UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Aurobindo Pharma USA Inc.
Petitioner

v.

Andrx Corporation,
Andrx Laboratories, Inc.
Andrx Laboratories (NJ), Inc.
Andrx EU Ltd.
Andrx Pharmaceuticals, LLC,
Teva Pharmaceutical Industries Ltd.
Patent Owner.

U.S. Patent No. 6,866,866 to Cheng et al.
Issue Date: March 15, 2005
Title: Controlled Release Metformin Compositions

Declaration of Dr. Fatemeh Akhlaghi, Pharm.D., Ph.D.

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I, Fatemeh Akhlaghi, declare as follows:

I. QUALIFICATIONS

1. My name is Dr. Fatemeh Akhlaghi. I have been working in the areas of pharmacokinetics, drug interaction, and research and clinical pharmacology since 1990.

2. In particular I have worked for the past 15 years on the clinical pharmacology of oral hypoglycemic agents, including metformin, to treat type 2 diabetes mellitus. I have in-depth understanding to the physiological and pathological factors affecting drug deposition in patients with type 2 diabetes. In addition to 70 peer-reviewed articles, I have published 15 articles on the pharmacokinetics of various drugs in patients with type 2 diabetes.

3. I am presently a full Professor (since 2011) at the University of Rhode Island School of Pharmacy and an Adjunct Professor of Medicine at Brown University Medical School (since July 2014). I am currently Professor of Pharmacokinetics and the Ernest Mario Distinguished Chair of Pharmaceutics in the College of Pharmacy, University of Rhode Island.

4. I received my Pharm.D. degree from the University of Mashhad, Iran in 1990, and my Ph.D. degree in Pharmaceutical Sciences from the University of Sydney Australia in 1997. I undertook a post-doctorate at the University of Sydney

until 1998, followed by a position as Senior Clinical Scientist, at the University of Cambridge, U.K. to 2001.

5. In February 2001, I was employed as an Assistant Professor at the University of Rhode Island. I received tenure in 2006, being appointed as an Associate Professor.

6. I have received numerous honors and award, including the Levy Maill Pattison Award at the University of Sydney, the Paul-Ehrlich Magic Bullet Award, Nurnberg, Germany, and the Outstanding Intellectual Property Award from the University of Rhode Island.

7. I have extensive experience in pharmacokinetics and pharmacodynamics, drug development, and design and execution of bioequivalence and drug interaction studies.

8. A summary of my experience, education, publications and other qualifications is provided in my CV, a copy of which is submitted separately. Ex. 1020.

II. SCOPE OF WORK

9. I understand that a petition is being filed with the United States Patent and Trademark Office ("USPTO") to challenge the validity of all of the claims of U.S. Patent No. 6,866,866 ("the '866 patent," Ex. 1001) through the USPTO

procedure known as *Inter Partes* Review. I have been retained by Aurobindo Pharma U.S.A. to provide my opinion as to the validity of the claims of the '866 patent.

10. I have reviewed the '866 patent and its prosecution history generated at the United States Patent and Trademark Office in full. Ex. 1006. I have also reviewed and considered various other documents in arriving at my opinions, and I cite them in this declaration. For convenience, documents cited in this declaration are listed in the Appendix in Section XII.

11. I am being compensated by the petitioner at the rate of $400/hour for my work. I have no financial interest in the outcome of this matter.

III. OVERVIEW OF THE '866 PATENT

12. The '866 patent is titled "Controlled Release Metformin Compositions," with first inventor Chih-Ming Chen. The '866 patent issued on March 15, 2005 claiming priority through U.S. Application No. 09/705,630 to a filing date of November 3, 2000.

13. As stated in the Abstract, the '866 patent discloses: "[a] composition for treating patients having non-insulin-dependent diabetes mellitus (NIDDM) by administering a controlled release oral solid dosage form containing preferably a biguanide drug, such as metformin, on a once-a-day basis. The dosage form provides a mean time to maximum plasma-concentration (T_{max}) of the drug which occurs at 5.5

to 7.5 hours after oral administration on a once-a-day basis to human patients. Preferably, the dose of drug is administered at dinnertime to a patient in the fed state."

14. The "Objects and Summary of the Invention" notes that: "[i]n preferred embodiments, the controlled release oral dosage form of the present invention is a tablet comprising (a) a core comprising: (i) the antihyperglycemic drug; (ii) optionally a binding agent, and (iii) optionally an absorption enhancer; (b) a membrane coating surrounding the core, and (c) at least one passageway in the membrane. (col. 3, ll 34-42).

15. I note the same controlled release oral dosage form was recited in this form in WO 99/047125 (Ex. 1002) at p. 3, lines 25-33, which having an international publication date of September 23, 199, qualifies as prior art to the '866 patent. I further note that the structure of such a dosage form is also identically taught in WO 00/12097 at p. 4, line 15-p. 5, line 2, which having an international publication date of March 9, 2000, also qualifies as prior art to the '866 patent

16. The specification of the '866 patent states "[t]he controlled release dosage form of the present invention provides a delayed T_{max} as compared to the T_{max} provided by GLUCOPHAGE®. The delayed T_{max} occurs from 5.5 to 7.5 hours after administration. The delayed T_{max} is said to have been selected such that after its administration at dinner time "the T_{max} would occur during the time when gluconeogenesis is usually at its highest (*e.g.*, around 2 am)." Col 5, lines 26-32.

17. I note, however, that the desirability of such a delayed T_{max} for a controlled release formulation of metformin HCl was already taught in WO 99/47128 to Timmins *et al.* (Ex. 1003), which having published on September 23, 1999 qualifies as prior art to the '866 patent.

18. Importantly it is taught in the specification that the pharmacokinetic parameters recited in the methods of the patent are not dependent on the particular controlled release formulation recited in the specification as "[o]ther controlled release technologies known to those skilled in the art can be used in order to achieve the controlled release formulations of the present invention, i.e., formulations which provide a mean T_{max} of the drug and/or other pharmacokinetic parameters described herein when orally administered to human patients." '866 patent, col 12, lines 42-46.

19. Thus the inventors and applicant admitted that it was within the skill of a person of ordinary skill in the art ("POSA") to produce the pharmacokinetic parameters recited in the '866 patent using other controlled release preparations.

20. During the prosecution of the application for the '866 patent the inventors again admitted directly to the Examiner that a POSA would easily alter the controlled release formulations of the prior art to produce the *in vivo* T_{max} range specified in the '866 patent. It was understood the POSA would be guided by drug release rate, measured by *in vitro* dissolution testing, to establish desired *in vivo* performance:

"In addition, at the time the application was filed, numerous controlled release technologies were well within the knowledge of pharmaceutical formulators having ordinary skill in the art. *Such pharmaceutical formulators know that controlled release technologies can be manipulated to provide a formulation which upon in-vivo testing will provide the* T_{max} *range of the present invention.* This fact is supported, e.g., by a simple review of patents discussed in the specification concerning formulation technologies, which patents provide ranges of ingredients. *These ranges represent the acknowledgement of those skilled in the art that a certain amount of experimentation is considered to be necessary to manipulate a controlled release technology to obtain a desired release pattern of the drug.* Such release patterns are demonstrated by the (well-known) use of in-vitro dissolution testing, which is considered by pharmaceutical formulators of ordinary skill in the art to provide guidance as to which particular formulations might provide the desired in-vivo performance."[1] *[Emphasis added]*

21. Thus the applicant (Andrx Labs) and the four inventors of the '866 patent acknowledged that a POSA could easily manipulate, with less than extensive experimentation, any controlled oral dosage form which had a similar *in vitro* dissolution profile to achieve the pharmacokinetic parameters recited in the '866 patent.

[1] File history of U.S. Patent No. 6,866,866 (EX1010), Amendment Under 37 C.F.R. 1.111, February 24, 2003, p. 8-p. 9.

22. As I note below, certain controlled release pharmaceutical oral dosage forms for metformin were already known that had identical or nearly identical *in vitro* release rates to that disclosed in the '866 patent.

23. I have been informed by Aurobindo's attorneys that the only patentability that might be associated with the dependent composition claims set forth in the '866 patent would be with respect to the non-obviousness of the pharmacokinetic parameters recited in the claims. As such pharmacokinetic parameters were already associated with or inherent in other known controlled release dosage forms, such could not be said to be non-obvious.

24. Furthermore I note that there is no mention anywhere in the specification or in the file history of an unexpected result or special advantage associated with any of these pharmacokinetic parameters recited in the dependent claims of the '866 patent. Thus none of these claims rise to a level of patentability.

25. Claim 1 is the only independent claim in the '866 patent. Thus all other claims, 2 – 25, depend upon claim 1 and by dependency assert each of the limitations of claim 1:

> A method for lowering blood glucose levels in human patients needing treatment for non-insulin-dependent diabetes mellitus (NIDDM), comprising orally administering to human patients on a once-a-day basis at least one oral controlled release dosage form comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and an effective amount of a controlled release carrier to

control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form, wherein following oral administration of a single dose, the dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 5.5 to 7.5 hours after administration following dinner.

26. With respect to claim 1 and its dependent claims, as expanded more below, I find each of the pharmacokinetic parameters recited to be obvious or inherently anticipated by the prior art, in particular by WO 99/47125, WO 99/47128 and WO 00/12097, alone or in combination, all of which by my calculations teach the same composition of the dosage form claimed in the '866 patent.

27. Claim 1 is the only independent claim of the patent with claims 2 – 25 being either directly or indirectly dependent on claim 1. Claim 1 recites a controlled release oral dosage form, suitable for once-a-day administration, for the reduction of serum glucose levels in human patients with NIDDM,[2] comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof, wherein, following oral administration the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the metformin from 5.5 to 7.5 hours following dinner.

28. Claims 2 and 3 recite mean T_{max} times ranging from 6.0-7.0 hours and 5.5-7.0 hours, respectively. Claims 4 and 5 recite dissolution profile limitations for

[2] "NIDDM"-Non Insulin Dependent Diabetes Mellitus

the controlled release oral dosage form of claim 1, using a USP type 2 paddle apparatus operated at 75 rpm, wherein the dissolution medium comprises 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) maintained at a temperature of 37 °C.

29. Claims 6-25 recite various pharmacokinetic functional limitations related to pharmaceutical performance of the dosage form that are dependent on dose and inherent to the *in vitro* release characteristics of metformin from the dosage form of claim 1. These limitations include mean C_{max}, mean AUC_{0-24}, $AUC_{0-\infty}$ and $t_{1/2}$ (the drug clearance half-life).

30. Claims 11-12, 15-17 and 19-21 are additionally directed to the oral administration of a 2000 mg once-a-day controlled release formulation of metformin of claim 1. Claim 18 is directed to a 1700 mg once-a-day dose of metformin, administered after an evening meal.

31. I stress, in regard to all of these claims, a POSA would expect the claimed pharmacokinetic parameters to be found inherently in the prior art, for example, as in the controlled release tablets of Chen *et al.*, WO 00/12097. By my analysis, those tablets comprise the same formulation and structure found in the tablets of the '866 patent. The Chen *et al.* tablets also exemplify the same *in vitro* release rate as the claimed tablets.

32. I am not an attorney. However, Aurobindo's attorneys have counseled me, as above, that "secondary considerations of obviousness" can render claims of a patent to be non-obvious if certain conditions are found. These conditions include unexpected results, long felt need, commercial success and other secondary considerations that in combination may overcome a case of obviousness under the law.

33. These other considerations include the failure of others to find a solution to the problem, skepticism by experts in regard to resolution of the problem, praise by others directly attributed to the claimed subject matter, teaching away by others from employing the claimed subject matter in the manner specified, recognition of a problem not discerned by others, and copying of the invention by competitors.

34. I note in my review of the file history of the '866 patent, the specification of the '866 patent, and the general searches I performed for this declaration, I did not uncover any evidence of such secondary consideration of non-obviousness of the claims of the '866 patent.

IV. BRIEF SUMMARY OF THE FILE HISTORY AND JUDICIAL HISTORY OF THE '866 PATENT

35. U.S. Patent No. 6,866,866 ("the '866 patent") issued on March 15, 2005. The patent issued subject to a disclaimer, with the term of the patent being extended or adjusted under 35 U.S.C. 154 (b) by 165 days. The '866 patent was filed on November 3, 2000 as Application No. 09/705,630.

36. U.S. Patent Application Serial No. 09/705,630 was initially filed with 42 claims. Independent claim 1 as filed read as follows:

> A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of at least one suitable antihyperglycemic drug or pharmaceutically acceptable salt thereof and a controlled release carrier, said dosage form being suitable for providing once-a-day oral administration of the agent or pharmaceutically acceptable salt thereof, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the agent from 5.5 to 7.5 hours after administration.

37. Claims 2-30 were either directly or indirectly dependent on claim 1. Claims 31-42 had dependencies on independent claim 30, an independent claim directed to a controlled release oral dosage form of a biguanide that provided upon a single dose a higher mean fluctuation index in plasma than two equal divided doses administered 12 hours apart.

38. A first Office Action on the merits of the Application was mailed to Applicants on December 31, 2001. All claims 1-42, were rejected.

39. Claims 21-25 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 21-25 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that they failed to point out

what is included or excluded by the claim language. The Examiner stated that the claims were omnibus type claims.

40. The examiner further rejected claims 1-28, 31-42 under 35 U.S.C. §102(a) being anticipated over Lewis *et al.* (WO 00/28989, Ex 1014). The Examiner averred that formulations of Lewis *et al.* and the claimed formulation were substantially the same and that the functional limitations instantly claimed were inherent in Lewis *et al.*

41. Claims 1-42 were rejected under 35 U.S.C. § 102(a) as being anticipated over Cheng *et al.* (WO 99/47125, Ex. 1002). As before, the limitations of the claimed formulations were deemed to be inherent in the formulations of Cheng *et al.* The offending reference additionally disclosed a semipermeable membrane surrounding the core.

42. Claims 1-28, 31-42 rejected under 35 U.S.C. § 102(a) as being anticipated over Moeckel *et al.* (U.S. Patent No. 5,955,106, Ex. 1013). According to the Examiner the reference disclosed controlled release metformin compositions and the reasons for rejection were the same as those for the Lewis *et al.* rejection.

43. Claims 1-28, 31-42 were also rejected as obvious under 35 U.S.C. 103(a) over Lewis *et al.* or Moeckel *et al.*, each alone or each in combination. It was the Examiner's opinion that both references taught controlled release compositions which were substantially the same to the newly claimed formulations, and that the

additionally claimed functional limitations were inherent in Lewis *et al.* or Moeckel *et al.* According to the Examiner, the burden was now shifted to the Applicants to demonstrate differences between the prior art and the instant claims.

44. Claims 1-42 were further rejected as obvious under 35 U.S.C. § 103 (a) over Cheng *et al.* (WO 99/47125, Ex. 1002). The Examiner noted, as with the rejections over Lewis *et al.* or Moeckel *et al.*, that the formulations were substantially the same and that the burden was now shifted to the Applicants to demonstrate differences between the prior art and the instant claims.

45. The Examiner additionally rejected claims 1-42 under the judicially-created doctrine of obviousness-type double patenting over claims 1-29 of U.S. Patent No. 6,099,859 (Ex. Ex. 1004), as similarly being unpatentable over claims 1-39 of U.S. Patent No. 6,284,275 (Ex. 1015), and being unpatentable over claims 1-4 of U.S. Patent No. 6,099,862 (Ex. 1016). The Examiner argued that the rejected claims were not patentably distinct as they were in genus-species relationship with the offending claims.

46. Claims 1-42 was further rejected on the basis of provisional obviousness-type double patenting based on co-pending applications 09/705,625, 09/726,193 and 09/594,637.

47. The Examiner conducted an interview on November 20, 2001, with Applicants' representatives. According to the Examiner's notes, the importance of

T_{max} and its relationship to gluconeogenesis was discussed, and that the closest prior art suggested a T_{max} of 8 (hours). The Examiner states that the Applicants requested reconsideration be given in view of the working examples disclosed.

48. In response to the Examiner's comments, Applicants filed an Amendment to the application on July 8, 2002 with claims 1-42 pending, and claims 21-25 amended. A terminal disclaimer was submitted over the co-pending applications.

49. Regarding the Examiner's anticipation and obviousness arguments, Applicants made comments regarding the Examiner's inherency theories and discussed the Cheng, Lewis and Moeckel references in that light. The Applicants argued that the Cheng reference taught a T_{max} of 8-12 hours after administration, and did not provide motivation to modify that formulation to from 5.5 to 7.5 hours as claimed. It was argued that Lewis *et al.* was silent at to the T_{max} of the disclosed formulations. It was again argued that the Moeckel reference was silent as to the T_{max} of the disclosed formulations.

50. On October 22, 2002 the Examiner again rejected claims 1-42. Claims 1-30 were rejected under 35 U.S.C. § 112, first paragraph, as the subject matter was not described in such a way as to enable one skilled in the art to make and use the invention. The claims read on all antihyperglycemic drug compositions where the T_{max} was 5.5-7.5 hours after administration, necessitating an exhaustive search for

embodiments suitable to practice the claimed invention, without sufficient disclosure to practice without undue experimentation.

51. Claims 21-30 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Claims31-42 were rejected under 35 U.S.C. § 102(b) over Cheng *et al.* (WO 99/47125) as disclosing the same composition taught by the specification.

52. In response to the Examiner's comments, Applicants filed an amendment on February 24, 2003. Therein, claims 2-3, 6, 28 and 31-42 were cancelled, and remaining claims 1, 4, 5, 7-27, 29 and 30 were amended and submitted for reexamination. In response to the Examiner's section 112, first paragraph rejections, claim 1 was amended to specifically recite "metformin" in place of "antihyperglycemic drug." Applicants stated that, in any event, Applicants were not required to exemplify every formulation, as it would be inefficient and unethical, and admitted that at the time of the application there were numerous controlled release technologies in the art, and that testing for drug-plasma levels was routine. Applicants stated:

> [t]herefore it is submitted that once the Tmax range which provides for a useful dosage form has been established, other controlled release technologies known in the prior art can be manipulated and tested to achieve this Tmax range without undue experimentation.

53. In support of this statement, reference was made to the pending application on page 19, line 21 to page 20, line 14. Applicants made the following, supplemental statements regarding the adaptation of prior art dosage forms to obtain the instant invention:

> "In addition, at the time the application was filed, numerous controlled release technologies were well within the knowledge of pharmaceutical formulators having ordinary skill in the art. Such pharmaceutical formulators know that controlled release technologies can be manipulated, e.g., by varying the amount of controlled release carrier (among other things), to provide a formulation which upon in-vivo testing will provide the Tmax range of the present invention. This fact is supported, e.g., by a simple review of patents discussed in the specification concerning formulation technologies, which patents provide ranges of ingredients. These ranges represent the acknowledgement of those skilled in the art that a certain amount of experimentation is considered to be necessary to manipulate a controlled release technology to obtain a desired release pattern of the drug. Such release patterns are demonstrated by the (well-known) use of in-vitro dissolution testing, which is considered by pharmaceutical formulators of ordinary skill in the art to provide guidance as to which particular formulations might provide the desired in-vivo performance."

54. In view of disclosures made in U.S. Patent No. 6,099,859 (which had issued from the application published internationally as WO 99/47125, Ex. 1002), Applicants stated that the claims had now been amended to state that "T_{max} of metformin at from 5.5-7.5 hours after single-dose administration following dinner." Claims 26-30 were amended to resolve the Examiner's section 112 indefiniteness concerns. Claims 31-42 were cancelled, mooting the Examiner's 102(b) rejection.

55. The Examiner, in the following office action of May 21, 2003, rejected claims 1, 4, 5, 9-27, 29 and 30 as obvious under 35 U.S.C. § 103(a) over WO 00/28989 in view of Chiao (Remington, 1995, Ex. 1017) or over Moeckel (U.S. Patent No. 5,955,106) in view of Chiao. Based on Applicants' previous admissions of the ease of modification of the prior art to obtain the invention, the Examiner concluded it would be routine to modify the release rates found in the prior art to that of the instant invention.

56. Claims 1, 4, 5, 9-27, 29 and 30 were also rejected as obvious under 35 U.S.C. § 103(a) over WO 99/47125 (Ex. 1002), using the teachings of U.S. Patent No. 3,845,770 (Ex. 1018), incorporated therein, to modify the release rate. The Examiner further proffered obvious-type double patenting rejections over claims of U.S. Patent Nos. 6,099,859 (Ex. 1004), 6,284,275 (Ex. 1015) and 6,099,862 (Ex. 1016). Provisional obvious-type double patenting rejections were made over claims of co-pending Application No. 09/726,193.

57. Claims 7 and 8 were subject to objection, but the Examiner noted that such would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

58. Applicants amended the application on September 8, 2004, based on recommendations made by Supervisory Examiner during an interview conducted on November 20, 2003. Claims 1-4 were shown as cancelled. Claim 5 was re-written in independent form. Claim 5, as amended, recited the limitation "wherein following oral administration of a single dose, dosage form provides a mean time to maximum plasma concentration (T_{max}) of the metformin from 5.5 to 7 hours after administration following dinner." The dependencies of the dependent claims were revised to reflect the amendments. The subject matter of claim 4 was re-inserted as new claim 43.

59. In respect of the previous rejections under section 103(a) over the Lewis, Chiao and Moeckel references, it was argued that the combined references did not teach the now claimed T_{max} range.

60. Regarding the previous rejections under section 103(a) over Cheng et al. (WO 99/47125), it was stated that during the interview the Examiner agreed that claim 5, with an upper limit of T_{max} of 7.0 hours, was now patentable over WO 99/47125, which taught a T_{max} lower value of 8 hours. By cancelling claim 1, Applicants had narrowed the claims to a range of 5.5 hours-7.0 hours from 5.5 hours-7.5 hours.

61. In my view this was a tacit admission by Applicants that an upper value of T_{max} of 7.5 hours was too close to lower range of the T_{max} of WO 99/47125 to be considered patentable.

62. It was stated in the amendment and was agreed that the previous obviousness-type double patenting rejections would not be maintained as per USPTO policy.

63. A Notice of Allowance was subsequently mailed to Applicants on December 19, 2003. The allowed claims were 1, 4, 5, 7-27 and 29. I note that the allowed claims were not those claims that had been pending. Claims 1 and 4 had previously been cancelled. Claims 30 and 43 were pending but not acknowledged by the Examiner.

64. Later, on January 9, 2004, Applicants submitted an Amendment under 37. C.F.R. § 1.312 containing a copy of Applicants' version of the pending claims. As previously stated, independent claim 5 recited a "(T_{max}) value of 5.5 to 7 hours after administration following dinner."

65. A supplemental Notice of Allowability was mailed to Applicants on November 30, 2004. It was stated that the allowed claims were 5, 7-27, 29, 30 and 43.

66. The patent issued on March 15, 2005. As published, independent claim 1 (originally claim 5 during prosecution) recited in error a "(T_{max}) of the metformin

from 5.5 to 7.5 hours after administration following dinner," rather than the approved language a "(T_{max}) of the metformin from 5.5 to 7.0 hours after administration following dinner."

67. I see that a Certificate of Correction was never issued to correct the error.

68. Aurobindo's attorneys have informed me that the '866 patent, once issued, was the subject of extended litigation in both the District of Delaware and the Federal Circuit after appeal.

69. I was informed that during this extended litigation in the District of Delaware, the patent owner (Sciele Pharma and eventually Andrx *et al.*) asserted claims of the '866 patent against Defendants Lupin Ltd/Lupin Pharmaceuticals, Inc. and Mylan, Inc./Mylan Pharmaceuticals, Inc. to protect the approved version of their extended release metformin drug, "Fortamet," listed under NDA 21-574.

70. Among other defenses, these Defendants argued that claims of the '866 patent were invalid as obvious, particularly over WO 99/47125 ("Cheng *et al.*) in view of WO 99/47128 ("Timmins"). After several rulings by the district court that found the claims to be valid, the asserted claims were eventually brought to the attention of the Court of Appeals of the Federal Circuit which ruled on the merits of the case on July 2, 2012. Federal Circuit in *Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1261 (Fed. Cir. 2012)

71. After carefully reviewing the asserted claims, the Federal Circuit determined that there was a "significant question of patentability" over "Cheng" (WO 99/47125) in view of "Timmins" (WO 99/47128). The Federal Circuit Court clearly stated that the district court's arguments finding the asserted claims valid were flawed:[3]

> We agree with Lupin that it has raised a substantial question of validity with respect to the '866 patent. *Amazon.com*, 239 F.3d at 1350. We conclude that the district court's obviousness analysis was flawed. It failed to correctly apply *KSR* focusing on what it perceived was "a fundamental factual difference between this case and *KSR*," namely that Cheng and Timmins were before the PTO during prosecution. *Sciele*, 2012 U.S. Dist. LEXIS 22782, at*9-10; *17-20. The court incorrectly rejected Lupin's substantive arguments regarding Timmins's disclosure of a T_{max} within the claimed range and the motivation to combine Cheng and Timmins.

72. The Federal Circuit Court stated that WO 99/47128 (Timmins) teaches controlled release metformin formulations that the POSA would understand to provide a T_{max} value in the range of 4.67-6.33 hours, that WO 99/47125 (Cheng) teaches formulations providing a T_{max} from 8-12 hours, and that Timmins teaches the POSA to lower the T_{max} of Cheng:

> "The '866 patent admits that Cheng 'discloses controlled release metformin formulations providing a T_{max} from 8 to 12 hours.' '866 patent col.2 ll.46-47. Although Timmins expressly discloses a median T_{max}, it

[3] Fed. Cir. [2012-1228], pp. 13-16.

also provides the raw data from which one skilled in the art could compute the range of possible mean Tmax values. J.A. 2501-02.[2] Based on this data, one skilled in the art would understand that the mean Tmax in Timmins must fall between 4.67 and 6.33 hours. Counsel for Shionogi agreed that the only element missing from Cheng is the Tmax range, and that Timmins discloses a range of possible mean Tmax between 4.67 and 6.33 hours…Timmins thus teaches one skilled in the art to lower the Tmax of Cheng (8 hours)."

73. The appeals court also ruled that there was significant motivation for the POSA to combine the teachings of Cheng and Timmins, citing several compelling reasons:

> We also conclude that the district court clearly erred in its conclusion that there was no motivation to combine Cheng and Timmins. Timmins describes a controlled release formulation of metformin and explains that its formulation releases metformin in the portion of the gastrointestinal tract where better absorption of the drug can occur. J.A. 2470-73. The earlier release of the drug increases bioavailability and leads to a lower Tmax. *Id.* Timmins explains that "improved bioavailability from an extended release dosage form that releases metformin at a rate likely to provide the desired plasma levels of drug for an extended time period [could result] from a dosage form that has extended residence time in the upper gastrointestinal tract." J.A. 2472-73. In other words, that earlier release, resulting in a lower Tmax, provides the benefit of "the desired plasma levels of drug for an extended time period." *Id.*

> Timmins also identifies a number of benefits stemming from an earlier extended release, including "reduction in dosing frequency, providing patient convenience that would probably improve compliance" as well as "an extended time period over which therapeutically beneficial plasma levels of drug were maintained." *Id. These benefits would motivate one skilled in the art to modify Cheng to achieve a lower Tmax range. Cf. KSR*, 550 U.S. at 424. *[Emphasis added]*

74. I also point out, as I have noted previously above, the Federal Circuit court found that during prosecution of the application that led to the '866 patent that the Applicant admitted "that one skilled in the art would be able to manipulate the processes and formulations of the [prior art] by other methods to obtain the claimed pharmacokinetic parameters of the present invention by routine experimentation" and concluded that "the applicant's characterization of the predictability and skill in the art during prosecution provides further evidence that it would have been a routine and obvious design choice to make an extended release dosage form with a lower Tmax:"

> The applicant's arguments during prosecution further buttress our belief that Lupin has raised a substantial question of validity with respect to the '866 patent. During prosecution the applicant indicated "that one skilled in the art would be able to manipulate the processes and formulations of the [prior art] by other methods to obtain the claimed pharmacokinetic parameters of the present invention by routine experimentation." J.A. 2621. While Shionogi argued, and the

district court seemed to accept, that this statement applies only to enablement, we are hard pressed to understand this distinction. Coupled with the motivation to lower the Tmax, as disclosed in Timmins, the applicant's characterization of the predictability and skill in the art during prosecution provides further evidence that it would have been a routine and obvious design choice to make an extended release dosage form with a lower Tmax. After all, "[i]f a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *KSR*, 550 U.S. at 417…We therefore believe the combination of Cheng and Timmins raises a substantial question as to the validity of the '866 patent. *Amazon.com*, 239 F.3d at 1350.

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75. I agree with the Federal Circuit's conclusions. As I discuss be
filed a
find that there was clear motivation to use the teaching of Timmins (Ex. 10
harma
decrease the T_{max} taught by Cheng (Ex. 1002) into the range claimed by th
patent. And I strongly agree that it would have been routine for a POSA to ma
change.

76. I understand that the case was then returned to the lower cc
reconsider the validity of the '866 patent, but that the case was settled before
judgement was made. I understand, however, the defendants were subseq
allowed by the settlement to begin marketing their versions.

77. I am also aware that Shionogi and Andrx Labs L.L.C. have
complaint (January 25, 2017) in the District of Delaware against Aurobindo P

USA, Inc. for infringement of the '866 patent and that the case has been assigned as Case 1:17-cv-00072-UNA

V. LEGAL STANDARDS

78. I have been instructed that a claimed invention is not patentable under 35 U.S.C. § 102 for anticipation (or for being "not novel") over a disclosure that is available as prior art if that single disclosure teaches every element of the claimed invention, either explicitly or inherently. I am told that to serve as an anticipation when the reference is silent about an asserted inherent characteristic, the gap in the reference may be filled with recourse to extrinsic evidence.

79. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and would be recognized by persons of ordinary skill. I understand that as long as there is evidence of record establishing inherency, the failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation.

80. I have been informed that a claimed invention is not patentable under 35 U.S.C. § 103, for obviousness, if the differences between the invention 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 the subject matter of the invention pertains. I understand that "a person of ordinary

skill in the art" is a hypothetical person who is presumed to have known the relevant art at the time of the invention. As discussed above, I understand that the relevant art for the purpose of this declaration at least includes references that were published before November 3, 2000.

81. I have been instructed that, a determination of obviousness requires inquiries into (i) the scope and content of the art when the invention was made; (ii) the differences between the art and the claims at issue; (iii) the level of ordinary skill in the pertinent art when the invention was made; and, to the extent they exist, any secondary considerations.

82. I understand that a claim can be found to be obvious if all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable and expected results to one of ordinary skill in the art.

83. I understand that improper hindsight must not be used when comparing the prior art to the invention for obviousness. Thus, a conclusion of obviousness must be firmly based on the knowledge and skill of a person of ordinary skill in the art at the time the invention was made.

84. I have been informed that obviousness may also be shown by demonstrating that it would have been obvious to modify what is taught in a single

piece of prior art to create the patented invention. I understand that obviousness may be demonstrated by showing that it would have been obvious to combine the teachings of more than one item of prior art. I understand that in order for a combination of references or teachings to render the claimed invention obvious, there must be some supporting rationale for combining the cited references or teachings as proposed.

85. I am informed that the following are examples of principles that may indicate that it would have been obvious to combine multiple teachings, resulting in the claimed combination, if the claimed combination involves: (i) the combination of prior art elements according to known methods to yield predictable results; (ii) the simple substitution of one known element for another to obtain predictable results; (iii) the use of a known technique to improve similar methods or products in the same way; (iv) the application of a known technique to a known method or product ready for improvement to yield predictable results; (v) the application of a technique or approach that would have been "obvious to try" (*e.g.*, choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success); (vi) predictable variations of a known work in one field of endeavor prompted for use in either the same field or a different field based on design incentives or other market forces; or (vii) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art

reference or to combine prior art reference teachings to arrive at the claimed invention.

86. I also understand that "secondary considerations" may be weighed against evidence of obviousness where appropriate.

87. I understand that such secondary considerations, where in evidence, may include: (i) commercial success of a product due to the merits of the claimed invention; (ii) a long-felt, but unsatisfied need for the invention; (iii) failure of others to find the solution provided by the claimed invention; (iv) deliberate copying of the invention by others; (v) unexpected results achieved by the invention; (vi) praise of the invention by others skilled in the art; (vii) lack of independent simultaneous invention within a comparatively short space of time; and (viii) teaching away from the invention in the prior art. Secondary considerations are relevant where there is a nexus between the evidence and the claimed invention.

VI. LEVEL OF ORDINARY SKILL AND RELEVANT TIME

88. The '866 patent derives from U.S. Patent Application Serial No. 09/705,630, filed on November 3, 2000. I have been informed that the critical date for the '866 patent is November 3, 2000.

89. I have been advised that I should read the patent and any art which I identify as being prior art from the perspective of a person of ordinary skill in the art

using common sense ("POSA"). I have been advised that a POSA is a person of ordinary creativity.

90. I have been asked to assume for the purposes of my declaration that the relevant timeframe for assessing the validity of claims of the '866 patent is prior to the critical date of November 3, 2000. However, my opinion would not change if a later date was applied as the critical date.

91. In determining the hypothetical POSA from which I am to view the specification of the patent, the patent file history, and any references that I cite herein, I understand that I am to select such POSA based on the level of skill I would expect of an ordinary person in the field of the '866 patent as of the critical date. I am well familiar with the level of skill in the field of the '866 patent before November 3 2000.

92. In my opinion, a POSA as of November 3, 2000, would typically have experience in the research or development of pharmaceuticals and have the ability to gather and interpret pharmacokinetic data and the relationship between drug release from a dosage form and its effect on pharmacokinetic parameters. The POSA would understand the references discussed in this Petition.

93. The POSA would include an individual with a Pharm.D. and/or Ph.D. with experience in pharmaceutical sciences, dosage forms, clinical pharmacology or related fields, such as pharmacology. As part of a team, the POSA may have

access to a person having experience in endocrinology with specific experience in metformin therapies for T2DM.

94. The POSA would understand work published in the field, including the publications discussed in this declaration.

95. In addition, as pharmaceutical development is an inherently collaborative process, the POSA could have access to, or be part of a team including, other skilled individuals, such as an M.D. with experience in the field of diabetes treatment.

96. In particular, one of ordinary skill in the art would likely have some combination of the following skills and experience: (i) experience with the research or development of pharmaceuticals; (ii) the ability to gather and interpret pharmacokinetic and pharmacodynamics data including dose-response curves; and (iii) the ability to understand results and findings presented or published by others in the field, including the publications discussed in this declaration.

VII. CLAIM CONSTRUCTION

97. Counsel has told me that under USPTO rules for an IPR petition each of the terms of the claims of the '866 patent are to be given their broadest reasonable interpretation to POSA as limited by the specification, and that without some specific reason otherwise that the terms are typically given their ordinary and accustomed meaning as would be understood by a POSA. I understand that reasonableness

implies that the claim terms and phrases are to be given an interpretation that is reasonable in terms of the disclosure in the specification to a POSA at the time of the invention.

98. In rendering my construction of terms in the claims, I have carefully followed such instruction. While some terms are defined in the '866 patent, and it is clear that many of the terms are used in the conventional sense, I found certain terms to need clarification, as set forth below:

99. "metformin"

The term "metformin" as it is used herein means metformin base or any pharmaceutically if acceptable salt e.g., metformin hydrochloride. (*Id.* col. 6, ll. 62-64)

100. "dosage form"

The term "dosage form" as it is used herein means at least one unit dosage form of the present invention (e.g. the daily dose of the antihyperglycemic agent can be contained in 2 unit dosage forms of the present invention for single once-a-day administration). (*Id.* col. 6, ll. 65-67 and col. 7, ll. 1-2)

101. "dinner time"

The term "dinnertime" or "at dinner" as it is used herein with respect to the dosing of the controlled release formulations of the invention means that the controlled release formulation is orally administered at a time when dinner is normally eaten

(regardless of whether a meal is actually eaten at that time, unless so specified herein), generally between about 4 p.m. and 8 p.m. (*Id.* col. 7, ll. 10-16)

102. "bedtime"

The term "bedtime" as it is used herein with respect to the dosing of the controlled release formulations of the invention means that the controlled release formulation is orally administered before the patient goes to bed in the evening, generally between about 8 p.m. and 12 p.m. (*Id.* col. 7, ll. 17-21)

103. "therapeutically effective reduction"

The term "therapeutically effective reduction" when used herein is meant to signify that blood glucose levels are reduced by approximately the same amount as an immediate release reference standard (e.g., GLUCOPHAGE®) or more, when the controlled release dosage form is orally administered to a human patient on a once-a-day basis. (*Id.* col. 7, ll. 22-27)

104. "sustained release"

The term "sustained release" and "controlled release" are used interchangeably in this application and are defined for purposes of the present invention as the release of the drug from the dosage form at such a rate that when a once-a-day dose of the drug is administered in the sustained release or controlled-release form, blood (*e.g.*, plasma) concentrations (levels) of the drug are maintained within the therapeutic range, but below toxic levels, over a period of time from about 12 to about 24 hours.

When the drug used in the present invention is metformin (preferably metformin hydrochloride) the controlled release solid oral dosage form containing such drug is also referred to as "Metformin XT." (*Id.* col. 7, ll. 28-39)

105. "C_{max}"

The term "C_{max}" is the highest plasma concentration of the drug attained within the dosing interval, i.e., about 24 hours. (*Id.* col. 7, ll. 40-42)

106. "C_{min}"

The term "C_{min}" is the minimum plasma concentration of the drug attained within the dosing interval, i.e. about 24 hours. (*Id.* col. 7, ll. 43-44)

107. "C_{avg}"

The term "C_{avg}" as used herein, means the plasma concentration of the drug within the dosing interval, i.e. about 24-hours, and is calculated as AUC/dosing interval. (*Id.* col. 7, ll. 46-48)

108. "T_{max}"

The term "T_{max}" is the time period which elapses after administration of the dosage form at which the plasma concentration of the drug attains the highest plasma concentration of drug attained within the dosing interval (i.e., about 24 hours). (*Id.* col. 7, ll. 49-53)

109. "$T_{1/2}$"

The term "$T_{1/2}$" as used in the patent is the time required for the plasma concentration of metformin during the elimination phase of concentration-time curve to decrease to one half of its previous concentration.. The POSA understands $T_{1/2}$ is an intrinsic pharmacological property of metformin, as it interacts uniquely with various dissipative mechanisms in a body, such as kidney function, and is independent of the dosage form used to deliver metformin.

110. "AUC"

The term "AUC" as used herein, means the area under the plasma concentration-time curve, as calculated by the trapezoidal rule over the complete 24-hour interval. (*Id.* col. 7, ll. 54-56)

111. "steady state"

The term "steady state" means that the blood plasma concentration curve for a given drug does not substantially fluctuate after repeated doses to dose of the formulation. (*Id.* col. 7, ll. 57-59)

112. "single dose"

The term "single dose" means that the human patient has received a single dose of the drug formulation and the drug plasma concentration has not achieved steady state. (*Id.* col. 7, ll. 60-63)

113. "multiple dose"

The term "multiple dose" means that the human patient has received at least two doses of the drug formulation in accordance with the dosing interval for that formulation (e.g., on a once-a-day basis). Patients who have received multiple doses of the controlled release formulations of the invention may or may not have attained steady state drug plasma levels, as the term multiple dose is defined herein. (*Id.* col. 7, ll. 63-67 and col 8, ll. 1-2)

114. "a patient"

The term "a patient" means that the discussion (or claim) is directed to the pharmacokinetic parameters of an individual patient and/or the mean pharmacokinetic values obtained from a population of patients, unless further specified. (*Id.* col. 8, ll. 3-7)

115. "mean",

The term "mean", when preceding a pharmacokinetic value (e.g. mean T_{max}) represents the arithmetic mean value of the pharmacokinetic values taken from a population of patients unless otherwise specified (e.g. geometric mean). (Id. col. 8, ll. 8-11)

116. "median",

The term "median," although not discussed in the patent (but which was subsequently used in legal proceedings) is a universally understood to be the value in a rank ordered set of values below and above which there is an equal number of

values. Mean and median are both statistical parameters which describe the central tendency of a set of values, in this case, T_{max} values. Depending on the distribution of values, the mean and median may or may not be equal.

117. "Degree of Fluctuation"

The term "Degree of Fluctuation" is expressed as $(C_{max}-C_{min})/C_{avg}$. (*Id.* col. 8, ll. 12-13)

118. "controlled release carrier"

This term is not specifically defined. It is noted that the controlled release dosage form may optionally include a controlled release carrier which is incorporated into a matrix along with the drug, or which is applied as a controlled release coating (*Id.* col. 12, ll. 49-52).

119. "the membrane"

The term "membrane" as embodied in the patent means a semipermeable membrane that is permeable to aqueous solutions such as bodily fluids and impermeable to the active drug or pharmaceutical ingredient (e.g. the formulations of Examples 1-3).[4] Flux enhancers (*i.e.*, PEG 400) may be added to the membrane to increase its porosity.[5] Drug may be released through mechanical holes or passageways in the porous membrane in solution or *in vivo*.[6]

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[4] U.S. Patent No. 6,866,866, col. 10, lines 35-41.

[5] *Id.*, col. 10, lines 53-63

[6] *Id.*, col. 11, lines 53-59.

120. "passageway"

As defined in the specification of the '866 patent, the term passageway includes an aperture, orifice, bore, hole, weakened area or an erodible element such as a gelatin plug that erodes to form an osmotic passageway for the release of the antihyperglycemic drug from the dosage form.[7]

121. After having determined the meaning of each of the claims of the '866, I assessed the scope and content of the prior art, the differences between the prior art and the '866 patent claims, if any, and the level of skill in the art. I determined whether the '866 patent claims would have been obvious to a person having ordinary skill in the art.

VIII. THE STATE OF THE ART

122. Below I describe some of the relevant aspects of what was generally known in the art on or before November 3, 2000.

123. Before November 3, 2000, it was known by the POSA that type 2 diabetes ("T2DM"), or "NIDDM," is a chronic metabolic condition that affects glucose homeostasis, whereby the body demonstrates insulin resistance and increased levels of blood glucose (hyperglycemia). It was also known that metformin is an antihyperglycemic (glucose-lowering) agent which improves glucose tolerance

[7] *Id.,* col. 11, lines 42-49.

in patients with T2DM, and that metformin lowers both basal and postprandial plasma glucose. It was also recognized generally by the POSA that metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

124. It was well known to the artisan at the time the application leading to the patent was filed that during extended fasting after the evening meal, and during sleep, the liver newly synthesizes glucose from non-carbohydrate physiologic sources ("gluconeogenesis") and that such peak occurs, according to the '866 patent near 2 AM.[8]

125. At least one immediate release dosage form "GLUCOPHAGE®" and at least one controlled release dosage form for metformin, " GLUCOPHAGE® XR," [9] a competitor product with overlapping release and pharmacokinetic characteristics as claimed in the '866 patent, had already been approved for marketing by Bristol-Myers Squibb in the United States by October 2000. GLUCOPHAGE® is referenced in the '866 patent and elsewhere in the prior art as a comparator product.

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[8] *Id.*, col. 5, lines31-32.

[9] NDA 021202 for GLUCOPHAGE® XR was approved on October 13, 2000: https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021202 (See also, EX1012)

126. The POSA would have also been aware of the art published prior to November 3, 2000 including at least: WO 00/12097 to Chen *et al.* ("Chen," Ex 1007) published on March 9, 2000; WO 1999/047125 to Cheng *et al.* ("Cheng", Ex.1002) with an international publication date of Sept. 23, 1999, and WO 99/47128 to Timmins *et al.* ("Timmins", Ex.1003) which published on September 23, 1999. The additional prior art references listed in my Appendix XII would also have been known to the artisan.

127. As I set forth below, the POSA would understand that the Chen, Cheng and Timmins references either alone, or alternatively, in combination teach the elements of the claims that issued in the '866 patent.

IX. THE ASSERTED REFERENCES DISCLOSE OR SUGGEST EACH OF THE CLAIMED FEATURES OF THE '866 PATENT

A. Brief Overview of the Asserted References

1. Chen *et al.*, WO 00/12097, with a publication date of March 9, 2000, claiming priority to U.S. Application filed on August 31, 1998, is Prior Art.

128. Chen *et al.*, WO 00/12097 in Example 1 objectively teaches tablets which are essentially identical to the tablets exemplified and claimed in '866 patent, including the number of passageways (holes) drilled in the sustained release membrane to allow metformin release. Regarding the compositions, the tablets of WO 00/12097 appear essentially identical to those of the '866 patent but for a minor

amount of the sulfonylurea, glipizide (a hypoglycemic drug), in the tablet core in the WO publication.

129. In particular, as for the dosage forms described in the '866 patent (as well as WO 99/47125, see below), the tablets of WO 00/12097 and the '866 patent each comprise a core containing metformin hydrochloride (active drug), povidone (binder), sodium lauryl sulfate (absorption enhancer) and magnesium stearate (lubricant) in very similar concentrations. The core is optionally coated by a seal coat comprising "Opadry." The optionally seal coated core is coated by a sustained release membrane comprising cellulose acetate, triacetin and PEG 400 (flux enhancer).

130. The WO 00/12097 publication notes that the disclosed tablets provide continuous and non-pulsating therapeutic levels of an antihyperglycemic drug, such as metformin, to an animal in need of such treatment over a twelve or twenty four hour period,[10] the same as evidenced by the '866 patent in Figures 1, 2 and 4.

131. Further, as I show below, when tested for metformin release by *in vitro* dissolution testing, tablets disclosed by the inventors of WO 00/12097 meet the preferred release limitations taught and claimed in the '866 patent (claims 4 and 5), giving release rates that are asserted by the inventors to provide a T_{max} of 5.5-7.5 hours, as in claim 1.

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[10] WO 00/12097, p. 4, lines 3-7.

132. The following table specifically compares mass compositions of the 850 mg tablet of Example 1 of WO 00/12097 and Example 2 of the '866 patent. The tablet component mass values are given directly in the '866 patent.[11] Only fractional values of components are listed in WO 00/12097.[12] (In that case I calculated the mass values based on the disclosure in WO 00/12097 that 850 mg of metformin HCl comprised 88.10% of the core mass.)[13]

	U.S. 6,866,866 Ex. 2	WO 00/12097 Ex. 1
Component	Mass, mg	Mass, mg
Core		
metformin HCl	850.0	850.0
Povidone, USP	61.1	61.1
Sodium Lauryl Sulfate	43.9	44.0
Mg Stearate	4.8	4.8
Glipizide	NA	5.0
Total	959.8	964.8
SR Membrane		
Cellulose Acetate	24.0	24.6
Triacetin	1.4	1.4
PEG 400	2.8	2.9
Total	988.0	993.8
#Passageways	2 holes	2 holes

133. I stress once more that the device in Example 1 of Chen (WO 00/12097) comprises two laser drilled passageways[14] ("holes") as does the device

[11] U.S. Patent No. 6,866,866, col. 14, lines 15-25 and lines 56-63.

[12] WO 00/12097, p. 11, line 25- p. 13, line 20.

[13] *Id.*, p. 12, line 2.

[14] *Id.*, p. 14, lines 9-10.

claimed the '866 patent.[15] Except for a small amount of glipizide, the tablets are objectively identical to Example 2 of the '866 patent, also an 850 mg tablet.

134. Based upon my analysis, the tablets of WO 00/12097 and the tablets claimed in the '886 patent differ slightly only in that the core of the latter comprises a small fraction, about 0.5%,[16] of the sulfonylurea drug, glipizide, while the patented device of the '866 patent lacks glipizide.

135. In my opinion, this additional, very minor component has no significant effect on the function of the tablet of WO 00/12097 with regards to pharmacokinetic properties of metformin, compared to tablets of the '866 patent.

136. Further, as advised to me by Aurobindo's attorneys, the presence of glipizide is not excluded from the claims of the '866 patent, because "comprising" transitional language is used in the only independent claim and this language does not exclude other unnamed active components in the core, such as glipizide.

137. Using identical dissolution testing methodologies, the release rate of metformin from Example 1 of WO 00/12097 also conforms to the preferred limitations claimed in the '866 patent. The following table demonstrates that fact:

	% Metformin Released,	
Time (hours)	WO 00/12097, Ex. 1, 850 mg[17]	'866 Patent

[15] U.S. Patent No. 6,866,866, col. 15, lines 7-8.

[16] The core of Example 1 of WO 00/12097 comprises 850 mg metformin hydrochloride and 5 mg of glipizide, a mass ratio of 170:1.

[17] WO 00/12097, p. 14, lines 11-22.

		Preferred Release Limit[18]
0	0	0
2	17	0-30
4	32	10-45
8	56	30-90
12	76	NLT 50
16	89	NLT 60
20	-[19]	NLT 70

138. Even more narrowly, the release rate of metformin from Example 1 of WO 00/12097 also conforms to the most preferred limitations claimed in the '866 patent. The following table once again demonstrates that fact:

	% Metformin Released,	
Time (hours)	WO 00/12097, Ex. 1, 850 mg[20]	'866 Patent Most Preferred Release Limit[21]
0	0	0
2	17	0-25
4	32	20-40
8	56	45-90
12	76	NLT 60
16	89	NLT 70
20	-[22]	NLT 80

139. By directly comparing of the amount of metformin released by the

[18] U.S. Patent No. 6,866,866, col. 12, lines 24-32. Also see, claim 4.

[19] Not reported, but 76% drug was released at the 12 hour test point, a value which also meets the required 16 and 20-hour release values of NLT (not less than) 60% and 70%, respectively.

[20] WO 00/12097, p. 14, lines 11-22.

[21] U.S. Patent No. 6,866,866, col. 12, lines 24-32. Also see, claim 5.

[22] Not reported, but 89% drug was released at the 16 hour test point, a value which also meets the 20 hour test value.

tablet of Example 1 of Chen to the amount of release required to meet the claim limits, I see that both the preferred and most preferred limitations are met in every case.

140. As I understand the meaning of the dependent claims 4 and 5, each claim incorporates the limitations (elements) of the independent claim upon which they depend. Claims 4 and 5 depend on Claim 1, which claims an *in vivo* T_{max} value of 5.5-7.5 hours for administration of the drug after dinner.

141. As such, I interpret the meaning of claims 1, 4 and 5 to be that the inventors have required that if the *in vitro* release limitations for metformin are met in claim 4 and 5, then the *in vivo* T_{max} condition required by claim 1 will also be simultaneously met.

142. Thus, I understand, according to the patent, that the controlled release tablet of Example 1 of WO 00/12097 meets the metformin release characteristics required by claims 4 and 5 and will, therefore, provide a T_{max} value of 5.5-7.5 hours *in vivo* after administration after dinner.

143. Indeed, particularly with all the other elements of the tablets being identical, a POSA would expect that the 850 mg tablet of Example 1 of WO 00/12097 and the tablets claimed in the '866 patent would produce a T_{max} value of 5.5-7.5 hours *in vivo* following administration after dinner.

144. I conclude, as would the POSA, that the tablets disclosed in WO 00/12097 in Example 1 and the tablets claimed in the '866 patent are functionally identical and will behave identically *in vivo*. As the tablets are otherwise essentially identical in all their structural characteristics, one would expect the other pharmacokinetic parameters recited in the dependent claims of the '866 patent to be highly similar when the same dosage of metformin was administered by either tablet.

2. Cheng et al., WO 99/047125, with an International publication date of Sept. 23, 1999, claiming priority from provisional application No. 90/045,330 filed on March 20, 1998, is Prior Art.

145. WO 99/47125 discloses a controlled release anti-hyperglycemic tablet that does not contain an expanding polymer (as in the case of GLUCOPHAGE® XR) and comprises a core containing an antihyperglycemic drug, a semipermeable membrane coating the core and at least one passageway in the membrane (Abstract).[23] As such, the publication discloses the same tablet structure later taught in WO 00/12097[24] as well as the tablet later claimed in the '866 patent.[25]

146. All of these tablets are constructed in the same fashion, with a unitary core surrounded by a semipermeable membrane with at least one passageway in the

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[23] See also, WO 99/47125, p. 3, lines 25-33.

[24] WO 00/12097, p. 4, line 15-p. 5, line 2.

[25] '866 Patent, claim 25.

membrane.

147. As I discussed just above, Chen *et al.*, WO 00/12097 (Ex. 1007) discloses a metformin hydrochloride tablet which differs from the '866 patent in that it comprises a very small fraction of glipizide in the tablet core. Further, it meets the *in vitro* release characteristics ascribed to the tablets of the '866 patent. The WO 99/47125 reference, Example 3, in contrast, discloses a tablet comprising metformin hydrochloride that appears identical to that described in the '866 patent in terms of the types and amounts of excipient components. The release rates appear approximately the same. Statistically the T_{max} in the WO 99/47125 publication cannot be said to fail to fit within that claimed within the '866 patent.

148. The only objective structural difference between the 850 mg tablet of Example 3 of WO 99/47125 and that of Example 2 of the '866 patent is that the tablet of Example 3 shows one laser drilled hole,[26] while that of Example 2 of the '866 patent shows two laser drilled holes. This possibly accounts for the faster rate of release of metformin from the tablets of the '866 patent.

149. My calculations again show that the composition and structure of the tablet of WO 99/47125 are essentially identical to that described in the '866 patent. This identity extends to the type, qualities and amounts of excipients used.

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[26] *Id.*, p. 15, lines 10-16. It is not clear what is meant by "an additional hole" as the example referenced mentions no hole.

150. WO 99/47125 specifically exemplifies an osmotic device (Example 3) with one additional laser drilled passageway on the plain side of the coated tablet. The device can provide continuous, non-pulsating therapeutic levels of an antihyperglycemic drug to an animal or human in need of such treatment over a twelve hour to twenty-four hour period. (p. 3, lines 7-13).

151. Although the device is stated to provide a T_{max} of 8-12 hours,[27] under all conditions of feeding, a T_{max} range of 4-10 hours is actually demonstrated (see Figures 4-8). Fig. 8 specifically shows a T_{max} of 10 hours after evening feeding (after dinner).

152. WO 99/47125 teaches that food decreases the extent of absorption, and slightly delays the absorption of metformin, as delivered by the GLUCOPHAGE® dosage form (page 2, lines 26-35).

153. I conclude that a difference between the tablets of the '866 patent and Example 3 of WO 99/47125 may be an extra passageway ("laser-drilled hole") providing for increased rate of release of metformin.

154. It is admitted the *in vitro* release rate of metformin from the tablets of WO 99/47125 results in a T_{max} of 8-12 hours *in vivo*.[28] The release rate of metformin

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[27] *Id.*, p. 3, lines 14-17.

[28] '866 patent, col. 2, lines 46-47.

from the tablets of the '866 patent is claimed to provide a T_{max} of 5.5-7.5 hours *in vivo* when administered after dinner.

155. In my opinion, being otherwise identical, it would be trivial for the POSA to increase the rate of release of metformin from the tablet of Example 3 of WO 99/47125 to match that shown in the '866 patent. This would match the T_{max} values *in vivo*. Indeed, the inventors of the patent stressed that such was true during statements made during the prosecution of the application that led to the '866 patent.

156. I note that although Example 3 of WO 99/47125 directly exemplifies one membrane passageway, the reference teaches with open language that there may be "at least one passageway in the semipermeable membrane."[29] The term "at least one passageway" would clearly include, for example, "two passageways" as in the '866 patent.

157. Thus, the only modification needed for the POSA to match the invention of the '866 patent would be a trivial one, to drill an extra hole in the tablet, an option plainly suggested by the language of the WO 99/47125 publication.

158. In my opinion, the motivation to do so is clearly provided by the disclosure of "Timmins *et al.*", which I discuss directly below.

3. Timmins *et al.*, WO 99/47128 was published on September 23, 1999. The publication, therefore qualifies as prior art to the '866 patent.

[29] WO 99/47125, p. 3, line 33.

159. Timmins *et al.* teaches among embodiments a biphasic controlled release delivery system for metformin HCL salt comprising an inner solid particulate phase with one or more hydrophilic polymers, and hydrophobic material, and an outer solid continuous phase in which the granules are embedded and dispersed throughout.

160. The Timmins disclosure covers Bristol-Myers Squibb's product, GLUCOPHAGE® XR, which was approved for marketing (October 13, 2000) before the priority date of the '866 patent. Timmins *et al.* teaches a T_{max} range of 4-8 hours, with a median (not mean) T_{max} of 5 hours for a single dose after dinner administration.[30] Being a competitor's product to their own extended release metformin product ("metformin XT" in the '866 patent, now "Fortamet"), the inventors would have been well aware of the Timmins reference which discloses that invention.

161. I note that "median" and "mean" are terms which are statistical measurements of the central tendency of a measured value from a population. I note that the T_{max} range of 4-8 hours overlaps mean T_{max} of 5.5-7.5 hours reported in patent 866.

162. During district court litigation, Aurobindo's attorneys have informed me that the district court had examined the Timmins and Cheng (Ex. 1002) references.

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[30] WO 99/47128, p. 34, lines 28-29.

It was the opinion of the district court that there was no motivation to combine these references to arrive at the invention of the '866 patent. However, the Federal Circuit court corrected this error in *Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1261 (Fed. Cir. 2012) (Ex. 1006)

163. As stated by the Federal Circuit, in pointing out the district court's error, there was, indeed, sufficient motivation to combine the Cheng and Timmins references.

164. The Federal Circuit stated, for instance: "lowering the T_{max} allows one skilled in the art to approach the drug profile of GLUCOPHAGE®, the industry standard drug," so as to reach the mean T_{max} of U.S. Patent No. 6,866,866 B1 (which asserts a mean time to maximum plasma concentration (T_{max}) of the metformin from 5.5. to 7.5 hours after administration following dinner):

> "The '866 patent admits that Cheng 'discloses controlled release metformin formulations providing a T_{max} from 8 to 12 hours.' '866 patent col.2 ll.46-47. Although Timmins expressly discloses a median T_{max}, it also provides the raw data from which one skilled in the art could compute the range of possible mean T_{max} values. J.A. 2501-02.[2] Based on this data, one skilled in the art would understand that the mean T_{max} in Timmins must fall between 4.67 and 6.33 hours. Counsel for Shionogi agreed that the only element missing from Cheng is the T_{max} range, and that Timmins discloses a range of possible mean T_{max} between 4.67 and 6.33 hours. See Oral Argument at 19:55-20:33, available at http://www.cafc.uscourts.gov/oral-argument-recordings/2012-1228/all.

Timmins thus teaches one skilled in the art to lower the T_{max} of Cheng (8 hours)." (Ex. 1006, p. 14)

165. Thus, as stated by the Federal Circuit court, and in my own opinion, the POSA would have used the teaching of Timmins (WO 99/47128) to lower the T_{max} value taught by Cheng (WO 99/47125) to reach a mean range of about 4.67-6.33 hours, well within the range claimed by the '866 patent.

B. Detailed Analysis of the Claims

1. Claims 1-25 Are Unpatentable Under 35 U.S.C. § 102 Over Chen *et al.*, WO 00/12097 (Ex. 1012) As Being Anticipated

166. Claim 1 is the sole independent claim of the '866 patent. Dependent claims 2-25 incorporate the pharmacokinetic parameter recited in claim 1 (T_{max}) and add further pharmacokinetic recitations consistent with a T_{max} of 5.5-7.5 hours.

167. In claim 1 the claimed T_{max} range is an empirical result, arising from the inherent release properties of drug from the claimed dosage form. Moreover, the physiological differences among human subject volunteers such as gastric emptying rate can generate variability in the pharmacokinetic parameters such as T_{max}. The other pharmacokinetic parameters cited in claims 2-25 are also empirical, inherent properties of the physical structure and release rate of drug from the claimed dosage form. In my opinion, any another dosage form with the same composition and physical structure, also meeting the required rate for drug release, would show all

the PK characteristics inherent in the properties of the dosage forms claimed in the '866 patent.

168. The 850 mg tablet described in Example 1 of WO 00/012097 to Chen *et al.* and the tablets of the '866 patent are essentially identical in composition and structure, except for a minor fraction of glipizide in the tablet of Example 1.

169. When tested by the same dissolution method, the release of metformin from the tablets of Example 1 of WO 00/012097 meet the preferred limitations for *in vitro* release required by the '866 patent in claim 5, dependent on claim 1. These preferred limitations were specified by the inventors to provide a Tmax, as in claim 1, of 5.5-7.5 hours.

170. Upon oral administration after dinner, as in claim 1, given the same metformin composition, and meeting the preferred release limitations required by the '866 patent, a POSA would expect a T_{max} of 5.5-7.5 hours also to be produced by the controlled release dosage form of Example 1 of WO 00/012097.

171. A table comparing the construction of Example 1 of the WO 00/12097 and Example 2 of '866 patent (both 850 mg tablets) is shown above in paragraph 98. The weight fractions of the metformin HCl component and the excipient components are essentially identical in the core and sustained release coating of both the 850 mg tablets in each case.

172. Further, the tablet of Example 1 of WO 00/12097 and tablets exemplified in the '866 patent both comprise two laser drilled holes, one on each side of the tablet.

173. As I point out above, the tablet of Example 1 of WO 00/12097 differs from device claimed in the '866 patent in that the core of the latter device comprises additionally about 0.5% of the sulfonylurea drug, glipizide, while the latter, the patented device of the '866 patent lacks glipizide. I do not view this to be a significant difference because of the very small concentration of glipizide.

174. Further, the presence of glipizide is not excluded from the claims of the '866 patent, as "comprising" transitional language is used in the only independent claim, language which does not exclude other unnamed active components.

175. When tested using the same *in vitro* dissolution testing methodology,[31] the release rate of Example 1 of WO 00/12097 meets the preferred and most preferred limitations taught in the '866 patent.

176. In that T_{max} will depend upon the release rate of metformin from the dosage device, all other elements of the tablets being identical, this equivalence requires that the two tablets will produce an equivalent *in vivo* T_{max}, according to the claims of the patent.

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[31] USP Type 2 Apparatus, 75 RPM, 900 ml, simulated gastric fluid (pH 7.5), 37°C.

177. Overall, given the close identicality of the tablet of Example 1 of WO 00/12097 (both in composition, structure and release rate) to the dosage forms claimed in the '866 patent, it is my opinion that the pharmacokinetic properties recited in claims 1-25, would be inherent in the properties of the Tablet 1 of WO 00/12097.

178. Given such identicality, it is my opinion that Tablet 1 of WO 00/12097 inherently anticipates claims 1-25 of the '866 patent.

179. My analysis is given in the table below:

Claim of U.S. Patent No. 6,866,866	Basis for Invalidity
1. A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form, said dosage form being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof, wherein following oral administration of a single dose, the dosage form provides a mean time to maximum plasma concentration (Tmax) of the metformin from 5.5 to 7.5 hours after administration following dinner.	Anticipated Under 35 U.S.C § 102 over Chen, WO 00/12097 (Ex. 1007) "The present invention relates to controlled release unit dose formulations containing an antihyperglycemic drug...As used in this specification the term "antihyperglycemic" refers to a drug that is useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM)..." (p. 1, lines 4-8) "In a preferred embodiment, the present invention relates to an oral dosage form comprising a unique combination of a biguanide...The biguanide is preferably metformin or buformin or a pharmaceutically acceptable salt thereof" (p. 1, lines 15-18)

	"The dosage form of the present invention can provide therapeutic levels of the drugs from twelve to twenty-four hour periods. In a preferred embodiment, the dosage form will be administered once a day and provide therapeutic levels of the drug throughout the day." (p. 2, lines 4-7) Example 1 described in WO 00/12097 is essentially identical in composition and structure to the examples provided in the '866 patent, including two laser-drilled holes. *See* paragraph 98. "Once the theoretical coating level is obtained, the sustained release coated tablets are dried in the fluidized bed coater for approximately 5 to 10 minutes. Then one hole is either mechanically drilled or laser drilled onto each side of the sustained release tablet. (p. 14, lines 7-10)" Example 1 meets *in vitro* release criteria, which according to the patent are necessary to provide a T_{max} of the metformin from 5.5 to 7.5 hours after administration following dinner. (*See* below, claims 4 and 5).
2. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after the administration of the dose.	Invalid under 35 U.S.C. § 102. Arguments for claim 1 are repeated. Meeting the preferred and most preferred release limitations as described in the specification for the invention as a whole and claims 4 and 5 below, claim 2, specifying a T_{max} of

	6.0 to 7.0 hours is anticipated by Example 1 of WO 00/12097.
3. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (Tmax) of metformin at from 5.5 to 7.0 hours after the administration of the dose.	Invalid under 35 U.S.C. § 102. Arguments for claim 1 are repeated. Meeting the preferred and most preferred release limitations as described in the specification for the invention as a whole and claims 4 and 5 below, claim 3, specifying a T_{max} of 6.0 to 7.0 hours is anticipated by Example 1 of WO 00/12097.
4. The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C: 0-30% of the metformin or salt thereof is released after 2 hours; 10-45% of the metformin or salt thereof is released after 4 hours; 30-90% of metformin or salt thereof is released after 8 hours; not less than 50% of the metformin or salt thereof is released after 12 hours; not less than 60% of the metformin or salt thereof is released after 16 hours; and not less than 70% of the metformin or salt thereof is released	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. The 850 mg tablet of Example 1 of WO 00/12097 meets the limitations of claim 4 when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C[32] as follows: **METFORMIN HCl RELEASE** TIME (hours) / % Released (pH 7.5) 2 / 17 4 / 32 8 / 56 12 / 76 16 / 89 The tablet of Example 1 meets the release limitations of claim 4 and incorporates the limits of claim 1, requiring a T_{max} of 5.5-7.5 hours.

[32] WO 00/12097, p. 14, lines 15-22.

<table>
<tr><td>after 20 hours.</td><td></td></tr>
<tr><td>5. The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-25% of the metformin or salt thereof is released after 2 hours;
20-40% of the metformin or salt thereof is released after 4 hours;
45-90% of the metformin or salt thereof is released after 8 hours;
not less than 60% of the metformin or salt thereof is released after 12 hours;
not less than 70% of the metformin or salt thereof is released after 16 hours;
and not less than 80% of the metformin or salt thereof is released after 20 hours.</td><td>Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated.

The 850 mg tablet of Example 1 of WO 00/12097 meets the limitations of claim 5 when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C[33] as follows:

METFORMIN HCl RELEASE

TIME (hours) — % Released (pH 7.5)
2 — 17
4 — 32
8 — 56
12 — 76
16 — 89

The tablet of Example 1 meets the release limitations of claim 5 and incorporates the limits of claim 1, requiring a T_{max} of 5.5-7.5 hours.</td></tr>
<tr><td>6. The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 4.5 to about 13 hours.</td><td>Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated.

Because of the closeidenticality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 6 are anticipated as inherent in Example 1 of WO 00/12097.</td></tr>
</table>

[33] WO 00/12097, p. 14, lines 15-22.

7. The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 5.5 to about 10 hours.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 7 are anticipated as inherent in Example 1 of WO 00/12097.
8. The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of metformin which is more than about 7 times the mean plasma level of said metformin at about 24 hours after the administration.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 8 are anticipated as inherent in Example 1 of WO 00/12097.
9. The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 7 times to about 14 times the plasma level of said metformin at about 24 hours after administration.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 9 are anticipated as inherent in Example 1 of WO 00/12097.
10. The controlled release oral dosage form of claim 1 which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 8 times to about 12 times the plasma level of said metformin at about 24 hours after administration.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 10 are anticipated as inherent in Example 1 of WO

	00/12097.
11. The controlled release oral dosage form of claim 1 which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 11 are anticipated as inherent in Example 1 of WO 00/12097, adjusted for an equivalent dosage. WO 00/12097 teaches no limitation on the mass of the tablets of the invention.
12. The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 12 are anticipated as inherent in Example 1 of WO 00/12097, adjusted for an equivalent dosage. WO 00/12097 teaches no limitation on the mass of the tablets of the invention.
13. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ of at least 80% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 13 are anticipated as inherent in Example 1 of WO 00/12097.

controlled release oral dosage form.	
14. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ of at least 90% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 14 are anticipated as inherent in Example 1 of WO 00/12097.
15. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 15 are anticipated as inherent in Example 1 of WO 00/12097, adjusted for an equivalent dosage. WO 00/12097 teaches no limitation on the mass of the tablets of the invention.
16. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 16 are anticipated as inherent in Example 1 of WO 00/12097, adjusted for an equivalent dosage. WO 00/12097 teaches no limitation on the mass of the tablets of the invention.

17. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ from about 19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 17 are anticipated as inherent in Example 1 of WO 00/12097, adjusted for an equivalent dosage. WO 00/12097 teaches no limitation on the mass of the tablets of the invention.
18. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}\infty}$ of 18277±2961 ng.hr/ml and a mean C_{max} of 1929±333 ng/ml, for administration of a 1700 mg once-a-day dose of metformin after an evening meal.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 18 are anticipated as inherent in Example 1 of WO 00/12097, adjusted for an equivalent dosage. WO 00/12097 teaches no limitation on the mass of the tablets of the invention.
19. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}\infty}$ of 20335±4360 ng.hr/ml and a mean C_{max} of from 2053±447 ng/ml, for administration of a 2000 mg once-a-day dose of metformin after an evening meal.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 19 are anticipated as inherent in Example 1 of WO 00/12097, adjusted for an equivalent dosage. WO 00/12097 teaches no limitation on the mass of the tablets of the invention.
20. The controlled release oral	Anticipated under 35 U.S.C. § 102.

dosage form of claim 1 which provides a mean AUC_{0-24} of 26818±7052 ng.hr/ml and a mean C_{max} of 2849±797 ng/ml, for, administration of a 2000 mg once-a-day dose of metformin after an evening meal.	Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 20 are anticipated as inherent in Example 1 of WO 00/12097, adjusted for an equivalent dosage. WO 00/12097 teaches no limitation on the mass of the tablets of the invention.
21. The controlled release oral dosage form of claim 1 which provides a mean AUC_{0-24} of 22590±3626 ng.hr/ml and a mean C_{max} of 2435±630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136±7996 ng.hr/ml and a mean C_{max} of 2288±736 ng/ml on the 14^{th} day of administration, for administration of a 2000 mg once-a-day dose of metformin after an evening meal.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 21 are anticipated as inherent in Example 1 of WO 00/12097, adjusted for an equivalent dosage. WO 00/12097 teaches no limitation on the mass of the tablets of the invention.
22. The controlled release oral dosage form of claim 12 which provides a mean $t_{1/2}$ from 2.8 to 4.4.	Anticipated under 35 U.S.C. § 102. Arguments from claims 1 and 12 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim limitations in claim 22 are anticipated as inherent in Example 1 of WO 00/12097, adjusted for an equivalent dosage. WO 00/12097 teaches no limitation on the mass of the tablets of the invention.

	It is additionally noted that $t_{1/2}$ is an intrinsic property of metformin and is not a property of the claimed dosage form.
23. The controlled release oral dosage form of claim 6, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 6.0 to 7.0 hours after the administration.	Anticipated under 35 U.S.C. § 102. Arguments from claims 1 and 6 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim to a Tmax of 6.0-7.0 hours in claim 23 are anticipated as inherent in Example 1 of WO 00/12097.
24. The controlled release oral dosage form of claim 6, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 5.5 to 7.0 hours after administration.	Anticipated under 35 U.S.C. § 102. Arguments from claims 1 and 6 are repeated. Because of the close identicality between the dosage form of Example 1 of WO 00/12097 and Example 3 of the '866 patent, the empirical claim to a Tmax of 5.5-7.0 hours in claim 24 are anticipated as inherent in Example 1 of WO 00/12097.
25. The controlled release dosage form of claim 1, wherein the metformin or pharmaceutically acceptable salt thereof is provided by at least one controlled-release tablet, said tablet comprising: (a) a core comprising: (i) the metformin or a pharmaceutically acceptable salt; (ii) optionally a binding agent; and (iii) optionally an absorption enhancer; (b) a membrane coating surrounding the core; and (c) at least	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Additionally, WO 00.12097 teaches: "The foregoing objectives are meet by a controlled release dosage form which comprises: (a) a core which comprises: (i)an hyperglycemic drug; …(iii) a binding agent; and (iv) optionally, an absorption enhancer; (b) optionally a seal coating layer around the

one passageway in the membrane.	core; (c) a semipermeable membrane surrounding the core; and (d) at least one passageway in the membrane..." (p. 4, line14-p. 5, line 1)

C. Claims 1-3 are Unpatentable Under 35 U.S.C. § 102 As Being anticipated by of WO 99/47128 ("Timmins *et al.*")

180. GLUCOPHAGE® XR (metformin hydrochloride, extended release tablets), marketed by Bristol-Myers Squibb (before the November 3, 2000, priority date of the '866 patent), is the implicit subject of WO 99/47128. Example 3 of WO 99/47128 teaches a controlled release, 500 mg metformin hydrochloride oral dosage form for the once-a-day administration of an effective dose of metformin or a salt thereof,[34] wherein with oral administration after dinner provides a T_{max} in the range of 4-8 hours, with median T_{max} of 5 hours.[35]

181. Claim 1 of the '866 patent lists a T_{max} of 5.5-7.5 hours after administration following dinner; claim 2 of the '866 patent claims a T_{max} of 6.0-7.0 hours after administration following dinner; and Claim 3 of the '866 patent claims a T_{max} of 5.5-7.0 hours after administration following dinner.

[34] WO 99/47128, p. 32, line 20-p. 33, line8.

[35] *Id.*, p. 34, line 29.

182. From the data of Timmins, the POSA would understand a mean T_{max} of between 4.67 and 6.33 hours according to the Federal Circuit review and opinion of 2012 on the '866 patent.[36]

183. The T_{max} of Timmins overlaps and intrudes into each of the ranges claimed by claims 1-3 of the '866 patent.

184. Based on these facts, I conclude that at least claims 1-3 of the '866 patent are taught in every detail by Timmins and are, therefore, anticipated by Timmins. I provide the claim chart below in support of my opinions.

Claim of U.S. Patent No. 6,866,866	Basis for Invalidity
1. A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form, said dosage form being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof, wherein following oral administration of a single dose, the dosage form provides a mean time to maximum plasma concentration (Tmax) of the metformin from 5.5 to 7.5 hours after administration following dinner.	Anticipated Under 35 U.S.C § 102 WO 99/47126 (Timmins., Ex. 1003) teaches a controlled release oral dosage form with controlled release carriers comprising metformin hydrochloride for the reduction of serum glucose levels in human patients suffering from NIDDM suitable for once-a-day oral administration after dinner. "Although Timmins expressly discloses a median Tmax [of 5 hours], it also provides the raw data from which one skilled in the art could compute the range of possible mean Tmax values…Based on this data, one skilled in the art would understand that the mean Tmax in Timmins *must fall between 4.67 and*

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	6.33 hours."[37] The Tmax value 6.33 hours taught by Timmins is within the claimed range of 5.5 to 7.5 hours after administration following dinner.
2. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after the administration of the dose.	Anticipated Under 35 U.S.C § 102. Arguments for claim 1 are repeated. The Tmax value 6.33 hours taught by Timmins is within the claimed range of 6.0 to 7.0 hours.
3. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (Tmax) of metformin at from 5.5 to 7.0 hours after the administration of the dose.	Anticipated Under 35 U.S.C § 102. Arguments for claim 1 are repeated. The Tmax value 6.33 hours taught by Timmins is within the claimed range of 5.5 to 7.0 hour.

C. Claims 1-25 are Unpatentable Under 35 U.S.C. § 103(a) As Being Obvious Over WO 99/47125)("Cheng *et al.*") (Ex. 1002) In View of WO 99/47128 ("Timmins *et al.*") (Ex. 1014)

185. GLUCOPHAGE® XR (metformin hydrochloride, extended release tablet), marketed by Bristol-Myers Squibb, is the subject of U.S. Patent No. 6,475,521 (Ex. 1015), the parent application for which was published internationally as WO 99/47128 ("Timmins," Ex.1014) on September 23, 1999.

186. Timmins discloses an extended release tablet of metformin (hydrochloride) comprising a biphasic (non-osmotic) delivery system which

[37] CAFC Opinion [2012-1228], p. 14, 2nd ¶. (Ex. 1005)

provides prolonged gastric residence time and a T_{max} of metformin ranging from 4 to 8 hours, with a median T_{max} of 5 hours.[38]

187. This device differs functionally from the device of the '866 patent which as an osmotically driven tablet. The osmotic tablets of the '866 patent function by allowing gastric or intestinal fluid to permeate into the osmotically active core, dissolving the active agent, and expelling it through the surrounding impermeable membrane through the passageways in the membrane.

188. As admitted in the '866 patent, it was known to the artisan at the time the application leading to the patent was filed that during extended fasting after the evening meal, and during sleep, the liver newly synthesizes glucose from non-carbohydrate physiologic sources ("gluconeogenesis") so as to maintain serum glucose levels during sleep fasting.

189. It was thus logical for the POSA to design a metformin dosage form that would provide a release rate of metformin (a drug which suppresses hepatic gluconeogenesis) such that the time (T_{max}) of maximum serum metformin (C_{max}) would coincide as much as possible with the time of maximum gluconeogenesis occurring during early morning hours.

190. Such prolonged release, however, accompanied with a lengthened T_{max}, was already known to the artisan, as Timmins (WO 99/47128) disclosed a

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[38] WO 99/47128, p. 34, lines 28-29.

median T_{max} of 5 hours (range 4-8 hours), from which the artisan would calculate a mean T_{max} of between 4.67 and 6.33 hours.[39]

191. The POSA would have known of the Timmins and Cheng publications, and would have had motivation, according to the Federal Circuit,[40] to combine the teachings of Cheng with that of Timmins to reduce the T_{max} value of 8-12 hours of Cheng to that of Timmins which was 4.67-6.33 hours, within the range of the claims of the '866 patent. Such modification of the dosage form of Cheng was admitted to be routine.[41]

192. Based on the composition and structure of the dosage form taught by Cheng this would have been easily accomplished by the POSA. The following table compares the compositions and structure of Example 3 of WO 99/47125 (Ex. 1002) and the device Example 2 of '866 patent (Ex. 1001) (850 mg tablet strength), a tablet within the claims of the '866 patent:

	Ex. 3, WO 99/47125		Ex. 2, '866 Patent	
Component	Mass, mg/Tab	Wt%	Mass, mg/Tab	Wt%
Core				
metformin HCL	850	86.0	850.0	86.0
povidone, USP[42]	61.1	6.18	61.1	6.18
sodium lauryl sulfate	43.9	4.44	43.9	4.44
magnesium	4.8	0.49	4.8	0.49

[39] CAFC 2012-1228, EX. 1007, p. 14.

[40] *Id.*, pp. 14-15.

[41] *Id.*, pp. 15-16.

[42] Approximate molecular weight 1,000,000; dynamic viscosity (10% w/vol solution at 20° C = 300-700 m Pa s.

stearate				
Total	960	97	960	97
Sustained Release Coating				
cellulose acetate[43]	24.5	2.48	24.0	2.43
triacetin	1.4	0.15	1.4	0.14
PEG 400	2.9	0.29	2.8	0.28
Total	989 mg	100%	988 mg	100%
Passageway(s)	1 laser-drilled hole		2 laser drilled holes	

The tablets are essentially compositionally identical, except for the additional laser-drilled hole in the tablets of the '866 patent.

193. The table illustrates that drug release from the tablet of Example 3 could easily be increased by the POSA, for example, merely by adding a second laser drilled hole. Based on the Timmins publication, and admissions that such modifications were "routine", the POSA would have no difficulty matching the T_{max} value taught by Timmins and thereby reaching within the claims of the '866 patent.

194. The Federal Circuit has already ruled that "Cheng in view of Timmins creates a substantial question of validity" of the '866 patent.[44] I agree and below I further elaborate on the validity of the claims of the '866 patent (*See* claim table, below). It is my position that once POSA modelled a dosage form with a metformin release rate meeting the T_{max} taught by Timmins, all of the PK parameters listed in the claims 2-25 of the '866 patent would be inherently produced.

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[43] Acetyl content 39.3-40.3%

[44] CFAC 2012-1228, p. 19.

195. Timmins teaches metformin dosages of 150 mg to 3000 mg daily, in 1, 2 and 4 divided doses.[45] Any dose adjustment required by the claims of the '866 patent is taught by Timmins.

196. Below I set forth a claim chart setting forth, in summary form, the bases of my opinions provided above. I conclude that claims 1-25 are invalid as obvious over the Cheng reference in view of the Timmins reference.

Claim of U.S. Patent No. 6,866,866	Basis for Invalidity
1. A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form, said dosage form being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof, wherein following oral administration of a single dose, the dosage form provides a mean time to maximum plasma concentration (Tmax) of the metformin from 5.5 to 7.5 hours after administration following dinner.	Obvious Under 35 U.S.C § 103(a) WO 99/47125 (Cheng *et al.*, Ex. 1002) teaches a controlled release oral dosage form comprising metformin hydrochloride for the reduction of serum glucose levels in human patients suffering from NIDDM suitable for once-a-day oral administration. The dosage forms described in Cheng *et al.* are identical in composition to the examples provided in the '866 patent (*vide supra*) except for an additional laser-drilled hole. The '866 patent admits that Cheng *et al.* "discloses controlled release metformin formulations providing a Tmax from 8 to 12 hours".[46] Timmins, WO 99/47128 (Ex. 1003),

[45] WO 99/47128, p. 29, lines 23-25.

[46] '866 patent col. 2 ll.46-47.

	teaches controlled release metformin compositions with a Tmax range of 4-8 hours of a single dose after dinner administration.[47] "Although Timmins expressly discloses a median Tmax [of 5 hours], it also provides the raw data from which one skilled in the art could compute the range of possible mean Tmax values…Based on this data, one skilled in the art would understand that the mean Tmax in Timmins *must fall between 4.67 and 6.33 hours*."[48] *[Emphasis added]* "Timmins also identifies a number of benefits stemming from an earlier extended release, including 'reduction in dosing frequency, providing patient convenience that would probably improve compliance' as well as 'an extended time period over which therapeutically beneficial plasma levels of drug were maintained'. These benefits would motivate one skilled in the art to modify Cheng to achieve a lower Tmax range. Cf. KSR, 550 U.S. at 424."[49] "Timmins thus teaches one skilled in the art to lower the Tmax of Cheng (8 hours)."[50] To achieve this reduction in Tmax, using any of the tablets described in Cheng *et al.*, the artisan would merely

[47] WO 00/47128 (Ex. 1002), p. 34, line 28.

[48] CAFC Opinion [2012-1228], p. 14, 2nd ¶. (Ex. 1005)

[49] Fed. Cir. [2012-1228], p. 15.

[50] *Id.*, p. 14.

	need to drill a second hole to achieve a more rapid release rate of drug, so as to obtain a Tmax taught by Timmins. "During the prosecution of the application the applicant indicated that one skilled in the art would be able to manipulate the processes and formulations of the [prior art] by other methods to obtain the claimed pharmacokinetic parameters of the present invention by routine experimentation."[51] See also Ex. 1010, Prosecution File History of Application Ser. No. 09/705,630, Amendment Under 37 C.F.R. § 1.111, February 24, 2003, p. 6 (bottom) to p.10, top. In particular, Applicants state that "[t]herefore, it is respectfully submitted that once the Tmax range which provides for a useful dosage form has been established, other controlled release technologies known in the art can be manipulated and tested to achieve this Tmax range without undue experimentation as discussed below."[52] The established Tmax range taught to the artisan by Timmins is within the range claimed in claim 1, and there was motivation to combine the

[51] *Id.*, p. 15-16.

[52] Amendment Under 37 C.F.R. § 1.111, February 24, 2003, Prosecution File History of Application Ser. No. 09/705,630, p. 7 (top). (Ex. 1010)

	teachings of Timmins with that of Cheng to produce a T_{max} value within the claimed range. Because the modification of Cheng to produce the desired T_{max} range required no more than routine modification, claim 1 is obvious under 35 U.S.C § 103(a).
2. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after the administration of the dose.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. The Tmax value 6.33 hours taught by Timmins is within the claimed range of 6.0 to 7.0 hours.
3. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (Tmax) of metformin at from 5.5 to 7.0 hours after the administration of the dose.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. The T_{max} value 6.33 hours taught by Timmins is within the claimed range of 5.5 to 7.0 hour.
4. The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C: 0-30% of the metformin or salt thereof is released after 2 hours; 10-45% of the metformin or salt thereof is released after 4 hours; 30-90% of metformin or salt thereof is released after 8 hours; not less than 50% of the metformin or	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. The claim limitations are those needed for an *in vitro* release rate to produce a T_{max} in the range claimed, and would be routinely established by an artisan of ordinary skill in the art, modifying the dosage forms of WO 99/47125 according to the instruction of Timmins, WO 99/47128.

salt thereof is released after 12 hours; not less than 60% of the metformin or salt thereof is released after 16 hours; and not less than 70% of the metformin or salt thereof is released after 20 hours.	
5. The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C: 0-25% of the metformin or salt thereof is released after 2 hours; 20-40% of the metformin or salt thereof is released after 4 hours; 45-90% of the metformin or salt thereof is released after 8 hours; not less than 60% of the metformin or salt thereof is released after 12 hours; not less than 70% of the metformin or salt thereof is released after 16 hours; and not less than 80% of the metformin or salt thereof is released after 20 hours.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. The claim limitations are those needed for an *in vitro* release rate to produce a Tmax in the range claimed, and would be routinely established by an artisan of ordinary skill in the art, modifying the dosage forms of WO 99/47125 according to the instruction of Timmins, WO 99/47128.
6. The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 4.5 to about 13 hours.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. The PK limitations in the claim are merely the result of measuring the result of the claimed dosage form after oral administration and are inherent in its composition and

	structure and release rate. The oral dosage forms exemplified in WO 99/47125 (Cheng *et al.*) are identical in composition to the corresponding dosage forms exemplified in the '866 patent and claimed in claim 1. Having routinely modified release rate of the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 6.
7. The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 5.5 to about 10 hours.	Invalid under 35 U.S.C. § 103(a) Arguments for claim 1 are repeated. *Ibid.* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 7.
8. The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of metformin which is more than about 7 times the mean plasma level of said metformin at about 24 hours after the administration.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid.* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 8.
9. The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of metformin which is from	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated.

about 7 times to about 14 times the plasma level of said metformin at about 24 hours after administration.	*Ibid.* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 9.
10. The controlled release oral dosage form of claim 1 which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 8 times to about 12 times the plasma level of said metformin at about 24 hours after administration.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid.* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 10.
11. The controlled release oral dosage form of claim 1 which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 11 upon administering a 2000 mg once-a-day dose.
12. The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid.* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the T_{max} values taught by WO 00/47128, the

	modified dosage form would inherently meet the limitations of claim 12 upon administering a 2000 mg once-a-day dose.
13. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ of at least 80% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the T_{max} values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 13.
14. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ of at least 90% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid.* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the T_{max} values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 14.
15. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid.* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the T_{max} values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 15 upon administering a 2000 mg once-a-day dose.

16. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid.* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the T_{max} values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 16 upon administering a 2000 mg once-a-day dose.
17. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ from about 19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid.* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 17 upon administering a 2000 mg once-a-day dose.
18. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}\infty}$ of 18277±2961 ng.hr/ml and a mean C_{max} of 1929±333 ng/ml, for administration of a 1700 mg once-a-day dose of metformin after an evening meal.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 18 upon administering a 1700 mg once-a-day dose after an evening meal.

19. The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0-\infty}$ of 20335±4360 ng.hr/ml and a mean C_{max} of from 2053±447 ng/ml, for administration of a 2000 mg once-a-day dose of metformin after an evening meal.	a) Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 19 upon administering a 2000 mg once-a-day dose after an evening meal.
20. The controlled release oral dosage form of claim 1 which provides a mean AUC_{0-24} of 26818±7052 ng.hr/ml and a mean C_{max} of 2849±797 ng/ml, for, administration of a 2000 mg once-a-day dose of metformin after an evening meal.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 20 upon administering a 2000 mg once-a-day dose after an evening meal.
21. The controlled release oral dosage form of claim 1 which provides a mean AUC_{0-24} of 22590±3626 ng.hr/ml and a mean C_{max} of 2435±630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136±7996 ng.hr/ml and a mean C_{max} of 2288±736 ng/ml on the 14^{th} day of administration, for administration of a 2000 mg once-a-day dose of metformin after an evening meal.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid* Having routinely modified the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 21 upon administering a 2000 mg once-a-day dose after an evening meal.

22. The controlled release oral dosage form of claim 12 which provides a mean $t_{1/2}$ from 2.8 to 4.4.	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 and 12 are repeated. *Ibid* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 22. Additionally, $t_{1/2}$ is not a patentable property of the dosage form; it is an inherent property of metformin itself.
23. The controlled release oral dosage form of claim 6, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 6.0 to 7.0 hours after the administration.	a) Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 and claim 6 are repeated. *Ibid* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet the limitations of claim 23.
24. The controlled release oral dosage form of claim 6, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 5.5 to 7.0 hours after administration.	a) Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 and claim 6 are repeated. *Ibid* Having routinely modified release rate of the dosage forms of Cheng et al. to meet the Tmax values taught by WO 00/47128, the modified dosage form would inherently meet

	the limitations of claim 24.
25. The controlled release dosage form of claim 1, wherein the metformin or pharmaceutically acceptable salt thereof is provided by at least one controlled-release tablet, said tablet comprising: (a) a core comprising: (i) the metformin or a pharmaceutically acceptable salt; (ii) optionally a binding agent; and (iii) optionally an absorption enhancer; (b) a membrane coating surrounding the core; and (c) at least one passageway in the membrane.	a) Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. WO 99/47125 discloses a controlled release tablet,[53] wherein: said tablet comprises: (a) a core comprising: (i) an antihyperglycemic drug (metformin) or a pharmaceutically acceptable salt; (ii) optionally a binding agent; and (iii) optionally an absorption enhancer; (b) a membrane coating surrounding the core; and (c) at least one passageway in the membrane, matching the limitations of claim 25

X. THE CLAIMED DOSAGE FORM DOES NOT PRODUCE UNEXPECTED RESULTS.

197. Regarding "unexpected results," counsel has informed me that "unexpected results" may be used to rebut a *prima facie* case of obviousness when the result is both significant and proffer a practical advantage when the prior art is taken into account.

198. I understand that these "unexpected results" must be correlated with the invention asserted in the claims, and commensurate therewith, and that these unexpected results must be different in kind and not merely in degree.

[53] WO 99/47125 (Ex. 1002), p. 3, lines 25-34; *e.g.*, page 10, line 1- page 12, line 10.

199. I note that the Patent Owner when given a chance to explain an unexpected result in respect of the pharmacokinetic parameters set forth in the continuations recited above in respect of U.S. Patent No. 6,866,866 ("'866 patent") failed to do so.

200. I also can divine no unexpected results associated with the specific pharmacokinetic parameters recited in claims 1 -25 of the '866 patent, either from my review of the literature, the specification of the '866 patent or the file history leading to the '866 patent.

201. I was also informed by counsel, that beyond an unexpected result, other secondary considerations may support patentability depending on strength and numerosity of such considerations. Beyond unexpected results, I understand other secondary considerations that may support patentability include long-felt need, commercial success, failure of others to find a solution to the problem, skepticism by experts in regard to resolution of the problem, praise by others directly attributed to the claimed subject matter, teaching away by others from employing the claimed subject matter in the manner specified, recognition of a problem not discerned by others, and copying of the invention by competitors.

202. I understand from counsel that for any secondary consideration to be probative of the issue of obviousness, there must be an established nexus between novel elements in the claim and asserted factor that argues against obviousness.

203. From my review of the literature of the many years I have been in the field, taking into account both my clinical expertise in pharmacy, and my expertise in pharmacokinetics and pharmacology, I find none of these factors to support non-obviousness.

Nor did I find any support for such secondary considerations, and a nexus to that cited in any of the claims of the '866 patent, in the specification of the '866 patent or in the file history leading to the '866 patent.

XI. CONCLUDING STATEMENTS

205. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

206. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: June 19, 2017

By: _____
Dr. Fatemeh Akhlaghi
Professor
University of Rhode Island School of Pharmacy

XII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent 6,866,866
1002	WO 99/47125 ("Cheng")
1003	WO 99/47128 ("Timmins")
1004	U.S. Patent 6,099,859
1005	Prosecution File History of U.S. Patent 6,866,866 (Application No. 09/705,630)
1006	Fed. Cir. [2012-1228] (July 2, 2012)
1007	WO 00/12097 ("Chen")
1008	Lupin Settlement
1009	Mylan Settlement
1010	Amendment Under 37 C.F.R. 1.111 (dated February 24, 2003), Application No. 09/705,630,
1011	U.S. Patent No. 6,475,521
1012	Labelling NDA 21202 (GLUCOPHAGE® AND GLUCOPHAGE® XR)
1013	U.S. Patent 5,955,106 ("Moeckel")

1014	WO 00/28989 ("Lewis")
1015	U.S. Patent 6,284,275
1016	U.S. Patent 6,009,862
1017	U.S. Patent 3,845,770
1018	Remington, 1995 ("Chiao")
1019	Akhlaghi Declaration (this document)
1020	*CV* of Professor Akhlaghi