Paper No.: ____
June 22, 2017

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(s)

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

PETITION FOR *INTER PARTES* REVIEWOF U.S. PATENT NO. 6,866,866 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42.1-.80, 42.100-.123

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IPR2017-00_____

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PETITIONERS' EXHIBIT LIST

Exhibit No.	Description
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1002	WO 99/47125 ("Cheng *et al*.")
1003	WO 99/47128 ("Timmins *et al*.")
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 *et al*.")
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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®)
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1019	Declaration of Dr. Fatemeh Akhlaghi
1020	CV of Dr. Fatemeh Akhlaghi

Pursuant to 35 U.S.C. § 311 and 37 C.F.R. Part 42, Aurobindo Pharma USA Inc. ("Petitioner") respectfully petitions for *Inter Partes* Review of U.S. Patent No. 6,866,866 ("the '866 Patent") (EX1001) which is co-assigned to Andrx Corporation *et al*., subsidiaries of Teva Pharmaceutical Industries Ltd. ("Patent Owner"), seeking cancellation of claims 1-25 thereof.

I. PAYMENT OF FEES

Pursuant to 37 C.F.R. section 42.103, these fees are being paid at the time of filing this petition, charged to Deposit Account 506744. Should any further fees be required by the present Petition, the Patent Trial and Appeal Board ("PTAB") is hereby authorized to charge the above referenced Deposit Account.

II. INTRODUCTION

A. Brief Overview of The '866 Patent

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.

The Abstract of '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."

It is further stated 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, lines 34-42)

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.

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." Col 12, lines 42-46.

Thereby 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.

Further, during the prosecution of the application for the '866 patent the inventors 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:[1]

> "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*

[1] Amendment Under 37 C.F.R. 1.111, February 24, 2003, Application No. 09/705,630 (EX1010).

> *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*."[2] *[Emphasis added]*

Thus, the applicant (Andrx Labs, LLC), 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.

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.

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

[2]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.

> 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.

Dr. Akhlaghi, in her declaration states (EX1019, ¶ 26) "With respect to claim 1 and its dependent claims…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."

As claims 2 – 25 are either directly or indirectly dependent on claim 1, 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. Because the pharmacokinetic parameters were already associated with or inherent in other known controlled release dosage forms, such could not be said to be non-obvious.

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 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 ^{o}C.

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).

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.

With regard to these additional pharmacokinetic parameters as recited in the dependent claims, Dr. Akhlaghi states (EX1019, ¶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."

B. Critical Date

The ‘866 patent derives from U.S. Patent Application Serial No. 09/705,630, filed on November 3, 2000. Thus, the critical date for the ‘866 patent is November 3, 2000.

III. STANDING (37 C.F.R. 42.104(a)); PROCEDURAL STATEMENTS

Petitioner certifies that (1) the ‘866 patent is available for IPR; and (2) Petitioners are not barred or estopped from requesting IPR of any claim of the ‘866 patent on the grounds identified herein. The required fee is paid through the Patent Review Processing System, as set forth above.

IV. MANDATORY NOTICES (37 C.F.R. 42.8(a)(1))

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

The real parties-in-interest for Petitioner are Aurobindo Pharma USA Inc. and Aurobindo Pharma Ltd.

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

1. Judicial Matters Involving the ‘866 Patent

On January 25, 2017, Patent Owner filed a complaint against Aurobindo in the District of Delaware (EX1007) asserting infringement of the ‘866 patent in the action *Shionogi Inc. and Andrx Labs. L.L.C. v. Aurobindo Pharma Ltd. et al.*, Civ. Act. No. 1:17-cv-00072-UNA (D. Del. 1-25-17).

The '866 patent has been the subject of extensive previous litigation, both in the District of Delaware, the Federal Circuit (EX1006), and in the District of

New Jersey, all of which has settled. *Sciele Pharma Inc. et al. v. Lupin Ltd, et al.*, D. Del. 1:09-cv-00037; *Shionogi Pharma Inc. et al. v. Mylan Inc., et al.*, D. Del. 1:10-cv-00135; *Shionogi Inc. et al. v. Nostrum Laboratories, Inc., et al.*, D.N.J. 1:12-cv-04402. The Federal Circuit ruled, in 2012, regarding the asserted claims of the '866 patent that "Cheng in view of Timmins [r]aises a [s]ubstantial [q]uestion of [v]alidity" (EX1006, p. 12) and remanded the case back to the District of Delaware for reconsideration. Plaintiffs Sciele Pharma Inc. (now Shionogi Pharma Inc.) and Andrx *et al.* subsequently settled with Defendants Lupin *et al.* (EX1008) and Mylan *et al.* (EX1009), Defendant Lupin being allowed by settlement to market its generic Fortamet drug as of September 1, 2011 and Mylan being allowed by settlement to market its generic Fortamet drug as of August 1, 2013.

2. Administrative Matters

Petitioner Aurobindo is not aware of any other pending administrative matters regarding IPR petitions for U.S. Patent No. 6,866,866.

C. Designation of Lead and Back-up Counsel (37 C.F.R. § 42.8(b)(3) and (b)(4).

Petitioner provides the following designation and service information. Petitioner respectfully requests that all correspondence related to this proceeding be sent to lead and back up counsel at the email addresses listed below. (37 C.F.R. § 42.8(b)(4)):

LEAD COUNSEL	BACK-UP COUNSEL
Steven J. Moore, Esq. (Reg. # 35,959) Email: steven.moore@withersworldwide.com Withers Bergman LLP Suite 400 1700 East Putnam Avenue Greenwich, CT 06870 Tel.: (203) 302-4069 Fax: (203) 302-6609	John Winterle (Reg. # 57,276) Email: john.winterle@withersworldwide.com Withers Bergman LLP Suite 400 1700 East Putnam Avenue Old Greenwich, CT 06870 Tel.: (203) 328-2225 Fax: (203) 285-1652
	Hans Peter Hoffmann (Reg. # 37,352) Email: peter.hoffmann@withersworldwide.com Withers Bergman Suite 400 1700 East Putnam Avenue Old Greenwich, CT 06870 Tel.: (203) 302-4076 Fax: (203) 302-6609
	Alan Gardner (Reg. # 69,495) Email: alan.gardner@withersworldwide.com Withers Bergman Suite 400 1700 East Putnam Avenue Old Greenwich, CT 06870 Tel.: (203) 302-4085 Fax: (203) 302-6609

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

Petitioner hereby consents to electronic service. Service should be made to the lead counsel and back-up counsel as noted above, as well to IPG-AUR@withersworldwide.com.

Correspondence can be sent by mail to lead counsel at the above address.

V. INDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

IPR of claims 1-25 of the '866 patent is requested on the grounds of unpatentability listed below. Per 37 C.F.R. § 42.6(d), copies of references are filed herewith. In support of the proposed grounds for unpatentability, this Petition includes the declaration of a technical expert, Dr. Akhlaghi (EX1019), explaining what the art would have conveyed to a POSA. Professor Akhlaghi is an expert in the field of pharmaceutical formulations and pharmacokinetics.

VI. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR IN RESPECT OF EACH CHALLENGED CLAIM (37 C.F.R. § 42.22(a))

Petitioner requests IPR of all of claims 1 – 25 of the '866 patent, and cancellation of the same, under 35 U.S.C. § 311 and AIA §6, on the following grounds:

References	Basis	Claims Challenged
Ground 1: Claims 1-25 Are Unpatentable Under 35 U.S.C. § 102 Over WO 00/12097 (EX1007) As Being Anticipated.	35 U.S.C. § 102	All challenged claims
Ground 2: Claims 1-3 Are Unpatentable Under 35 U.S.C. § 102 Over View of WO 99/47128 (EX1003) As Being Anticipated.	35 U.S.C. § 102	Claims 1-3
Ground 3: Claims 1-25 Are Unpatentable Under 35 U.S.C. § 103(a) As Being Obvious Over WO 99/47125 (EX1002)	35 U.S.C. § 103	All challenged claims.

In View of WO 99/47128 (EX1003)		

VII. PERSON OF ORDINARY SKILL IN THE ART IN RESPECT OF U.S. PATENT NO. 6,866,866

As explained in the Declaration of Professor Akhlaghi (EX1019, ¶¶ 91-96), a POSA with respect to the '866 patent in the relevant field as of November 3, 2000 a POSA 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.

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

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

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. 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.

This Petition is supported by the declaration of Professor Akhlaghi who received her Ph.D. from the University of Sydney. (EX1019)

VIII. BACKGROUND OF TECHNOLOGY AND PRIOR ART

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). Metformin is an antihyperglycemic (glucose-lowering) agent which improves glucose tolerance in patients with type 2 diabetes.

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 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.

Further, 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.[3] As such the POSA would have been aware of the advantages of evening administration of an antihyperglycemic drug, with extended drug release, such that the maximum drug concentration (C_{max}) is reached at a time (T_{max}) when gluconeogenesis peaks.

At least one immediate release dosage form "GLUCOPHAGE®" and at least one controlled release dosage form for metformin, "GLUCOPHAGE XR®," a competitor product to FORTAMET® (covered by the '866 patent) with overlapping release and pharmacokinetic characteristics to those claimed in the '866 patent, had already been approved for marketing by Bristol-Myers Squibb in the United States by October 2000.[4] GLUCOPHAGE® is referenced in the '866

[3] *Id*., col. 5, lines31-32.
[4] 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

patent (and elsewhere) in the prior art as a comparator product. Andrx would have been alerted to the release characteristics of the GLUCOPHAGE XR® product because of their competition for the same NIDDM market.

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," EX1007) published on March 9, 2000; WO 1999/047125 to Cheng *et al.* ("Cheng", EX1002) with an international publication date of Sept. 23, 1999, and WO 99/47128 to Timmins *et al.* ("Timmins", EX1003) which published on September 23, 1999. These three references are discussed in detail below. The additional prior art references listed in Appendix XIII of Dr. Akhlaghi's declaration (EX1019) would also have been known to the POSA.

Chen *et al*., WO 00/12097 in Example 3 teaches tablets which are objectively 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. The tablets of WO 00/12097 are 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. Such a minor amount of glipizide would be recognized by a POSA as not contributing to a change of the pharmaceutical parameters associated with metformin release. (Akhlaghi Declaration, EX1019, ¶ 135)

As for the dosage forms described in the '866 patent, 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) in both the WO/12097 publication and the '866 patent.

WO 00/12097 notes that the disclosed tablets provide continuous therapeutic levels of an antihyperglycemic drug over a twelve or twenty four hour period,[5] the same as evidenced by the '866 patent in Figures 1, 2 and 4.

A. Claims 1-25 of the '866 Patent are Unpatentable under 35 U.S.C. § 102(a) over Chen, WO 00/12097

Dr. Akhlaghi specifically compares compositions of the 850 mg tablets of Example 1 of WO 00/12097 and Example 2 of the '866 patent. Akhlaghi Declaration, EX1019, ¶ 132). The compositions are seen to be essentially identical with respect to core and membrane composition, drug content, and excipient content and type.

The tablet of Example 1 of Chen (WO 00/12097) comprises two laser drilled

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

passageways[6] ("holes") as does the device claimed the '866 patent.[7] Except for a small amount of glipizide, the Dr. Akhlaghi notes that tablets are objectively identical to Example 2 of the '866 patent, also an 850 mg tablet, differing slightly only in that the core of the latter comprises a small fraction, about 0.5%,[8] of the sulfonylurea drug, glipizide, while the patented device of the '866 patent lacks glipizide. In Dr. Akhlaghi's opinion (EX1019, ¶ 135), this additional, very minor core component has no significant effect on the function of the tablet of Example 1 of WO 00/12097 with regards to the pharmacokinetic properties of metformin, when compared to tablets claimed in the '866 patent. 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 in the tablet core, such as glipizide.

The release rate of metformin from Example 1 of WO 00/12097 conforms to the preferred limitations claimed in the '866 patent. The following table demonstrates that fact:

[6] *Id*., p. 14, lines 9-10.
[7] U.S. Patent No. 6,866,866, col. 15, lines 7-8.
[8] 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.

	% Metformin Released,	
Time (hours)	WO 00/12097, EX1, 850 mg[9]	'866 Patent Preferred Release Limit[10]
0	0	0
2	17	0-30
4	32	10-45
8	56	30-90
12	76	NLT 50
16	89	NLT 60
20	-[11]	NLT 70

Further, 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, EX1, 850 mg[12]	'866 Patent Most Preferred Release Limit[13]
0	0	0
2	17	0-25
4	32	20-40
8	56	45-90
12	76	NLT 60
16	89	NLT 70

[9]WO 00/12097, p. 14, lines 11-22.
[10] U.S. Patent No. 6,866,866, col. 12, lines 24-32. Also see, claim 4.
[11] 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.
[12] WO 00/12097, p. 14, lines 11-22.
[13] U.S. Patent No. 6,866,866, col. 12, lines 24-32. Also see, claim 5.

20	-[14]	NLT 80

Thus, the preferred and most preferred release limitations are met in every case.

As Dr. Akhlaghi concludes (EX1019, ¶ 144) "…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 and structurally identical and will behave identically *in vivo*…[and thus the POSA]…would expect the other pharmacokinetic parameters recited in the dependent claims of the '866 patent to be the same when the same dosage of metformin was administered by either tablet."

B. Claims 1-3 Of The '866 Patent Are Unpatentable As Anticipated Under 35 U.S.C §102(a) Over Timmins, WO 99/47128 (EX1003)

Timmins *et al.,* WO 99/47128 is prior art. Timmins 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. 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 teaches a T_{max} range of 4-8 hours, with a median (not mean) T_{max} of 5 hours for a single dose

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

after dinner administration.[15]

Example 3 of Timmins 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,[16] wherein with oral administration after dinner provides a T_{max} in the range of 4-8 hours, with median T_{max} of 5 hours.[17]

From the data of Timmins, the POSA would understand that a mean T_{max} of between 4.67 and 6.33 hours is taught, according to the Federal Circuit review and opinion of 2012 on the '866 patent in *Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1261 (Fed. Cir. 2012) (EX1006). The T_{max} of Timmins overlaps and intrudes into each of the ranges claimed by claims 1-3 of the '866 patent. Claims 1-3 of the '866 patent are taught in every detail by Timmins and are, therefore, anticipated by Timmins.

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 focused on the Timmins reference and would have understood its significance and teaching, and would have wanted to match its Tmax, so as to produce a product asserted in claims 1 – 3 of the '866 patent.

[15] WO 99/47128, p. 34, lines 28-29.
[16] WO 99/47128, p. 32, line 20-p. 33, line8.
[17] *Id*., p. 34, line 29.

C. Claims 1-25 Of The '866 Patent Are Unpatentable As Obvious Under 103 Over Cheng WO 99/47125 (EX1002) In Light Of Timmins WO 99/47128 (EX1003)

Cheng *et al*., WO 99/047125 is prior art. 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).[18] As such, the publication discloses the same tablet structure later taught in WO 00/12097[19] as well as the tablet later claimed in the '866 patent.[20] These tablets are each constructed in the same fashion, with a unitary core surrounded by a semipermeable membrane with at least one passageway in the membrane.

Dr. Akhlaghi's calculations (EX1019, ¶ 149) again show the composition and structure of the 850 mg tablet of Example 3 of WO 99/47125 to be essentially identical to that described in the '866 patent. This identity extends to the type, qualities and amounts of excipients used.

WO 99/47125 discloses a tablet comprising metformin hydrochloride that is essentially identical to that described in the '866 patent in terms of the types and

[18] See also, WO 99/47125, p. 3, lines 25-33.
[19] WO 00/12097, p. 4, line 15-p. 5, line 2.
[20] '866 Patent, claim 25.

amounts of excipient components, and releases metformin approximately the same as the tablets disclosed in the '866 patent. A small difference might be expected by the POSA expected by the POSA as the 850 mg tablet of Example 3 of WO 99/47125 may evidence one laser drilled hole,[21] while that of Example 2 of the '866 patent shows two laser drilled holes. This would be expected by a POSA to lead to a faster rate of release of metformin from the tablets of the '866 patent.

The osmotic device of WO 99/47125 (Example 3) is said to 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). Although the device is stated to provide a T_{max} of 8-12 hours,[22] 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).

Dr. Akhlaghi concludes that if there is a significant structural difference between the tablets of the '866 patent and Example 3 of WO 99/47125 that would comprise the possible extra passageway ("laser-drilled hole") which would be expected to provide for a nominal increased rate of release of metformin.

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[21] *Id.*, p. 15, lines 10-16. Dr. Akhlaghi notes that it is not clear what is meant by "an additional hole" as the example reference mentions no hole (EX1019 ¶ 148). This may mean there was only one hole or may mean there were two holes.
[22] *Id.*, p. 3, lines 14-17.

Dr. Akhlaghi concludes that if there is a significant structural difference that "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." (EX1019, ¶ 155) As stated by the Applicants in the prosecution file history of the '866 patent (EX1010, p. 7- p. 8), could easily match the T_{max} values *in vivo*, "irrespective of the technology employed."

The only modification needed for the POSA to closer match the invention of the '866 patent with the Example 3 of WO 99/47125 would be a trivial, that is, to drill an additional hole in the tablet, or if there are two holes being defined in WO 99/47125 to drill them exactly the same, an option plainly suggested by the language of the WO 99/47125 publication. (EX1002; Akhlaghi Declaration, EX1019; ¶¶ 148). Once this change is made, a POSA would expect the T_{max} of the altered product to be concisely within the Tmax range recited in claim 1, and to match the other pharmacokinetic parameters recited in the claims dependent on claim 1 of the '866 patent (i.e., claim 2 – 25). The Federal Circuit court previously ruled on the significance of Timmins and Cheng combination in *Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1261 (Fed. Cir. 2012) (EX1006)**.** The Federal Circuit concluded there was more than sufficient motivation to combine the Cheng and Timmins references to arrive at the invention of the '866 patent.

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)." (EX1006, p. 14)

Thus, as stated by the Federal Circuit court, 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. Once the tablet of WO 99/47125 was altered to lead to the T_{max} of the '866 patent a POSA would expect the other pharmacokinetic parameters recited in the dependent claims to claim 1 (Akhlaghi Declaration,

EX1019, ¶ 177), thereby making the same obvious as well.

IX. CLAIM CONSTRUCTION IN LIGHT OF POSA

A. Claim Construction Standard

At the Patent Trial and Appeal Board ("PTAB") in the context of an IPR, 37 C.F.R. § 42.100(b) instructs that claims are to be construed in accord to the "broadest reasonable interpretation." Thus, 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.

1. "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)

2. "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)

3. "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)

4. "bed time"

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)

5. "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)

6. "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)

7. "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)

8. "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)

9. "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)

10. "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)

11. "$t_{1/2}$"

The term "$t_{1/2}$" as used in the patent is the time required for the plasma concentration of metformin to decrease to ½ of its previous concentration measured at an earlier testing point, usually C_{max}. The POSA understands $t_{1/2}$ is an intrinsic pharmaceutical property of metformin, as it interacts uniquely with various dissipative mechanisms in a body, and is independent of the dosage form used to deliver metformin

12. "AUC"

The term "AUC" as used herein, means 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)

13. "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)

14. "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)

15. "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)

16. "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)

17. "mean",

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

18. "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 an 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 be equal.

19. "Degree of Fluctuation"

The term "Degree of Fluctuation" is expressed as (Cmax−Cmin)/Cavg. (*Id.* col. 8, ll. 12-13)

20. "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) .

21. "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).[23] Flux enhancers (*i.e.*, PEG 400) may be added to the membrane to increase its porosity.[24] Drug may be released through mechanical holes or passageways in the porous membrane in solution or *in vivo*.[25]

[23] U.S. Patent No. 6,866,866, col. 10, lines 35-41.
[24] *Id.*, col. 10, lines 53-63
[25] *Id.*, col. 11, lines 53-59.

22. "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.[26]

Having assessed the meaning of the ‘866 patent claims, we now assess 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. We then determine whether the ‘866 patent claims would have been anticipated or obvious to a person having ordinary skill in the art.

X. DETAILED ANALYSIS OF GROUNDS FOR TRIAL

A. Ground 1: Claims 1-25 Are Unpatentable Under 35 U.S.C. § 102 Over Chen WO 00/12097 (EX1007) As Being Anticipated.

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 in addition to the T_{max} of 5.5-7.5 hours.

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. (Akhlaghi Declaration, EX1019, ¶ 167) The other pharmacokinetic parameters cited in claims

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

2-25 are also empirical, inherent properties of the physical structure and release rate of drug from the claimed dosage form (*Id*.). A dosage form with the same composition and physical structure, also meeting the required rate for drug release, would likewise inherently show each and all of the PK characteristics inherent in the dosage forms claimed in the '866 patent.

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.

When tested by the same dissolution method, the release of metformin from the tablets of Example 1 of WO 00/012097 met the preferred and most preferred limitations for *in vitro* release required by the '866 patent in claim 5, dependent on claim 1 (see pp. 21-22, above). These preferred and most preferred limitations were specified by the inventors to provide a mean T_{max}, as in claim 1, of 5.5-7.5 hours after administration after dinner ('866 patent, EX1001, col. 12, lines 24-33; also claims 4 and 5, col 22, lines 1-53)

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. (Akhlaghi Declaration, EX1019, ¶ 170)

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 ¶ 98 of Dr. Akhlaghi's declaration. The weight fractions of metformin HCl and the excipient components are essentially identical in the core and sustained release coating of both the 850 mg tablets in each case.

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. The tablet of Example 1 of WO 00/12097 objectively differs from the device claimed in the '886 patent only 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. In Dr. Akhlaghi's opinion, this is not a significant difference because of the very small concentration of glipizide (EX1019, ¶ 173).

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 such as glipizide.

When tested using the same *in vitro* dissolution testing methodology,[27] the release rate of Example 1 of WO 00/12097 meets the preferred and most preferred limitations taught in the '866 patent. Because T_{max} will depend upon the release

[27] USP Type 2 Apparatus, 75 RPM, 900 ml. simulated gastric fluid, 37 ^{o}C.

rate of metformin from the dosage device, all other elements of the tablets being closely identical, the release equivalence requires that the two tablets will produce an equivalent *in vivo* T_{max}, according to claims 1, 4 and 5 of the patent. (Akhlaghi Declaration, EX 1019, ¶ 176) With the close identity 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, the pharmacokinetic properties recited in claims 1-25, would be inherent in the properties of the Tablet 1 of WO 00/12097. (Akhlaghi Declaration, EX 1019, ¶ 177)

Given such close identity, Tablet 1 of WO 00/12097 inherently anticipates claims 1-25 of the '866 patent. An 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	Anticipated Under 35 U.S.C § 102 over Chen, WO 00/12097 (EX1007) "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

metformin from 5.5 to 7.5 hours after administration following dinner.	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)" *[Emphasis added]* 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

<table>
<tr><td></td><td>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. (vide infra)</td></tr>
<tr><td>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.</td><td>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. (vide infra)</td></tr>
<tr><td>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</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 for metformin release 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[28] as follows:

METFORMIN HCl RELEASE

<table><tr><th>TIME (hours)</th><th>% Released (pH 7.5)</th></tr><tr><td>2</td><td>17</td></tr><tr><td>4</td><td>32</td></tr><tr><td>8</td><td>56</td></tr><tr><td>12</td><td>76</td></tr><tr><td>16</td><td>89</td></tr></table>
The tablet of Example 1 meets the release limitations of claim 4 and inheriting the limits of claim 1, requires a T_{max} of 5.5-7.5 hours.</td></tr>
</table>

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

<table>
<tr><td>hours;
and not less than 70% of the metformin or salt thereof is released 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 for metformin release 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[29] 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 inheriting the limits of claim 1, requires 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 close identity 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>

[29] 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 identity 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 identity 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 identity 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 identity 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 identity 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 identity 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_{0-24hr} of at least 80% of the mean AUC_{0-24} 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 identity 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.
14. The controlled release oral dosage form of claim 1 which	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated.

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.	Because of the close identity 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 identity 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 identity 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	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identity between the dosage form of Example 1 of WO

administration of a 2000 mg once-a-day dose of metformin.	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 $AUC_{0-\infty}$ 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 identity 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 $AUC_{0-\infty}$ 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 identity 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 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.	Anticipated under 35 U.S.C. § 102. Arguments from claim 1 are repeated. Because of the close identity 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 identity 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 identity 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	Anticipated under 35 U.S.C. § 102. Arguments from claims 1 and 6 are repeated. Because of the close identity between

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

B. Ground 2: At Least Claims 1-3 Are Unpatentable Under 35 U.S.C. § 102 Over Timmins WO 00/47128 (EX1003) As Being Anticipated.

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,[30] wherein with oral administration after dinner provides a T_{max} in the range of 4-8 hours, with median T_{max} of 5 hours.[31] 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.

From the data of Timmins, the POSA would understand a mean T_{max} of between 4.67 and 6.33 hours is taught, according to the Federal Circuit review and opinion of 2012 on the '866 patent. (EX1006, p. 14.) The T_{max} of Timmins overlaps and intrudes into each of the ranges claimed by claims 1-3 of the '866 patent. (Akhlaghi Declaration, EX1019, ¶ 183)

Claims 1-3 of the '866 patent are taught in every detail by Timmins and are, therefore, anticipated by Timmins. The following claim chart is provided.

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	Anticipated Under 35 U.S.C § 102 WO 99/47126 (Timmins, EX1003) teaches a controlled release oral dosage form with controlled release carriers comprising metformin hydrochloride for the reduction of serum glucose levels in human

[30] WO 99/47128, p. 32, line 20-p. 33, line8.
[31] *Id*., p. 34, line 29.

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.	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 6.33 hours*."[32] The T_{max} 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 T_{max} 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 T_{max} value 6.33 hours taught by Timmins is within the claimed range of 5.5 to 7.0 hour.

[32] CAFC Opinion [2012-1228], p. 14, 2nd ¶. (EX1005)

C. Ground 3: Claims 1-25 are Unpatentable Under 35 U.S.C. § 103(a) As Being Obvious Over Cheng WO 99/47125 (EX1002) In View of Timmins WO 99/47128 (EX1003).

Of particular note, it was admitted by the inventors of the '866 patent there were numerous controlled release devices in the prior art that worked on the osmotic principle,[33] and it was also clearly stated in the prosecution file history that it would be merely routine to modify these older devices to obtain the proper release rate, leading to the patented claims (*vide supra*) if T_{max} were previously known. Given that admission, after extended litigation, the Federal Circuit ruled (EX1006, pp. 12-16) that there were substantial grounds of obviousness for invalidating the asserted claims of U.S. Patent No. 6,866,866 over WO 99/47125 (EX1002) in view of WO 99/47128 (EX1003).

Timmins (WO 99/47128) discloses an extended release tablet of metformin (hydrochloride) comprising a biphasic (non-osmotic) delivery system which 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.[34] Timmins disclosed a 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.[35]

The POSA would have known of the Timmins and Cheng publications, and

[33] *See* U.S. Patent No. 6,866,866, col. 1, lines 19-35.
[34] WO 99/47128, p. 34, lines 28-29.
[35] CAFC 2012-1228, EX1007, p. 14.

would have had motivation, according to the Federal Circuit,[36] to combine the teachings of Cheng with that of Timmins to reduce the T_{max} value of 8-12 hours of Cheng to around 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.[37]

Based on the composition and structure of the dosage form taught by Cheng this would have been easily accomplished by the POSA. The tablets are essentially compositionally identical, except for the additional laser-drilled hole in the tablets of the '866 patent.[38] 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. Such modifications were admitted to be "routine", and the POSA would have no difficulty matching the T_{max} value taught by Timmins and thereby reaching within the claims of the '866 patent.

The Federal Circuit has already ruled that "Cheng in view of Timmins creates a substantial question of validity" of the '866 patent.[39] 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

[36] *Id.*, pp. 14-15.
[37] *Id.*, pp. 15-16.
[38] Akhlaghi Declaration (EX1019, ¶ 192)
[39] CFAC 2012-1228, EX1006, p. 19.

produced.

Timmins teaches metformin dosages of 150 mg to 3000 mg daily, in 1, 2 and 4 divided doses.[40] Any dose adjustment required by the claims of the '866 patent is taught by Timmins. (Akhlaghi Declaration, EX1019, ¶ 195, p 69.)

Below is a claim chart providing bases for invalidity the claims 1-25 are invalid as obvious over the Cheng reference in view of the Timmins reference.

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

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*., EX1002) 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”.[41] Timmins, WO 99/47128 (EX1003), teaches controlled release metformin compositions with a Tmax range of 4-8 hours of a single dose after dinner administration.[42] "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*

[41] ’866 patent col. 2 ll.46-47.
[42] WO 00/47128 (EX1002), p. 34, line 28.

	6.33 hours."[43] *[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."[44] "Timmins thus teaches one skilled in the art to lower the Tmax of Cheng (8 hours)."[45] To achieve this reduction in Tmax, using any of the tablets described in Cheng *et al*., the artisan would merely 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

[43] CAFC Opinion [2012-1228], p. 14, 2nd ¶. (EX1005)
[44] Fed. Cir. [2012-1228], p. 15.
[45] *Id*., p. 14.

	experimentation."[46] See also EX1010, 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."[47] 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 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	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated.

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

[47] Amendment Under 37 C.F.R. § 1.111, February 24, 2003, Prosecution File History of Application Ser. No. 09/705,630, p. 7 (top). (EX1010)

concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after the administration of the dose.	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 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.	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.
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	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. The claim limitations are those

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.	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 about 7 times to about 14 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 9.
10. The controlled release oral dosage form of claim 1 which provides a mean maximum plasma concentration (C_{max})	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated.

of metformin which is from about 8 times to about 12 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 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	Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. *Ibid* Having routinely modified release

dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.	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_{0-24hr} of at least 90% of the mean AUC_{0-24} 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_{0-24hr} 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_{0-24hr} 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 $AUC_{0\text{-}\infty}$ 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.	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	a) Invalid under 35 U.S.C. § 103(a). Arguments for claim 1 are repeated. WO 99/47125 discloses a controlled release tablet,[48] wherein:

[48] WO 99/47125 (EX1002), p. 3, lines 25-34; *e.g.*, page 10, line 1- page 12, line 10.

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.	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

D. Objective Indicia of Non-obviousness

As stated by Dr. Akhlaghi in her declaration at ¶¶ 197-204 the bases cited by the examiner for allowing the claims do not support a finding that the ‘866 patent claims are valid for any indicia of non-obviousness including: 1) there was no long felt need for the purported invention; 2) no evidence of commercial success can overcome the showing of obviousness; 3) other “unexpected results” fail to rebut the strong showing of obviousness

Regarding "unexpected results" the Patent Owner stated in the '866 patent that:

> "[i]t has surprisingly been found that when biguanides such as metformin are administered orally in a controlled release dosage form suitable for once-a-day dosing in the 'fed' state, preferably at dinner, the bioavailability is improved as compared to the administration of the controlled release dosage form in the 'fasted' state. This is in contrast to GLUCOPHAGE®, which exhibits opposite characteristics."

However, such results cannot be said to "surprising" as the Petitioner is aware that such results had previously been demonstrated for the once-a-day controlled

release device of WO 99/47125, wherein, compared to GLUCOPHAGE®, metformin bioavailability was improved upon going from the fasted state to the fed, dinner state,[49] and there is no evidence of non-obviousness, (Akhlaghi Declaration, EX1019, ¶ 203)

Petitioner requests the right to rebut with evidence any other objective evidence of non-obviousness provided by the patent holder as in *Amneal Pharms. LLC v. Supernus Pharms. Inc.* IPR 2013-00368, Paper No. 8 at 13 (PTAB, Dec. 17, 2013).

XI. CONCLUSION

For the reasons set forth above, each of the claims 1-25 of the '866 patent is unpatentable in view of the prior art. Petitioner therefore respectfully requests that an *inter partes* review of the claims be instituted and that claims 1-25 be cancelled.

Date: June 19, 2017

Respectfully submitted,

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[49] WO 99/47125 (EX1002), p. 16, lines 8-14.

Certificate of Service

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for Inter Partes review of U.S. Patent No. 6,866,866 (and accompanying Exhibits 1001-1020) by U.S. CERTIFIED MAIL, on this June 19th, on the Patent Owner at the correspondence address of the Patent Owner as follows:

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