is also infringed, Plaintiff has failed to prove that Defendant's ANDA Product infringes claims 8, 11, and 14 of the '033 patent by a preponderance of the evidence.

V. CONCLUSION

For the foregoing reasons, Defendant proved by clear and convincing evidence that claims 1, 8, 11, and 14 of the '033 patent are invalid for obviousness. Defendant failed to prove by clear and convincing evidence that claims 1, 8, 11, and 14 of the '033 patent are invalid for indefiniteness. Plaintiff has failed to prove by preponderance of the evidence that Defendant's ANDA Product infringes claims 1, 8, 11, and 14 of the '033 patent.

The Court will enter a final judgment in accordance with this opinion following the general format proposed by Alkem. (D.I. 237-2).