IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

FOREST LABORATORIES, LLC and FOREST LABORATORIES HOLDINGS, LTD.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 14-1119-SLR
SIGMAPHARM LABORATORIES, LLC, et al.,	)	
Defendants.	)	

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OPINION

Dated: June 30, 2017
Wilmington, Delaware

ROBINSON, Senior District Judge

I. INTRODUCTION

This consolidated case arises out of the filing of Abbreviated New Drug Applications ("ANDAs") by defendants Sigmapharm Laboratories, LLC ("Sigmapharm"); Breckenridge Pharmaceutical, Inc. ("Breckenridge"); Hikma Pharmaceuticals, LLC, Hikma Pharmaceuticals, PLC, and West-Ward Pharmaceutical Corporation (collectively, "Hikma"); Alembic Pharmaceuticals Ltd., Alembic Global Holding S.A., and Alembic Pharmaceuticals, Inc. (collectively, "Alembic"); and Amneal Pharmaceuticals, LLC, Amneal Pharmaceuticals of New York, LLC, and Amneal Pharmaceuticals Co. India PVT.LTD (collectively, "Amneal"). All defendants may be collectively referred to as "defendants." Each of the defendants has submitted an ANDA in an attempt to market generic versions of asenapine before the expiration of U.S. Patent No. 5,763,476 ("the '476 patent"), which claims sublingual or buccal compositions of asenapine and methods of using such compositions to treat mental disorders, including schizophrenia. Plaintiffs Forest Laboratories, LLC and Forest Laboratories Holdings, Ltd. (collectively, "Forest" or "plaintiffs") brought patent infringement suits against each of the defendants, which suits were consolidated into the above captioned suit. In the case tried before the court, each of the defendants conceded infringement of claim 1 of the '476 patent and two of the four defendants (Amneal and Hikma) conceded infringement of claim 4.[1] Therefore, the focus of the trial (conducted in the fall of 2016) was infringement of claim 4 and the validity of the '476 patent. The court has

[1]The issue of Sigmapharm's infringement of claims 1 and 4 has been stayed by the court. (D.I. 278) Sigmapharm has agreed to be bound by the validity determinations reached by the court. (*Id.*)

jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is appropriate pursuant to 28 U.S.C. § 1400(b). Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law, pursuant to Federal Rule of Civil Procedure 52(a).

II. FINDINGS OF FACT

A. Development of Saphris®

Saphris®[2] is an atypical antipsychotic containing asenapine maleate approved for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder. (PTX 54 at 1, 3) Saphris is the only antipsychotic[3] that is administered sublingually. (D.I. 311 at 85:9-12; D.I. 315 at 1039:5-13) Sublingual administration requires patients to put the formulation under the tongue and wait for the formulation to dissolve. Patients taking Saphris sublingually also cannot eat or drink for ten minutes following administration. (PTX 54 at 1, 3, 37)

Asenapine was not initially developed as a sublingual tablet but, instead, as a standard conventional tablet given orally. This is shown in a series of publications by Organon, the company that first developed asenapine for use in humans. (PTX 33; PTX 37; PTX 53) One of the first publications concerning asenapine is Sitsen, J. M. Ad., et al., Org 5222: Preliminary Clinical Results 15-18 (Raven Press, Ltd., 1992) ("Sitsen 1992"). (PTX 37) Sitsen 1992 explains that while there were drugs then

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[2]The '476 patent is listed in the Food and Drug Administration's ("FDA's") publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations" (known as the "Orange Book") for Saphris® ("Saphris"). (D.I. 1, ¶ 9)

[3]First generation antipsychotics are referred to as "typical" antipsychotics; second generation antipsychotics are referred to as "atypical" antipsychotics.

available for the treatment of schizophrenia, they were not satisfactory due to their debilitating side effects. (*Id.* at 15) In particular, the available first generation antipsychotics caused serious movement disorders, referred to as "extrapyramidal" side effects ("EPS"), including Parkinsonism and tardyskinesia—side effects that persisted even when the patients stopped taking the medicines. (D.I. 311 at 71:12-25, 85:20-86:5; D.I. 313 at 612:18-613:2, 618:18-619:20)

At the time of the publication of Sitsen 1992, there were two second generation or "atypical" antipsychotics available, clozapine and risperidone. Although clozapine caused fewer movement disorders, it caused other serious side effects including a rare white blood cell condition, termed "agranulocytosis," that was potentially fatal and had to be closely monitored. (D.I. 313 at 730:4-12; D.I. 315 at 1059:9-1061:23) For this reason, clozapine was used sparingly and was only approved for the most treatment-resistant of schizophrenia patients. Risperidone caused an increase in prolactin, which resulted in the serious side effect of breast growth and lactation, even in men. (DTX 63, 955 at figure 4D, 960; D.I. 311 at 70:25-71:11; D.I. 313 at 672:3-673:18, 674:10-24; D.I. 315 at 1057:1-1058:12)

Sitsen 1992 explained that there was a need for an effective second generation atypical antipsychotic that could be widely used for schizophrenic patients. (PTX 37 at 3) Sitsen 1992 declared that asenapine (referred to by its internal Organon designation "Org 5222"), an atypical antipsychotic, satisfied that need. Org 5222 was described as "a new antipsychotic drug with high in vitro affinity for dopamine D1 and D2 receptors and for several types of serotonin (5-HT) receptors." (*Id.* at 3) "Its behavioral pharmacology suggests antipsychotic properties with a relatively low

propensity to induce movement disorders." (*Id.*) "Org 5222 is a novel antipsychotic drug with a pharmacological profile that is different from that of the classical antipsychotics haloperidol[4] and chlorpromazine." (*Id.* at 5)

Sitsen 1992 also discussed early clinical studies with asenapine that provided promising results. The article explained that healthy male volunteers received oral doses of Org 5222 up to 30 mg, and reported that "[a]t the highest dose levels some volunteers experienced mild drowsiness and/or moderate fatigue. No other clinically significant or dose-related changes in biochemical, hematological, or urinary parameters were found." (PTX 37 at 4) When the article referred to "oral doses," it referred to a conventional tablet that is swallowed, passes through the digestive system, and is subject to "first-pass metabolism," where the drug is metabolized by the liver before it enters the blood. (D.I. 314 at 939:25-940:11) Similarly, Sitsen 1992 reported that, in a different clinical trial using multi-dosing of asenapine, there was a slight elevation of liver enzymes that were reversible after discontinuation of treatment. (PTX 37 at 4) The article reported that this side effect was considered safe, and skilled artisans understood that this sort of side effect was not considered serious, particularly for a drug that was being used to treat schizophrenia. (D.I. 314 at 845:3-847:23, 944:1-15) Sitsen 1992 concluded that "[p]reliminary results of a pilot trial comparing the effects of Org 5222 . . . suggest [it] is an effective antipsychotic drug that lacks sedative properties and extrapyramidal side effects," and that "Org 5222 is well tolerated by

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[4]"Haloperidol" is a first generation antipsychotic that was the gold standard for treating schizophrenia at the time. (D.I. 313 at 616:7-17, 945:6-11) It, however, had the movement disorders and other debilitating side effects characteristic of the first generation antipsychotics. (D.I. 313 at 616:18-24)

healthy persons and schizophrenic patients." (PTX 37 at 5)

In terms of efficacy, the article discussed an early clinical trial comparing the effects of Org 5222 and haloperidol in schizophrenia patients. The clinical study showed "that Org 5222 is an effective antipsychotic drug that lacks sedative properties and extrapyramidal side effects." (PTX 37 at 5) Although more patients dropped out of the trial who were on asenapine than who were on haloperidol, the patients who dropped out on asenapine did so because of lack of treatment effect. (*Id.*) As explained by "De Boer 1993,"[5] "[t]he main reason for patient dropout was inadequate treatment effect occurring more frequently in the Org 5222 group," but that the asenapine arm of the study was "significantly more ill than other patients in the study." (PTX 33 at 6) That is, the higher dropout rate observed in the asenapine group was likely due to the fact that the patients were more difficult to treat than the patients in the haloperidol group, not that asenapine was ineffective. (D.I. 314 at 946:2-22, 947:24-948:19)

Organon published an abstract in 1993, Vrijmoed-de Vries, An Update on the Clinical Development of the Atypical Antipsychotic Org 5222, Schizophrenia Res. 9.2, 260-261 (1993) ("Vrijmoed 1993"). (PTX 53) This abstract again reported the same clinical study in both Sitsen 1992 and De Boer 1993. (*Id.* at 3) As before, the abstract reported that "Org 5222 appear[s] to be a relatively safe, atypical antipsychotic drug up to a single dose of 30 mg and multiple (14 days) oral doses of 5 mg twice daily." (PTX 53 at 3) "Org 5222 showed similar antipsychotic effects as compared to haloperidol but

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[5]De Boer, T., et al., Org-5222, Drugs of the Future 1993, 18(12): 1117-1123 (1993) ("De Boer 1993"). (PTX 33)

in a lesser proportion of patients. Treatment with Org 5222 was safe, and induced far less extrapyramidal side-effects than haloperidol." (*Id.* at 3)

Vrijmoed 1993 then stated that, based on the good results Organon had obtained so far, Organon was currently engaged in "large scale Phase II studies in (sub)chronic schizophrenic patients . . . in Scandinavia." (PTX 53 at 3) More specifically, Vrijmoed 1993 reported that two large Phase II studies of Org 5222 were ongoing to further confirm efficacy in schizophrenic patients using higher doses of asenapine (including 0.4 mg, 1.0 mg, 2.0 mg, and 4.0 mg), and that "[n]o clinically relevant adverse experiences have been reported up to date" in those studies using those doses. (PTX 53 at 3)

Taken together, skilled artisans reviewing the published early clinical studies of orally administered asenapine would understand that orally administered asenapine was safe and clinically effective at relatively low doses. (D.I. 314 at 844:4-19, 847:24-848:11, 942:16-949:19, 955:12-16; *see also* D.I. 312 at 316:25-317:10, 446:4-15) Therefore, Organon continued to perform dose ranging and pharmacokinetic studies with asenapine. (PTX 23; PTX 24) One such study, conducted in December 1991, was designed to preliminarily assess the safety of and tolerance for asenapine administered intravenously ("IV"), and to obtain preliminary data on the bioavailability of orally administered asenapine in healthy male volunteers. (PTX 23 at 3) The design of the study included a controlled-rate IV infusion in two healthy volunteers. (PTX 23 at 4, 5) "Subjects receiving the highest tolerated intravenous dose were to be given a single oral dose of 30 mg of Org 5222 after a washout period of seven days." (*Id.*) Because variations in metabolism among individuals can affect bioavailability results, the study

was designed such that the same individuals received the IV and the oral doses. (D.I. 314 at 952:12-953:9) Organon planned for eight subjects to participate in the IV study, with two subjects infused at each of four doses - 0.7 mg, 1.5 mg, 3 mg, and 4.5 mg - over 30 minutes. (PTX 23 at 4) The study, however, was terminated after the first two subjects were given the 0.7 mg IV dose. (PTX 23 at 5, 32-33, 177-78)

"Subject 1," who received the 0.7 mg IV dose, collapsed in asystole (no electrical activity in the heart), i.e., the subject's heart had stopped beating and the patient went into cardiac arrest forty-five minutes after start of infusion while having his sitting blood pressure measured. (PTX 23 at 5, 32-33) After cardiac massage (5 sternal thrusts), the patient briefly gained consciousness, asked what was happening, and then lost consciousness again. (*Id.* at 33) The massage stimulated nodal bradycardia, which is a "survival mechanism," but the heart then reverted to asystole. (*Id.*) Two doses of atropine, a drug used to help a patient in cardiac arrest situations, were then administered at forty-nine and fifty-four minutes. (*Id.* at 32) After experiencing the asystolic event, Subject 1 was sent to an independent cardiologist. (*Id.* at 5, 32-33, 177-78) The cardiologist concluded that Subject 1, in fact, had suffered from an asystolic event. (*Id.* at 177) The cardiologist concluded that Subject 1 was fit and showed no evidence of any cardiac issues or cardiovascular disease. (*Id.*) The cardiologist concluded that the asystolic event "almost certainly has to be classed as a drug induced effect with a serious adverse effect on the conducting system of the heart." (PTX 399 at 46-47) Accordingly, the investigators concluded that IV infusion of asenapine "was not well tolerated," and the study was terminated. (PTX 23 at 5, 35)

Organon concluded that it could no longer conduct any further studies of asenapine using IV administration of the drug. (D.I. 311 at 256:19-257:17) Organon then tried to determine what happened, and assessed the peak plasma levels of the parent compound, Org 5222 (asenapine), and of the metabolite, Org 30526 (desmethyl-Org 5222). (PTX 23 at 5-6, 10-11) The data demonstrated that the level of metabolite in both subjects was below the level of quantification, a finding consistent with the fact that, because the IV formulation was administered directly into the vein, the study drug did not undergo "first-pass metabolism," that is, it was not metabolized upon initial administration. (D.I. 314 at 815:1-4, 939:5-941:4) The level of the parent compound in the blood of Subject 2 was higher than in Subject 1, demonstrating that it was the level of the parent compound and not any metabolite that caused the cardiotoxic effect. (*Id.* at 815:14-816:5, 963:12-24)

After the IV study, the Organon scientists focused on the conventional oral tablet formulation with which they had early success. As noted, they did so believing that the cardiotoxicity observed was due to the parent compound, not a metabolite of asenapine. (PTX 24 at 49) In June 1992, Organon designed another study to examine the pharmacokinetic profile of asenapine and recruited twelve healthy volunteers to use asenapine both after a single oral dose (30 mg) and at steady state (5 days, 15 mg twice daily). (*Id.* at 4) The study planned to compare twelve subjects in two groups of six. (*Id.*) When another subject (again, "Subject 1") suffered a serious adverse event, the study was terminated. Two hours and twenty-five minutes after dosing, Subject 1 was sitting up when he suddenly felt dizzy and nauseous. (*Id.* at 6, 42) The electrocardiogram monitor alarmed indicating asystole. (*Id.*) The study report indicates

that the subject suffered from an asystolic episode of 8.7 seconds. (*Id.*) After five minutes, Subject 1 subjectively improved and, after ten minutes supine, he said that he felt normal. (*Id.* at 42) The subject felt dizzy again approximately two hours later. (*Id.*) This dizziness occurred five minutes after sitting up from supine and after food consumption. (*Id.*) The clinical trial team determined that Subject 1 had suffered from an asystolic event. (*Id.* at 42-44, 135) Subject 1 was referred to a cardiologist, who determined that he was healthy, had no evidence of cardiac disease, and that the asystolic episode was "directly related to the drug." (*Id.* at 42; PTX 399 at 57)

As before, Organon examined the levels of both the parent compound and the metabolite in Subject 1 (as well as the other subjects), and determined that Subject 1 had the highest level of the parent compound in his blood stream. (D.I. 314 at 824:3-14, 964:15-965:1) Because a conventional tablet was used in this oral study, there was "first-pass metabolism" and detectable levels of metabolite in the subjects' blood. However, Subject 4, the subject with the highest level of the metabolite, did not have a cardiotoxic event. (*Id.* at 824:15-825:10) When the IV data and the oral data are viewed in conjunction, they show that it was the level of the parent compound and not the metabolite that was responsible for the cardiotoxic events. (*Id.* at 825:1-25, 965:2-11)

Recognizing that the previously unknown serious cardiotoxic events observed during IV and oral administration of asenapine would result in termination of the development of asenapine, Organon scientists (including the inventors of the '476 patent, Drs. Delbressine and Wieringa) conducted a "brainstorming session" to develop

possible avenues of further research. (PTX 393 at 1-4) Consistent with the data discussed above, the Organon scientists hypothesized that the plasma Cmax levels of the parent compound, asenapine, should not rise above 600 pg/ml. (*Id.* at 1) Organon then postulated several different routes of administration, including rectal, nasal, pulmonal (lungs), buccal, sublingual, plasters, and depot injections. (*Id.* at 3-4) Of these possible routes of administration, Organon stated that buccal/sublingual, plasters, and depot injections were "worth a try." (*Id.*) Drs. Delbressine and Wieringa were the individuals who suggested using the buccal/sublingual route of administration, although they were not convinced that the sublingual dosage form would solve the problem. (D.I. 311 at 263:17-21, 269:17-270:18, 284:5-16)

A beagle dog study was then conducted to "compare the cardiovascular effects of orally and sublingually administered Org 5222 in the conscious dog in doses yielding similar plasma levels to determine whether sublingual Org 5222 might constitute a safer route of administration." (PTX 25 at 3-4, 9, 14-19, 59) The results of the beagle dog study led to the conclusion that "Org 5222 administered sublingually has fewer cardiovascular effects than when given orally. Thus, even in doses yielding plasma levels approximately one order of magnitude higher than anticipated therapeutic levels, sublingually given Org 5222 is devoid of prohibitive cardiovascular effects." (*Id.* at 4)

Based on these results, Organon determined that it could take the next incremental step in further developing asenapine using the sublingual route of administration. (D.I. 311 at 269:17-270:18) The dog study showed[6] a clear trend of

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[6]Defendants' experts challenged the beagle dog study decades after its conclusion. (D.I. 317 at 1330:6-14) The court rejects such post-hoc criticisms, as

increased heart effects with an oral tablet, but no such trend was observed with the sublingual forms. (D.I. 314 at 831:2-832:11, 833:9-13; *see also* D.I. 312 at 464:1-16) This provided Organon with proof of concept and allowed it to develop the sublingual dosage form for which it ultimately obtained FDA approval on August 13, 2009. (D.I. 311 at 269:24-270:18, 272:14-19; 926:6-9)

Dr. Illum testified that it was "amazing" that the sublingual dosage form solved the problem; even today, she cannot understand why:

> Q. Sitting here today, do you find it surprising that a sublingual dosage formsolved these problems, the cardiotoxic events?
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> A. I actually find it totally amazing. I can't understand it. If you look at the sublingual dosage form as it is today where you actually administer five milligrams or 10 milligrams or up to 20 milligrams a day, if you look at the plasma levels that you actually obtain even after just five milligrams of sublingual asenapine, you actually achieve a plasma level as up to 4,000 picograms per ml, which is way above what you found in both the IV study and the oral study in terms of the parent compound, and you don't see any side effects, serious side effects with the sublingual formulation, and I find that amazing. Can't understand it.

(D.I. 314 at 968:24-969:13; *see also id.* at 830:11-20, 833:14-19; D.I. 311 at 269:17-271:19)[7]

Organon had extensive experience with asenapine as well as studies using beagle dogs, and designed a study that would allow Organon to determine whether or not sublingual administration could be used to alleviate the severe cardiotoxic effects shown in the IV and oral studies. (D.I. 311 at 280:24-281:4, 283:3-11; *see also* '476 patent, 4:47-5:58)

[7]Defendants rely on two events years later to try to discount the significance of the sublingual form solving the cardiotoxic problem. (PTX 399 at 14) But both of these events were during a stress test or "postural challenge" where the patients were forced to stand and then sit rapidly. (*Id.*) Two subjects during the test had an asystolic event. One subject, however, was taking placebo, and while the other was on sublingual asenapine, neither event could be linked to asenapine as opposed to the design of the study. (*Id.*) These events were not "serious events" of the sort discussed above, the study was not discontinued, and the patients (including the one on asenapine) were

B. The '476 Patent

1. Route of administration

Based on the discovery described above, the inventors filed an application that issued as the '476 patent describing sublingual (under the tongue) or buccal (inside of the cheek) pharmaceutical compositions of asenapine "for the treatment of mental disorders, such as psychosis and schizophrenia." ('476 patent, abstract) The '476 patent's focus on sublingual and buccal dosage forms is repeatedly demonstrated throughout the patent. For example, the title of the '476 patent is "Sublingual or Buccal Pharmaceutical Compositions," and the specification states that "[t]he invention relates to a sublingual or buccal pharmaceutical composition, and more specifically to a sublingual or buccal composition for the treatment of various mental disorders." ('476 patent, title; 1:6-9) The specification further provides that "[t]he invention therefore relates to a sublingual or buccal pharmaceutical composition comprising [asenapine] . . . ," and "the use of [asenapine] for the manufacture of a sublingual or buccal pharmaceutical composition for treating mental disorders, such as psychosis and schizophrenia." ('476 patent, 1:24-38; 3:1-5) The specification states that "[p]referred pharmaceutical compositions are solid pharmaceutical compositions which rapidly disintegrate in the mouth of a subject, upon insertion into the buccal pouch or upon placement under the tongue." ('476 patent, 1:56-59)

The patent gives a brief description of the history of development discussed

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allowed to continue on the study. (*Id.*; D.I. 316 at 1189:2-1190:19)

above: "Phase I clinical studies on the effects of perorally[8] administered [asenapine] however, revealed that serious cardiotoxic effects, e.g. postural hypotension and/or impairment of baroreceptor functioning occurred. Surprisingly, it has now been found that on sublingual or buccal administration, [asenapine] has substantially less cardiovascular side effects." ('476 patent, 1:24-32) The preferred sublingual and buccal pharmaceutical compositions "rapidly disintegrate in the mouth of a subject, upon insertion into the buccal pouch or upon placement under the tongue." ('476 patent, 1:56-59) The '476 patent also notes that these sublingual and buccal dosage forms may come in the form of tablets, lozenges, or freeze-dried compositions. ('476 patent, 1:66-2:15)

The patent also includes data from the beagle dog study. ('476 patent, 4:47-5:58; D.I. 314 at 830:21-832:10) Table 1 compares the change in mean heart rate between oral and sublingual administration at several different plasma concentrations. ('476 patent, 5:32-46) The data shows that at every concentration, sublingual administration had less effects on mean heart rate change than oral administration. (*Id.*) The '476 patent concludes that "[t]achycardia accompanying orthostatic hypotension was more marked after oral than after sublingual administration of Org 5222. Direct haemodynamic and electrophysiological effects were also less marked after sublingual than after oral administration with regard to negative inotropy and QTc prolongation." ('476 patent, 5:49-54)

Based on the invention as disclosed in the specification, asserted claim 4 recites:

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[8]Skilled artisans understand that "peroral" administration refers to orally administering asenapine. (D.I. 312 at 401:11-14; D.I. 314 at 942:13-15)

"A method for treating tension, excitation, anxiety, and psychotic and schizophrenic disorders, comprising administering sublingually or buccally an effective amount of a pharmaceutical composition comprising trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1Hdibenz[2,3:6,7]oxepino[4,5-c]pyrrole [asenapine] or a pharmaceutically acceptable salt thereof." ('476 patent, 6:10-15)

Like claim 4, claim 1 also initially contained express language that the composition was "suitable for sublingual or buccal administration." In particular, during prosecution, independent claim 1 originally recited: "A pharmaceutical composition as a medicinally active compound: trans-5-chloro- 2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole [asenapine] or a pharmaceutically acceptable salt thereof; and pharmaceutically acceptable auxiliaries, the composition being suitable for sublingual or buccal administration of said active compound." (PTX 2 at 126-27) The examiner, however, thought that this language was not sufficient to capture only sublingual formulations because the word "suitable" allowed the formulation to be taken by an conventional oral route. The examiner explained:

> The method of administering the instant compound sublingual[ly] or buccally is novel and unobvious. It would not have been obvious that certain side effects could be avoided by this mode of administration. Therefore, the method claim 5 is allowable. Furthermore, any composition whose physical characteristics make the composition unique to sublingual or buccal administration . . . would also be allowable. However, the composition claims are not so limited.

(PTX 2 at 140; D.I. 314 at 973:1-21) The reason the composition claims were "not so limited," according to the examiner, was because (as currently written) "[a]t best, the compositions as claimed may be used for either mode of administration (sublingually or orally, rectally, etc.). The recitation, 'suitable for sublingually or buccal administration,'

does not result in a structural difference between the claimed invention and the prior art." (PTX 2 at 140)

In response to the examiner's suggestion, the applicants amended the language of claim 1 to add the language "wherein the composition is a solid composition and disintegrates within 30 seconds in water at 37° C." (PTX 2 at 148) The applicants explained:

> The Office Action indicated that any composition whose physical characteristics make the composition unique to sublingual or buccal administration . . . would be allowable. Applicants submit that the distinguishing feature of disintegration time is exactly such a characteristic. The feature of disintegration time was not recognized as being important in van der Burg. It is this feature of rapid disintegration which distinguishes a sublingual composition from a peroral one and which makes the compositions of the present invention suitable to avoid the adverse effects observed with peroral administration.
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> ***
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> As noted on page 1 of the present specification, peroral administration of the active compound of the present invention results in serious cardiotoxic affects. To obtain the good effects of the compositions of the present invention, it is necessary that the medicine be delivered by sublingual or buccal administration.

(PTX 2 at 144, 145) In response, the examiner allowed claim 1 to issue as follows: "A pharmaceutical composition comprising as a medicinally active compound: trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5- c]pyrrole [asenapine] or a pharmaceutically acceptable salt thereof; wherein the composition is a solid composition and disintegrates within 30 seconds in water at 37° C." ('476 patent, 5:61-6:3)

2. Treatment of mental disorders

As noted above, claim 4 of the '476 patent discloses a method for treating "tension, excitation, anxiety, and psychotic and schizophrenic disorders," comprising the

sublingual or buccal administration of asenapine. The focus of the invention is the route of administration; the '476 patent spends little time on discussing the purpose for which asenapine will be administered. Specifically, the '476 patent calls out the treatment (or treating) "various" "mental disorders," "such as psychosis and schizophrenia." ('476 patent, abstract; 1:8-9, 3:4-5) The specification also presages the language of claim 4: "The compositions of the invention are useful in treating mammals, including humans, suffering from diseases which are susceptible to treatment by [asenapine]. Such diseases include mental disorders, such as tension, excitation, anxiety, psychosis, and schizophrenia." ('476 patent, 1:39-44) The specification describes that De Boer's review of "the first safety and efficacy studies [of Org 5222] in human volunteers and in schizophrenic patients" "established that Org 5222 . . . is a very potent dopamine and serotonin antagonist with potential antipsychotic activity." ('476 patent, 1: 14-23)

Notably, there is no mention in the '476 patent of "bipolar I disorder" or of "manic or mixed episodes associated with bipolar I disorder," even though such descriptors were well known in the art in 1994. (*See, e.g.,* PTX 201 at 3; PTX 339 at 4) Those of skill in the art also recognized in 1994 that "bipolar I disorder" was a "mood" disorder, as opposed to "schizophrenia and other psychotic disorders." (*See* PTX 197 at 4) It is evident that the language of the '476 patent is directed to "diseases" and "disorders," not to symptoms of such. The parties agree that, in 1994, there was no recognized disorder labeled "excitation disorder." (D.I. 311 at 163:2-17; 509:8) Finally, the parties agree that "excitation" may be a symptom of many disorders; the parties disagree about whether "excitation" is the "defining essential feature of mania," as opined by Dr.

McIntryre, one of Forest's experts. (D.I. 311 at 102:9-19; D.I. 312 at 509:8-14)

III. CONCLUSIONS OF LAW

A. Scope of Claims 1 and 4

Defendants have argued that the amendment made during prosecution, as discussed above, broadened claim 1 to cover any composition—administered sublingually or not—that disintegrates within 30 seconds. The court concludes that defendants' interpretation of the amendment and claim 1 is inconsistent with the specification and the prosecution history. Indeed, defendants' assertion that claim 1 covers an orally (also referred to as perorally) administered tablet would expand its scope to cover the very subject matter that the applicants specifically distinguished their invention from during prosecution and in their patent specification. Defendants' expert, Dr. Jacobs, himself conceded that statements made during prosecution indicate that sublingual administration is "required." (D.I. 312 at 404:25-406:23)

The repeated statements in the specification, including those indicating that it was the sublingual compositions that solved the cardiac problems that were caused by oral administration, plainly convey that the compositions of claim 1 are limited to sublingual or buccal dosage forms and do not cover compositions that are administered orally. *See Poly-Am., L.P. v. API Indus., Inc.*, 839 F.3d 1131, 1137 (Fed. Cir. 2016); *Luminara Worldwide, LLC v. Liown Elecs. Co.*, 814 F.3d 1343, 1353 (Fed. Cir. 2016) ("When a patentee 'describes the features of the 'present invention' as a whole,' he implicitly alerts the reader that 'this description limits the scope of the invention.'").

It is settled law that claims may be limited by how the specification describes the

invention. *See, e.g., UltimatePointer, L.L.C. v. Nintendo Co.*, 816 F.3d 816, 823-24 (Fed. Cir. 2016); *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 653 F.3d 1296, 1305 (Fed. Cir. 2011) ("[W]hile the claims leave open the possibility that the recited 'body' may encompass a syringe body composed of more than one piece, the specifications tell us otherwise."). Claim 1, therefore, is limited to sublingual or buccal compositions "to tether the claims to what the specifications indicate the inventor actually invented." *Id.*

Further, "when the patentee unequivocally and unambiguously disavows a certain meaning to obtain a patent, the doctrine of prosecution history disclaimer narrows the meaning of the claim consistent with the scope of the claim surrendered." *Forest Labs. Holdings Ltd., v. Mylan Inc.*, 2016 WL 3677148, at *8 (D. Del. July 11, 2016) (quoting *Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1095 (Fed. Cir. 2013)). "Such statements can take the form of either amendment or argument." *Id.* "The entirety of a patent's file history captures the public record of the patentee's representations concerning the scope and meaning of the claims." *Id.* Here, the statements made during prosecution demonstrate that the inventors limited the claims to sublingual or buccal compositions (and specifically excluded peroral administration) to avoid the cardiotoxic effects observed upon oral administration.

B. Infringement

As noted, all defendants have conceded infringement of claim 1, as well as dependent claims 2, 5, and 6 of the '476 patent. (*See* D.I. 102, D.I. 177, D.I. 183, D.I. 238, and D.I. 279) Only defendants Alembic and Breckenridge challenge infringement

of claim 4; defendants Amneal and Hikma do not.[9]

Consistent with the parties' dispute, claim 4 contains essentially three relevant limitations: "A method for treating . . . [1] excitation . . .disorders, comprising [2] administering sublingually or buccally an [3] effective amount of a pharmaceutical composition [asenapine] or a pharmaceutically acceptable salt thereof." Defendants Alembic's and Breckenridge's proposed labels provide literal instructions to carry out elements [2] and [3] of the claim, i.e., [2] sublingually administering [3] an effective amount of asenapine maleate to treat the indicated disorder, that is, manic episodes associated with bipolar I disorder. (PTX 56 at 1, 3-4; PTX 59 at 1, 3-4) The defendants' labels explicitly state: "Read these Instructions for Use before you start using asenapine sublingual tablets and each time you get a refill." (PTX 56 at 36-38; PTX 59 at 39-42) Further, the "Dosage and Administration" section of Alembic's and Breckenridge's labels provide specific instructions on how to administer their asenapine sublingual tablets:

> Do not swallow tablet. Asenapine sublingual tablets should be placed under the tongue and left to dissolve completely. The tablet will dissolve in saliva within seconds. Eating and drinking should be avoided for 10 minutes after administration (2.1, 17).

(PTX 56 at 1, 3 at § 2.1, 37 at "Figure D"; PTX 59 at 1, 3 at § 2.1, 41-42 at "Figure D") Defendants' labels provide instructions and a chart reciting effective doses to treat bipolar mania (PTX 56 at 1, 3 at § 2.1, 37 at "Figure D"; PTX 59 at 1, 3 at § 2.1, 41-42

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[9]Amneal and Hikma have stipulated to infringement of claims 4, 9, and 10. (D.I. 102, D.I. 183) Plaintiffs, Alembic, and Breckenridge have stipulated that, "if claim 4 of the '476 patent is found to be infringed, then dependent claims 9 and 10 are also infringed, and if claim 4 of the '476 patent is found to be not infringed, then dependent claims 9 and 10 are also not infringed." (D.I. 279 at 2)

at "Figure D"), as well as provide instructions and a chart reciting effective doses to treat manic episodes (PTX 56 at 1 "Dosage and Administration," and "Dosage Forms and Strengths"; PTX 59 at 1 "Dosage and Administration," and "Dosage Forms and Strengths.").

Consequently, there is no meaningful dispute between the parties that physicians and/or patients who will use Alembic's and Breckenridge's generic asenapine products will literally perform elements [2] and [3] of claim 4 and directly infringe those limitations. The only issue for the court to decide concerns limitation [1] in the claim, that is, whether defendants infringe claim 4 even though their generic asenapine products are indicated only for the treatment of "manic episodes" associated with bipolar I disorder.

1. Standard of review

A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). To prove direct infringement, the patentee must establish that one or more claims of the patent read on the accused device literally or under the doctrine of equivalents. *See Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc.*, 261 F.3d 1329, 1336 (Fed. Cir. 2001). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995), aff'd, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope, a question of law. *See id.* at 976-77; *see also Teva Pharms. USA, Inc. v. Sandoz, Inc.*, _ U.S. _, 135 S. Ct. 831, 837

(2015). The trier of fact must then compare the properly construed claims with the accused infringing product. *See Markman*, 52 F.3d at 976. This second step is a question of fact. *Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1337 (Fed. Cir. 2015) (citing *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998)). "Direct infringement requires a party to perform each and every step or element of a claimed method or product." *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1320 (Fed. Cir. 2009) (quoting *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007)). "If any claim limitation is absent . . ., there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *Ferring B.V. v. Watson Labs., Inc.-Florida*, 764 F.3d 1401, 1411 (Fed. Cir. 2014) (citing *Wahpeton Canvas Co., Inc. v. Frontier, Inc.*, 870 F.2d 1546, 1552 (Fed. Cir. 1989) ("One who does not infringe an independent claim cannot infringe a claim dependent on (and thus containing all the limitations of) that claim.")). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552) (internal quotations omitted). The patent owner has the burden of proving literal infringement by a preponderance of the evidence. *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, _ U.S. _, 134 S. Ct. 1749, 1758 (2014).

It is not an act of infringement to seek approval to market a generic drug for a use that is not covered by a patent. *See Warner-Lambert Co. v. Apotex Corp.*, 316

F.3d 1348, 1354-55 (Fed. Cir. 2003). The Federal Circuit has not found infringement when the product label does not address the patented methods. *See Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009) ("The question . . . is whether [the] instructions teach an infringing use of the device such that we are willing to infer from those instructions an affirmative intent to infringe the patent."); see also *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1321-22 (Fed. Cir. 2012) (infringement can be found only where the defendants' ANDAs sought approval for the use protected by the patent).

Inducement of infringement requires "active steps taken to encourage direct infringement." *Takeda Pharm. v. West Ward Pharm. Corp.*, 785 F.3d 625, 630 (Fed. Cir. 2015) (citation omitted) ("*Takeda*"). In the Hatch-Waxman context, the Federal Circuit has held that "[t]he label must encourage, recommend, or promote infringement. . . . [I]t is well established that 'mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringment must be proven.'" *Id.* at 631 (quoting *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003)). As this court has held, even if the evidence of likely infringing use (direct infringement by third parties) were undisputed, "the question remains whether the proposed label is a sufficient catalyst to constitute 'active steps taken to encourage direct infringement'" of the patent in suit. *Takeda Pharm. v. West Ward Pharm. Corp.*, 72 F. Supp. 3d 539, 546 (D. Del. 2014), aff'd, 785 F.3d 625 (Fed. Cir. 2015).

The court recognizes that circumstantial evidence of intent may suffice, as there

is rarely direct evidence of such. *See, e.g.*, *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). And, indeed, in the context of ANDAs, the Federal Circuit has examined not only the label, but other conduct as well, e.g., the generic's planned distribution of its ANDA product "despite being aware of the infringement problem presented by the proposed label." *Id.* at 1060. Ultimately, however, the question remains whether the court is "willing to infer" from the evidence of record "an affirmative intent to infringe the patent." *Takeda*, 785 F.3d at 631.

2. Direct infringement under the doctrine of equivalents

The court construed the phrase "tension, excitation, anxiety, and psychotic and schizophrenic disorders" as not literally including the treatment of bipolar disorder, including manic or mixed episodes associated with bipolar I disorder. (D.I. 133 at 2) The court explained that the word "bipolar" was not used or described in the specification and, indeed, the use of asenapine to treat bipolar disorder was claimed in a later patent application. (*Id.*; *see also* D.I. 58, ex. 5) The court also relied on the declaration of defendants' expert, Dr. Frazer, who explained that bipolar disorder is a "'mood disorder,' separate and apart from schizophrenia and other "psychotic disorders." (*Id.*)

The court will not review claim construction again, but will address Forest's argument that the term "excitation" in the claim includes within its literal scope "mania" and, therefore, the claim covers the treatment of the manic component of bipolar disease. To put the point differently, Forest argues that, to the extent there are any differences between the treatment of manic episodes associated with bipolar I disorder

with asenapine and the treatment of excitation with asenapine recited in claim 4, such differences are insubstantial; i.e., the two treatments are equivalent.

Forest's doctrine of equivalents theory depends almost entirely on the opinion of its expert, Dr. McIntyre, who identified multiple references during his testimony and also opined based upon the "psychiatry community['s] . . . vocabulary" and his "everyday discussions with colleagues." (D.I. 311 at 128:18-19, 164:17-23) Although none of the references discussed by Dr. McIntyre characterize "excitation" as a "disorder," nonetheless, Dr. McIntyre opined that "excitation" is the defining feature of manic episodes and, therefore, treating "excitation" is equivalent to treating "manic episodes."

The references cited by Dr. McIntyre do acknowledge that "excitation" is a symptom of manic episodes, e.g.: (1) PTX 201 at 5, the DSM-IV:[10] "A Manic Episode is defined by a distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood;" (2) PTX 339 at 5, the ICD-10,[11] describes "mania without psychotic symptoms" as "[m]ood is elevated out of keeping with the individual's circumstances and may vary from carefree joviality to almost uncontrollable excitement. Elation is accompanied by increased energy, resulting in overactivity, pressure of speech, and a decreased need for sleep;" (3) PTX 215 at 4, a 1993 paper by P.F. Liddle entitled "The psychomotor disorders: disorders of the supervisory mental processes," concluded that "the observed differences between manic and

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[10]The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, published by the American Psychiatric Association.

[11]The ICD-10 Classification of Mental and Behavioural Disorders, published by the World Health Organization.

schizophrenic thought disorder might be accounted for by the greater tendency for disorganization in schizophrenia to co-exist with psychomotor poverty whereas in mania, disorganization co-exists with psychomotor excitation;" (4) PTX 341 at 6, the "Manic Rating Scale" ("MRS"), which identifies "elevated mood" as an indicator of a manic episode; (5) PTX 381 at 5, the "Positive and Negative Syndrome Scale ('PANSS') Rating Criteria, which identifies "excitement"[12] as one of seven (P4) "positive" symptoms (along with seven "negative" symptoms and sixteen "general psychopathology" symptoms) to review in order to reach a "bipolar index" (*id.* at 3);[13] and (6) DTX 205 at 518, a 1949 paper discussing the use of lithium to treat mania, described therein as "psychotic excitement."

Despite Dr. McIntyre's efforts to convince the court that those of skill in the art in 1994, as a general proposition, equated the term "excitation" with "mania," the court remains unconvinced. In the first instance, there is no reference of record that literally describes "excitation" as the defining feature of mania. Instead, the references refer to "excitement" (and the words Dr. McIntyre equates with excitement) as one of several criteria that must be present to properly diagnose a manic episode of bipolar I disorder. The DSM-IV, for instance, describes the criteria for a manic episode to be, first, "[a]

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[12]"Excitement" is defined in the PANSS as "hyperactivity as reflected in accelerated motor behaviour, heightened responsivity to stimuli, hypervigilance or excessive mood lability." (PTX 381 at 5)

[13]Two of the references cited by Dr. McIntyre post-date 1994 and are "conceptual" in nature, in that they do not reflect what those of skill in the art believed in 1994, but represented instead the authors' proposal to broaden the definition of mania to include a "connection to excitation." (PTX 213 at 1; *see also* PTX 214) If anything, such references reinforce defendants' view that, in 1994, "mania" was not the equivalent of "excitation" or essentially characterized by it.

distinct period of abnormally and persistently elevated, expansive, **or** irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary);" and second, "[d]uring the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree," including such symptoms as "inflated self-esteem or grandiosity," "decreased need for sleep," more talkative than usual," "flight of ideas," "distractibility," "increase in goal-directed activity," and "excessive involvement in pleasurable activities that have a high potential for painful consequences." (PTX 197 at 240) (emphasis added)

In sum, there is no dispute that "excitation" is not itself a disorder.[14] There is also no dispute that "excitation" can be symptomatic of many disorders. (D.I. 311 at 165:5-173:24, D.I. 312 at 509:8-15; PTX 197) The court, however, finds no persuasive objective evidence that those of skill in the art in 1994 considered "excitation" the *sine qua non* of "mania" such that the two terms would be equated for purposes of treating a patient with asenapine.[15] Consistent with the testimony of defendants' expert, Dr.

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[14]Indeed, claim 4 as originally drafted disclosed the use of asenapine for treating "mental disorders." (PTX 2 at 2) The claim was rejected because "the skilled worker would not reasonably expect that administration of a single set of compounds would effectively treat all" "mental disorders." (*Id.* at 121) The claim was approved when it was amended to be consistent with the specification, that is, the use of asenapine to treat "tension, excitation, anxiety, and psychotic and schizophrenic disorders." (*See id.* at 137) In allowing claim 4, the examiner cited to a prior art reference, U.S. Patent No. 4,145 434 ("Van der Burg"), which actually was much more precise in its use of the vocabulary of psychiatry: "The compounds herein referred to . . . can be used in the treatment of **states of** tension, excitation and anxiety, and in the treatment of psychotic and schizophrenix **conditions**." (PTX 133 at 1:46-50) (emphasis added)

[15]The vocabulary of psychiatry, like the language of a claim, is meant to establish meaningful guidelines for use by those of skill in the art. In this case, the vocabulary chosen by the inventors of the '476 patent was imprecise and inconsistent with the vocabulary of the profession to which it was addressed, a deficiency that Dr. McIntyre

Hollander, the court concludes that Forest has not carried its burden to prove direct infringement by the doctrine of equivalents, when Alembic's and Breckenridge's proposed labels limit the indications of use to manic and mixed episodes of bipolar I disorder.

3. Indirect infringement

In the absence of direct infringement, there can be no liability for indirect infringement. Nevertheless, the court will address Forest's evidence relating to inducement for completeness. Alembic's and Breckenridge's original ANDA submissions (like the other defendants at bar) contained proposed labels that included all of the Saphris approved indications – schizophrenia and manic and mixed episodes associated with bipolar I disorder. (PTX 426 at 2; PTX 620 at 1) Subsequent to the court's claim construction order, Alembic and Breckenridge submitted new labels to the FDA that proposed removing schizophrenia as an indication. (PTX 56 at 1; PTX 59 at 1) Although the court has not yet been informed that the FDA has allowed or approved the proposed amended labels, the court concludes that Forest has not carried its burden to prove indirect infringement, if such labels are ultimately approved.

As noted, Alembic and Breckenridge deliberately removed the word "schizophrenia" from their proposed labels. Defendants did not, however, remove the description of asenapine as an "atypical antipsychotic." ("Indications and Usage" sections of PTX 59 at 1 and PTX 56 at 1)[16] Based on the historical and current use and

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could not remedy.

[16]The phrases "atypical antipsychotic drugs" and "antipsychotic agents" are also used in the labels when discussing side effects and adverse events. (*See, e.g.,* PTX 56

understanding of the phrase "atypical antipsychotic" by those skilled in the art, Forest argues that this phrase specifically instructs doctors to use defendants' products for the treatment of schizophrenia. (D.I. 311 at 136:11-137:20) Forest relies on the following evidence of record to support its position. First, every FDA-approved atypical antipsychotic is approved for the treatment of schizophrenia. (D.I. 311 at 136:11-20; D.I. 313 at 592:16-21; PTX 615 at 48, table A-2; DTX 59 at 1545) According to Forest, skilled artisans understand that "[a]ntipsychotic drugs have become the cornerstone of treatment for schizophrenia." (PTX 232 at 2; *see also* PTX 338 at 32; D.I. 311 at 137:21-140:5, 142:25-143:13) For the initial treatment of schizophrenia, the treatment guidelines indicate that monotherapy with an oral second generation antipsychotic (other than clozapine) should be used, with asenapine being such a drug. (PTX 338 at 29; PTX 340 at 2) The fact that the treatment guidelines use the term "antipsychotic" in this context further reinforces the notion that antipsychotics are synonymous with treating schizophrenia. According to Forest, the proposed labels also provide sufficient instructions for doctors and patients to administer the generic asenapine products sublingually, and to use an "effective amount" of asenapine to treat schizophrenia, as required by claim 4. More specifically, defendants' proposed labels include a section titled "Dosage Forms and Strengths," which indicates that their asenapine sublingual tablets are available in 5 mg and 10 mg doses. (PTX 56 at 1, 3; PTX 59 at 1, 4) The

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at 6-7, 11-13, 34; PTX 59 at 6-7, 10, 12-13, 37) In addition, Alembic retained data obtained from clinical trials in schizophrenic patients in its proposed label, without identifying the patient population as "schizophrenic." (PTX, 614 at 19; D.I. 311 at 146:9-148:11; D.I. 313 at 596:19-23)

recommended dosing for schizophrenia and bipolar mania are similar. The Saphris label indicates that the starting dose for schizophrenia is 5 mg sublingually twice daily, with a recommended dose of 5 to 10 mg sublingually twice daily and a maximum dose of 10 mg sublingually twice daily. (PTX 54 at 1) The proposed generic labels indicate a starting dose for bipolar mania of 10 mg sublingually twice daily, a recommended dose of 5 to 10 mg sublingually twice daily, and a maximum dose of 10 mg sublingually twice daily. (PTX 56 at 1; PTX 59 at 1) Forest argues that, based on the information contained in the labels, doctors (based on their training and knowledge of the Saphris label, which is cross-referenced in defendants' labels), can use defendants' 5 mg and 10 mg dosage forms to prescribe and administer an "effective amount" of generic asenapine to treat a patient's schizophrenia. (D.I. 311 at 145:20-146:8) In addition to defendants' labeling, Forest argues that, because neither defendant has reduced their projected sales figures or manufacturing projections to reflect the smaller target market of bipolar I disorder, this is additional circumstantial evidence of a specific intent to induce infringement. (*See, e.g.,* PTX 434 at 45-46; PTX 547 at 4; PTX 548; PTX 549; D.I. 311 at 216:18-217:21, 240:18-242:3, 243:10-23, 247:8-24)

Despite these essentially undisputed facts, the Federal Circuit has held that even the "knowledge of off-label infringing uses" will not establish inducement. *Takeda*, 785 F.3d at 632. In *Takeda*, the relevant patents at issue covered several methods of administering colchicine products to treat acute gout flares. The defendant in that case sought approval from the FDA to market a colchicine product for prophylaxis of gout flares. Takeda filed suit, asserting induced infringement under 35 U.S.C. § 271(b) based on the labeling of defendant's product. In rejecting Takeda's claims, the Federal

Circuit acknowledged the possibility of infringing off-label uses, including the fact that the defendant had been informed by the FDA that "it may be natural for the provider to use [the generic colchicine product] for acute treatment" of gout, even though defendant had sought FDA approval of its colchicine product only for prophylaxis of gout flares. *Id.* Moreover, the guidelines from the American College of Rheumatology ("ACR") recommended prescribing the branded colchicine product for acute gout flares. *Id.* Finally, the label itself in *Takeda* stated that, "[i]f you have a gout flare while taking [the generic colchicine], tell your healthcare provider." *Id.*

The Federal Circuit explained, however, that the Hatch-Waxman Act "was designed to enable the sale of drugs for non-patented uses even though this would result in some off-label infringing uses." *Id.* at 631. Moreover, the FDA's information and the ACR guidelines were "irrelevant to the question of inducement. All of this, without more, is mere knowledge of infringing uses and does not establish inducement." *Id.* The Court noted that there were a "host of alternatives for treating gout flares" and, therefore, the generic colchicine product was not an "inevitable" choice. Finally, the fact that Takeda had submitted physicians' declarations "allegedly showing what physicians would do when patients consult them about acute gout flares" did not persuade the Court: "Speculation or even proof that some, or even many, doctors would presrcibe [the generic colchicine product] for acute flares is hardly evidence of inevitability. This evidence does not show anything more than that there may be some infringing uses of [said generic]." *Id.* at 633.

The facts at bar are unusual,[17] but not more compelling than the facts reviewed by the Federal Circuit in *Takeda.* The court concludes that the evidence proferred by Forest in this regard is insufficient to establish a specific intent on the part of Alembic or on the part of Breckenridge to induce infringement of claim 4 of the '476 patent.

C. Invalidity due to Obviousness

1. Standard of review.

Because a patent is presumed valid under 35 U.S.C. § 282, a challenger must prove invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2245 (2011); *Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348 (Fed. Cir. 2004). Further, "[w]hen the prior art was before the examiner during prosecution of the application, there is a particularly heavy burden in establishing invalidity." *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1378 (Fed. Cir. 2006) (citing *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990)).[18] If a reference was not before the examiner during prosecution but is cumulative of others that were before the examiner, the heavy burden of proof still applies. *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1368 (Fed. Cir. 2004).

"Obviousness is a question of law, which depends on underlying factual inquiries." *Forest Labs.*, 2016 WL 3677148, at *18. Courts consider the so-called

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[17]Where Forest has argued that "excitation" is synonymous with "mania", and "antipsychotic" is synonymous with treating schizophrenia.

[18]As mentioned above, each of defendants' primary prior art references was considered during prosecution of the '476 patent, that is, U.S. Patent Nos. 4,145,434 ("the '434 patent" or "Van der Burg") (PTX 133), and 4,371,516 ("the '516 patent") (PTX 28), as well as UK Patent Application GB 2,111,423 ("the '423 application") (PTX 30).

Graham factors, which include (1) the scope and content of the prior art, (2) differences between the prior art and the claimed subject matter as a whole, (3) the level of skill in the art, and (4) objective evidence of nonobviousness (also known as secondary considerations of nonobviousness). *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

To meet its burden of establishing obviousness, a defendant has the burden to show that one skilled in the art would have been motivated to take the necessary steps to arrive at the claimed invention with a "reasonable expectation of success." *Forest Labs.,* 2016 WL 3677148, at *18; *see also Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013); *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-92, 1295 (Fed. Cir. 2012); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.,* 676 F.3d 1063, 1069 (Fed. Cir. 2012); *In re Kubin,* 561 F.3d 1351, 1360 (Fed. Cir. 2009). And in carrying out this analysis, "[t]he inventor's own path itself never leads to a conclusion of obviousness; that is hindsight." *Otsuka*, 678 F.3d at 1296.

Furthermore, "[i]t is impermissible . . . to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965). All teachings must be considered, "including that which might lead away from the claimed invention." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). The prior art as a whole must also be examined as of the date of invention. *See Otsuka*, 678 F.3d at

1295 ("Taken as a whole, however, the prior art taught away from using OPC–4392 as a starting point for further antipsychotic research."); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) ("Viewed as a whole, the prior art would not have prompted one of ordinary skill to require retention of the a3 region.").

2. Analysis

Defendants rely on the teachings of three different prior art combinations to demonstrate that the subject matter of claim 1 of the '476 patent is obvious: (1) Sitsen (PTX 37)[19] in view of the '516 patent (PTX 28); (2) Van der Berg '434 patent (PTX 133) in view of the '516 patent; or (3) Van der Berg '434 patent in view of the '423 application (PTX 30), each combined with the knowledge of the ordinarily skilled artisan. There is no dispute that by March 1994, asenapine had been described as having "CNS-depressant activity." ('476 patent, 1:9-13 (describing the '434 patent), PTX 133) Likewise, it is undisputed that by March 1994, rapidly disintegrating solid oral formulations were being developed as an alternative for conventional oral tablets that had to be swallowed.[20] (*See* PTX 28 ('516 patent), PTX 30 ('423 application)) Defendants argue that the prior art identified above would have motivated persons of skill in the art to formulate asenapine ("a new and promising antipsychotic in 1994," D.I.

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[19]Sitsen, of course, is the 1992 publication reporting the preliminary clinical results of "Org 5222" by the researchers at Organon. As noted, "[t]he inventors own path" should not be one taken by a challenger to prove obviousness. *See Otsuka*, 678 F.3d at 1296.

[20]The fact that the court has limited the scope of claim 1 of the '476 patent to sublingual administration undermines defendants' invalidity challenge to the extent they are relying on prior art that simply teaches rapid disintegration.

288 at 26) as a rapidly disintegrating composition (consistent with the improved composition platforms disclosed in the '516 patent and '423 application) with a reasonable expectation of success.

The '476 patent itself acknowledges and cites three of the four references relied on by defendants as disclosing asenapine and examples of how to make rapidly disintegrating formulations. ('476 patent, 1:9-11, 2:3-6, 2:30-33) These references were before the examiner during prosecution and, nevertheless, the examiner allowed the claims to issue.

a. Unknown problem

The evidence at trial demonstrates that skilled artisans reviewing the publications of the publically reported clinical studies would have understood that orally administered asenapine was safe, bioavailable, and clinically effective even at relatively low doses. The art further showed that Organon was in the process of conducting "large" scale Phase II trials in Scandinavia with the conventional oral tablet, and that there were no safety concerns or clinically meaningful adverse advents as a consequence of the trials. Sitsen 1992, De Boer 1993, and Vrijmoed 1993 demonstrate that Organon was presenting data about its drug to the scientific community. There was nothing in the prior art that would have indicated that the oral tablet had problems, such that skilled artisans would have been motivated to invest the resources necessary to completely change the route of administration. (D.I. 314 at 955:12-16, 960:23-961:6) Skilled artisans would have also understood that no reputable drug company would have taken a formulation to large Phase II trials if there were problems with the formulation of the drug. (D.I. 314 at 955:7-11) The court discerns no motivation from the record evidence

to use a sublingual formulation—a formulation that had never before been used for an antipsychotic drug. (D.I. 312 at 412:24-413:11)

b. Nonobvious solution

Courts have recognized that solving an unrecognized problem in the art can itself be an nonobvious patentable invention, even where the solution is obvious once the problem is known. *Eibel Process Co. v. Minn. & Ontario Paper Co.,* 261 U.S. 45, 68 (1923). "There can of course arise situations wherein identification of the problem is itself the invention." *Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 381 F.3d 1371, 1377 (Fed. Cir. 2004); *see also In re Zurko,* 111 F.3d 887, 890 (Fed. Cir. 1997) ("[T]o say that the missing step comes from the nature of the problem to be solved begs the question because the Board has failed to show that this problem had been previously identified anywhere in the prior art."). If the solution to the unknown problem is itself nonobvious, then this further establishes the patentability of the claimed invention. *Leo Pharm.*, 726 F.3d at 1356-57.

The record at bar demonstrates that it was unknown in the art that oral or IV administration of asenapine could cause severe cardiotoxic side effects. These serious side effects put the entirety of Organon's asenapine program at risk. (D.I. 311 at 269:24-270:18, D.I. 314 at 826:12-17) Moreover, the available data (including the IV data) indicated that it was the parent compound that was likely responsible for the cardiotoxic effects, and that a sublingual formulation avoids first-pass metabolism and makes more—not less—of the parent compound directly available to the patient. (D.I. 314 at 825:4-826:11, 962:23-965:11) The sublingual solution to the cardiotoxicity

problem was not "predictable" or "expected." (D.I. 314 at 968:24-969:13) There were numerous other formulations that could have been experimented with to try to solve the problem, but no reasonable expectation that any of them would have. Accordingly, the use of a sublingual formulation was not obvious.

c. Defendants' analysis

Defendants' primary theory is that skilled artisans would have been motivated to develop a sublingual formulation of asenapine because there was a bioavailability concern with orally administered asenapine. Defendants rely on Vrijmoed 1993 to support their "poor" bioavailability theory. As noted above, Vrijmoed 1993 discussed the successful clinical trials of orally administered asenapine and how Organon was then conducting large scale Phase II trials. Nevertheless, based on their experts' interpretation of Vriijmoed 1993, defendants argue that the data therein shows poor bioavailability.

More credible is Dr. Illum's testimony that Vriijmoed 1993 does not actually disclose bioavailability data for asenapine. (*Compare* D.I. 314 at 949:20-953:9 *with* D.I. 312 at 433:24-434:3; D.I. 316 at 1175:17-1176:13) Vrijmoed 1993 (PTX 53) disclosed peak plasma concentrations (also referred to as Cmax) of asenapine in the blood of healthy patients who were given oral and IV formulations of asenapine. (PTX 53 at 3) A comparison of peak plasma concentration (Cmax) levels is not analogous to a comparison of bioavailability, as there is no indication of AUC ("area under the curve") values, which is used to determine bioavailability. (D.I. 314 at 949:20-952:8; *see also* D.I. 312 at 429:17-430:5) In addition, to actually calculate bioavailability, one needs to compare data from the same subject due to variations among individuals as to how

drugs are metabolized. (D.I. 314 at 952:9-953:9) This was not done in Vrijmoed 1993. Vrijmoed 1993 does not disclose an issue with the oral bioavailability of asenapine. (*Id.* at 949:20-952:8)

Even if the prior art disclosed that orally administered asenapine had "poor" bioavailability, skilled artisans would have focused on the clinical result observed during oral administration and considered whether the bioavailability is sufficient to cause the desired therapeutic effects at reasonable doses and with acceptable side effects. (D.I. 314 at 850:9-22) As acknowledged by Dr. Frazer, even with low bioavailability, a drug can be efficacious. (D.I. 316 at 1176:14-22) Here, the prior art, including Vrijmoed 1993, demonstrates that asenapine, even at low doses, "was an effective antipsychotic drug that lacks sedative properties and extrapyramidal side effects." (PTX 53 at 3; D.I. 314 at 843:12-846:3, 847:24-849:16, 942:16-955:16; *see also* PTX 33; PTX 37; PTX 38) There would have been no reason for a skilled artisan to abandon the oral administration of asenapine in favor of sublingual administration, a dosage form never before used for antipsychotics.

Further, there is evidence of record demonstrating that the use of sublingual or buccal routes of administration do not necessarily result in increased bioavailability. (D.I. 314 at 955:17-956:4, 960:17-22) Defendants rely on a "Motwani" reference as allegedly providing the primary motivation to use sublingual administration to improve bioavailability. (PTX 36) Of the fourteen drugs administered sublingually in Motwani, however, nine of the sublingually administered drugs were merely comparable to their orally administered counterparts in terms of bioavailability, and two of the fourteen were actually much worse in terms of bioavailability. (PTX 36 at 4, 6; D.I. 314 at 955:17-

960:22)

Such data would not have reasonably motivated those skilled in the art to use a sublingual dosage form if they wanted to solve a bioavailability problem, as it would not have provided any reasonable expectation of achieving such a result. (D.I. 314 at 956:17-960:22) Therefore, Motwani would not have motivated a skilled artisan to make a sublingual dosage form to address an alleged bioavailability problem and, even if one did, the skilled artisan would have had no reasonable expectation that it would work.

If a skilled artisan did in fact want to increase asenapine's bioavailability, the most common, logical, conventional, and cost-effective means of doing this would have been to increase the dose administered to the patient.[21] (*Id.* at 953:10-23; D.I. 316 at 1170:23-1172:6) This would be considerably less expensive than developing a new formulation, conducting pre-clinical studies with that formulation, and re-starting the clinical program to assess whether that new formulation would result in the safe and efficacious administration of the drug. (D.I. 314 at 953:10-23) This is especially persuasive reasoning given patient compliance concerns and the special instructions

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[21]Defendants argue in this regard that one skilled in the art would not have looked to increase the oral dose due to the published side effects associated with asenapine, particularly the "increased liver enzyme concentrations" there were reported in Sitsen 1992. (PTX 37 at 4) In response, Dr. Gendreau testified that a temporary reversible increase in liver enzymes would not dissuade one skilled in the art from increasing the dose, particularly for an antipsychotic. (D.I. 314 at 844:20-847:9, 944:10-15) Defendants also contend that, as of 1994, one skilled in the art would have believed that increasing efficacy by increasing the oral dose of asenapine would not have been easily achievable because of reported dopamine or "D2" receptor binding profiles for asenapine. Forest countered with evidence that, as of 1994, it was recognized that atypical antipsychotics exerted their clinical effects through both dopamine (D2) and serotinin (5-HT) receptor antagonism. (PTX 33 at 1; PTX 37 at 3, 5) Asenapine, therefore, fit the classic profile for an atypical antipsychotic.

doctors need to provide patients when taking sublingual dosage forms. (D.I. 311 at 87:13-88:17; D.I. 315 at 1032:9-1039:3) As explained by Dr. McIntyre, clinicians with experience in treating schizophrenic patients understand that sublingual dosage forms are more burdensome to schizophrenic patients in that they require the patient to hold the dosage form in the mouth under the tongue for a period of time, and also require that the patient refrain from drinking or swallowing for a period of time (ten minutes in the case of Saphris). (PTX 54 at 36-37; D.I. 315 at 1033:17-1035:24, 1094:7-1096:13) Defendants' own expert clinician, Dr. Hollander, agreed that sublingual administration would not improve patient compliance. (D.I. 313 at 705:15-706:4)[22] Moreover, that asenapine remains the only sublingually administered antipsychotic further demonstrates the limited utility of sublingual administration for this class of drugs. (D.I. 315 at 1038:5-1040:11)

d. Objective indicia

The objective indicia of nonobviousness, such as unexpected results and long-felt need, "can be the most probative evidence of nonobviousness." *Leo Pharm.*, 726 F.3d at 1358 (citing *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010). All evidence, including the independent objective considerations such as unexpected results and long-felt need, must be considered before the court reaches an obviousness determination as a means to guard against the impermissible use of hindsight. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983) By considering the objective evidence before making an obviousness determination,

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[22]This testimony contradicts the testimony of defendants' non-clinician, Dr. Jacobs. (D.I. 312 at 334:21-335:5, 370:2-14)

courts avoid the trap of impermissibly using hindsight to reconstruct the invention from the prior art by "develop[ing] a hunch that the claimed invention was obvious, and then construct[ing] a selective version of the facts that confirms that hunch." *In re Cyclobenzaprine*, 676 F.3d at 1079.

(1) Unexpected results

Unexpected results are an important indicia of nonobviousness. *United States v. Adams*, 383 U.S. 39, 51-52 (1966). Unexpected results need not be described in the text of the patent and are relevant "even if that evidence was obtained after the patent's filing or issue date." *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011) (citation omitted). The record at bar demonstrates that it continues to be a surprising and unexpected result of the claimed invention that the sublingual route of administration successfully resolved the serious cardiotoxic event reported in the '476 patent. ('476 patent, 4:47-5:58; D.I. 311 at 271:15-19; D.I. 314 at 830:11-20, 968:7-969:13) Based on the IV study, even the inventors of the '476 patent believed that sublingual administration would also result in a negative outcome. (D.I. 311 at 269:24-270:18) And there is nothing in the prior art suggesting that sublingual administration could be used to resolve this type of side effect. (D.I. 314 at 966:2-9) That asenapine, administered sublingually, was ultimately used in multiple Phase III clinical trials and was determined by the FDA to not only be efficacious but safe, is itself surprising and unexpected. Moreover, the fact that after approval of Saphris, there have not been any reported events of asystole or the need for the FDA to add additional warnings to the Saphris label, further confirm the surprising and

unexpected nature of the claimed invention. (D.I. 314 at 840:20-841:13)

(2) Long-felt need

Evidence of a long-felt and unsolved need in the industry for the solution offered by the patented invention supports a finding that the invention would not have been obvious at the time the invention was made. *See, e.g.*, *Georgia-Pacific Corp. v. U.S. Gypsum Co.,* 195 F.3d 1322, 1330 (Fed. Cir. 1999) ("[T]he evidence presented . . . demonstrated the need for a better exterior system, the lack of suggestion in the prior art to use a system with a glass mat-faced board to meet this need, and the success the patented system achieved."). Prior to 1994, typical antipsychotics were the primary therapeutic options for treating schizophrenia and mania. These typical antipsychotics, however, possessed debilitating side effects, including EPS, and a significant number of patients did not respond to treatment. (D.I. 313 at 658:22-660:23; D.I. 315 at 1043:1-1046:4, 1051:3-1053:9)

Clozapine was the first FDA-approved atypical antipsychotic. While it caused fewer movement disorders, it was known to require constant blood monitoring while the patient was taking the medication. (DTX 201 at 1; PTX 263 at 4) The use of clozapine prior to 1994, despite its life-threatening side effect, "underscores the substantial lack of progress in the development of more effective and safer antipsychotic drugs." (PTX 273 at 7)

Risperidone, the only other atypical antipsychotic available as of 1994, was also an effective therapeutic treatment but had its own drawbacks, the most prevalent being increased weight gain, metabolic issues (both of which are the primary issues with antipsychotics), and increasing prolactin, which can cause lactation and breast

development. (D.I. 315 at 1057:1-1058:12, 1074:19-1075:24, D.I. 313 at 666:23-668:21) Consequently, risperidone had a discontinuation rate of about 74%. (PTX 232 at 1; D.I. 315 at 1069:10)

Given the problems with typical antipsychotics and the two atypical antipsychotics available as of 1994, skilled artisans recognized the need for additional antipsychotic drugs that had minimal EPS symptoms as well as a favorable weight gain, metabolic, and prolactin profile. Asenapine met this criteria. (PTX 216 at 7-8; D.I. 315 at 1058:21-1059:8, 1075:25-1077-25)

In addition, because of the heterogeneity in efficacy and tolerability, skilled artisans recognized the benefit of having multiple treatment options. (D.I. 313 at 624:2-18, 666:3-10; 676:13- 19; 682:12-15; 687:18-22; PTX 282 at 10; PTX 233 at 2; *see also* PTX 234 at 25; DTX 59 at 1545) For the above reasons, sublingually administered asenapine meets the long-felt but unmet need for a safe, effective, and tolerable atypical antipsychotic useful to treat schizophrenia and mania.[23]

D. Invalidity due to Lack of Written Description

Defendants allege that the claims of the '476 patent lack adequate written description because the specification does not adequately describe asenapine free base. (D.I. 317 at 1214:10-15) In other words, defendants do not allege that the

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[23]Although defendants argue that the sublingual nature of the formulation is irrelevant to the clinical properties of asenapine, the court agrees with Forest that, because of the severe cardiotoxic effects associated with oral and IV administration, none of the above discussed benefits associated with asenapine would have been possible if the drug were not administered sublingually. (D.I. 315 at 1082:2-1084:9, 1085:1-6, 1087:17-1088:1)

commercial embodiment of the '476 patent, Saphris (asenapine maleate), is not supported by the '476 patent. Instead, defendants argue only that asenapine free base fails under § 112 and, therefore, the asserted claims as a whole should be held invalid.

The written description requirement under 35 U.S.C. § 112, ¶ 1 "is a question of fact, judged from the perspective of one of ordinary skill in the art as of the relevant filing date." *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1363 (Fed. Cir. 2006) (citation omitted). The Federal Circuit has indicated that the written description requirement "does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010) (en banc). The written description requirement is met if the description allows persons skilled in the art to recognize that the inventor invented what is claimed. *Id.* at 1351 (citation omitted). The "written description is about whether the skilled reader of the patent disclosure can recognize that what was claimed corresponds to what was described; it is not about whether the patentee has proven to the skilled reader that the invention works, or how to make it work, which is an enablement issue." *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1191 (Fed. Cir. 2014).

"No length requirement exists for a disclosure to adequately describe an invention"—the adequacy of the description depends on its content in relation to the invention. *Falko-Gunter*, 448 F.3d at 1365-66 (citation omitted). "[O]nly enough must be included to convince a person of skill in the art that the inventor possessed the

invention." *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005). The extent of the required disclosure varies depending on the nature and scope of the claims, on the complexity and predictability of the relevant technology, and on factors such as: existing scientific and technological knowledge in the particular field; the content of the prior art; the maturity of the technology; and the predictability of the aspect at issue. *Ariad*, 598 F.3d at 1351 (citing *Capon v. Eshhar*, 418 F.3d 1349, 1357-59 (Fed. Cir. 2005)). Finally, "[t]o overcome the presumption of validity of patents, the accused must show that the claims lack a written description by clear and convincing evidence." *Hynix Semiconductor Inc. v. Rambus Inc.*, 645 F.3d 1336, 1351 (Fed. Cir. 2011).

The evidence adduced at trial demonstrates that a skilled artisan would understand that the inventors of the '476 patent were in possession of compositions comprising asenapine free base and methods of using these compositions to treat the claimed conditions. Both claims 1 and 4 recite a "pharmaceutical composition comprising . . . : trans-5-chloro-2-methyl-2,3,3a,12btetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole or a pharmaceutically acceptable salt thereof." ('476 patent at 5:60-6:3, 6:10-15) The parties' experts agree that "trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole" is the chemical designation for the free base of asenapine.[24] (*See, e.g.*, D.I. 317 at 1246:1-22, 1278:3-15; '476 patent at 1:9-11) Defendants' expert, Dr. Gould, also acknowledged that

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[24]For convenience, "asenapine free base" is used hereafter as a shorthand for the formal chemical name in citations to and quotations of the '476 patent specification.

asenapine free base was known in the prior art. (D.I. 317 at 1221:23-25) Not only does the '476 patent explicitly describe asenapine in its free base form, it indicates that "[t]he invention therefore relates to a sublingual or buccal pharmaceutical composition comprising [asenapine free base] . . . ." ('476 patent, abstract; 1:33-36; D.I. 317 at 1278:18-1279:5) The specification further states that these compositions comprising asenapine free base "are useful in treating mammals, including humans, suffering from diseases which are susceptible to treatment by [asenapine free base]," including "mental disorders, such as tension, excitation, anxiety, psychosis and schizophrenia," which are the same disorders recited in claim 4. ('476 patent, abstract; 1:33-36; 1:43-44; D.I. 317 at 1279:9-19) As such, the '476 patent demonstrates to a skilled artisan that the inventors were in possession of sublingual and buccal compositions comprising asenapine free base and use of such compositions to treat the disorders claimed in claim 4.

The fact that there is no explicit example of a sublingual or buccal composition containing asenapine free base or use of such a composition is not dispositive. Under controlling precedent, explicit examples are not needed to provide adequate written description support. *Ariad*, 598 F.3d at 1352; *Falko-Gunter*, 448 F.3d at 1366. Moreover, skilled artisans familiar with sublingual and buccal compositions know that, starting with asenapine maleate, once the composition is placed under the tongue, asenapine maleate will disassociate from its salt leaving asenapine free base, which will cross the oral mucosa, enter the blood stream, and provide a therapeutic effect. (D.I. 317 at 1238:20-1239:18, 1241:24-1243:11, 1275:16-1277:9, 1293:2-1294:9) Accordingly, whether an example in the patent uses asenapine maleate or asenapine

free base, skilled artisans reviewing the '476 patent would understand that the inventors had actually invented the subject matter recited in claim 4, including the free base form of asenapine, because it is this form that provides the therapeutic effect to treat the disorders identified in claim 4. Therefore, based on the disclosure of the '476 patent, a skilled artisan would have recognized that the inventors were in possession of the claimed compositions of asenapine, including in its free base form, for use in the claimed methods. The asserted claims have adequate written description support.

E. Invalidity due to Lack of Enablement

The enablement requirement of 35 U.S.C. § 112, ¶ 1, provides that the "specification shall contain a written description of the invention . . . as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . ." Enablement is determined as of the filing date of the patent application and incorporates not only the specification, but also the knowledge of those skilled in the art at the time of the invention. *Union Carbide Chem. & Plastics Tech. Corp. v. Shell Oil Co.*, 308 F.3d 1167, 1185 (Fed. Cir. 2002). "[T]he scope of enablement . . . is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation." *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1070-71 (Fed. Cir. 2005) (citations omitted). The specification, therefore, need not need to include "that which is already known to and available to one of ordinary skill in the art." *Koito Mfg. Co. v. Turn-Key-Tech*, LLC, 381 F.3d 1142, 1156 (Fed. Cir. 2004) (citations omitted). Further, "[t]he fact that some experimentation is necessary does not preclude

enablement; what is required is that the amount of experimentation 'must not be unduly extensive.'" *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996) (citation omitted).

In determining what constitutes undue experimentation, the Federal Circuit has articulated eight factors that can be considered in the analysis: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970).

Defendants' non-enablement contention rests on the allegation that a single embodiment (a composition comprising asenapine free base) out of many is not enabled. This argument is legally insufficient. *See In re Angstadt*, 537 F.2d 498, 502-503 (C.C.P.A. 1976) (holding that patent applicants are not required to enable every species encompassed by their claims); *Endo Pharms. Inc. v. Mylan Pharms. Inc.*, 2014 WL 334178, at *30 (D. Del. Jan. 28, 2014) ("An applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention . . . The salt-hydrate is merely a different form of the claimed compound . . . As such, the patent need not independently describe or enable a discrete salt-hydrate combination."). Defendants have failed to establish, by clear and convincing evidence,

that the asserted claims are not enabled.[25]

IV. CONCLUSION

For the reasons stated, Forest has not carried its burden to prove, by a preponderance of the evidence, that defendants Alembic and Breckenridge infringe claim 4 of the '476 patent. Defendants have failed to carry their burden to prove, by clear and convincing evidence, that claims 1 and 4 of the '476 patent are invalid by reason of obviousness, lack of written description, or lack of enablement. An order shall issue.

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[25]Even were this not so, the evidence of record demonstrates that it would have been routine for skilled artisans to incorporate asenapine free base into sublingual and buccal pharmaceutical compositions that disintegrate within 30 seconds in water at 37° C for use in the asserted claims. As an initial matter, the specification of the '476 patent, through its disclosure of examples 1-7, provides extensive guidance on formulating asenapine into sublingual and buccal dosage forms that disintegrate within 30 seconds in water at 37° C. ('476 patent, 3:19-4:45; D.I. 317 at 1281:6-1282:15) Forest also presented credible expert testimony that it would have been routine to formulate asenapine free base using well-known formulation systems from at least the 1970s to generate rapidly disintegrating buccal and sublingual compositions. (*See, e.g.*, D.I. 314 at 979:6-982:12, 983:10-20; D.I. 315 at 990:21- 991:11, 1025:20-1028:4; D.I. 317 at 1294:18-1296:15) Even defendants' expert, Dr. Jacobs, testified that "pharmaceutical compositions that disintegrated within 30 seconds were available," and that "it would have been routine to [make these compositions]" as of 1994. (D.I. 312 at 382:4-383:3)