RANBAXY
PHARMACEUTICALS INC.

January 10, 2003

VIA FACSIMILE (212) 573-1939

CONFIRMATION VIA CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Dr. Peter Richardson
Senior Assistant General Counsel
and General Patent Counsel
Pfizer, Inc.
Legal Division
150 East 42nd Street, 5th Floor
New York, NY 10017-5755

Re: ATORVASTATIN
ANDA NO: 76-477
U.S. PATENT NO.: 4,681,893

Dear Dr. Richardson:

Pursuant to Section 505(j)(2)(B) of the Food, Drug and Cosmetic Act ("FDCA") and 21 C.F.R. 314.95, you are hereby notified as follows:

(1) Ranbaxy Laboratories Limited ("RLL") has previously submitted and the FDA has received an abbreviated new drug application ("ANDA") under FDCA Section 505(j)(2)(B)(ii) which contains bioavailability or bioequivalence data in order to obtain approval to engage in the commercial manufacture, use or sale of a drug product containing atorvastatin.

(2) RLL's ANDA referred to in paragraph (1) has been assigned No. 76-477.

(3) The established name for the drug product is atorvastatin, and the name of the drug product as listed on page 3-37 of the 22nd edition of the FDA publication entitled *Approved Drug Products With Therapeutic Equivalence Evaluations (2002)* (the "Orange Book") is Lipitor®, equivalent to 10 mg, 20 mg, 40 mg and 80 mg of atorvastatin.

(4) RLL's proposed drug product is in the form of capsules, which contain the equivalent of 10 mg, 20 mg, 40 mg and 80 mg of atorvastatin as the active ingredient.

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(5) On November 4, 2002, RLL sent a paragraph IV letter to Pfizer (received by Pfizer on November 6 per the return postcard) for ANDA 76-477 with respect to U.S. Patent Nos. 5,686,104; 5,969,156; and 6,126,971. The 45-day period allowed under 21 CFR 314.95 (2002), has now expired. Pfizer did not file suit against RLL within this time period and hence cannot now file suit with respect to such patents.

(6) RLL has already amended its paragraph III certification in respect to U.S. Patent No. 4,681,893 ("the '893 patent") to a paragraph IV certification. This letter will describe the factual and legal basis for this paragraph IV certification. Broadly speaking, the '893 patent will not be infringed by the manufacture, use, sale, or offer to sell of the drug product for which ANDA No. 76-477 has been submitted, as of the day of expiry of the originally issued, unextended patent.

The term extension of the '893 patent

The terms of certain patents may be extended under 35 U.S.C. § 156. Warner-Lambert applied for such a term extension under § 156 for the '893 Patent on February 7, 1997. The provisions of § 156 that are relevant to our analysis have not changed since then. Subsection (a) of § 156 defines the qualifications for patent term extension and provides in relevant part:

> (a) The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under § 154(b),[1] if –
>
> (4) the product has been subject to a regulatory review period before its commercial marketing or use ....

Subsection (f) of § 156 is a definitions section, which provides in relevant part:

> (f) For purposes of this section:
>
> (1) The term "product" means:
>
> (A) A drug product.
>
> (2) The term "drug product" means the active ingredient of –
>
> (A) a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act) ...
>
> including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.

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1 Term adjustments under 35 U.S.C. § 154(b) are granted for delays in prosecution attributable to the PTO.

In *Hoechst-Roussel Pharms., Inc. v. Lehman*, 109 F.3d 756 (Fed. Cir. 1997), the Court of Appeals for the Federal Circuit defined the phrase "which claims" in the context of 35 U.S.C. § 156(a). According to the Hoechst court, a patent "claims" a product when a claim specifically describes the product. Further, a patent cannot claim that which the specification does not enable. *Grant v. Raymond*, 31 U.S. 218, 247–48 (1832); *see also Christianson v. Colt Indus. Oper. Corp.*, 822 F.2d 1544, 1562 (Fed. Cir. 1987), *vacated on jurisdictional grounds and remanded*, 486 U.S. 800 (1988).

U.S. Patent No. 4,681,893 Is Not Infringed As of the Expiry of the Unextended Patent[2]

U.S. Patent No. 4,681,893 ("the '893 patent") entitled "Trans-6-[2-(3- or 4-Carboxamido-substituted Pyrrole-1-yl)alkyl]-4-Hydroxypyran-2-one Inhibitors of Cholesterol Synthesis" issued on July 21, 1987, 1987 to Bruce D. Roth from application serial number 06/868,867 ("the '867 Application"), filed May 30, 1986.

Because the '893 Patent was in force on June 8, 1995, it appears to be entitled to a term that is 20 years from the earliest U.S. filing date (*i.e.*, May 30, 2006). *See* 35 U.S.C. § 154(c)(1) (2002).[3] On July 15, 1998, the PTO granted the '893 Patent a 1,213-day patent term extension under 35 U.S.C. § 156 which, if valid, would change the expiration date of the '893 Patent from May 30, 2006 to September 24, 2009. *See Merck & Co., Inc. v. Kessler*, 80 F.3d 1543, 1550 (Fed. Cir. 1996).[4]

This patent contains a total of 9 claims, of which Claim 1 is independent, while Claims 2-7 are directly or indirectly dependent from Claim 1. Claim 8 refers to Claim 1 and recites a pharmaceutical composition of the '893 Patent. Claim 9 refers to Claim 1 and recites a method of using these compounds.

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[2] By identifying one particular ground and/or time period for RLL's non-infringement of the claims of the '893 Patent, this letter does not, in any way, imply that other grounds beyond that discussed are either insignificant or do not exist.

[3] 35 U.S.C. § 154(c)(1) (2002) provides:

> The term of a patent that is in force on or the results from an application filed before the date that is 6 months after the date of the enactment of the Uruguay Round Agreements Act shall be the greater of the 20-year term as provided in subsection (a), or 17 years from grant, subject to any terminal disclaimers.

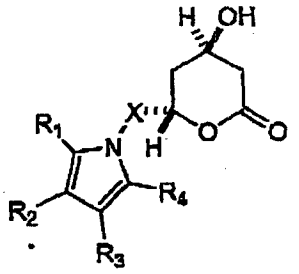
The Uruguay Round Agreements Act was enacted on December 8, 1994.

[4] "[P]re-June 8, 1995, patents are entitled to add on the restoration extension to a 20-year from filing term regardless of when such extension is granted except for those patents kept in force on June 8, 1995, only because of a restoration extension." *Merck & Co., Inc. v. Kessler*, 80 F.3d 1543, 1550 (Fed. Cir. 1996), *cert. denied*, 519 U.S. 1101, 117 S.Ct. 788 (1997), *and cert. denied*, 519 U.S. 1101, 117 S.Ct. 788 (1997), *and cert. denied*, 519 U.S. 1101, 117 S.Ct. 788 (1997), *and cert. denied*, 519 U.S. 1101, 117 S.Ct. 789 (1997).

The Claims of the '893 patent

The claims are set forth below.[5]

1. A compound of structural formula I



I

wherein

X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH(CH_3)-$;

R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; phenyl; phenyl substituted with

fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms;

either of R_2 or R_3 is $-CONR_5R_6$

where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; phenyl; phenyl substituted with

fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms;

and the other of R_2 or R_3 is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with

fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms;

R_4 is alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; or trifluoromethyl;

or a hydroxy acid or pharmaceutically acceptable salts thereof, corresponding to the opened lactone ring of the compounds of structural formula I above.

2. A compound as defined by claim 1 wherein X is $-CH_2CH_2-$.

3. A compound as defined by claim 2 wherein R_1 is phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of

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5 Throughout this letter, Claim 1 has been reformatted in the interest of space.

from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

4. A compound as defined by claim 2 wherein R_4 is alkyl of from one to six carbon atoms.

5. A compound as defined by claim 1 having the name trans-(±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.[6]

6. A compound as defined by claim 1 having the name trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-trifluoromethyl-1H-pyrrole-3-carboxamide.

7. A compound as defined by claim 1 having the name trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-trifluoromethyl-1H-pyrrole-3-carboxamide.

8. A pharmaceutical composition, useful as a hypocholesterolemic agent, comprising a hypocholesterolemic effective amount of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

9. A method of inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering a pharmaceutical composition as defined by claim 8.

The Written Description of the '893 patent

The '893 Patent states that it relates to "compounds and pharmaceutical compositions useful as hypocholesterolemic and hypolipidemic agents." The '893 patent at 1:9–11. The specification discloses

compounds of structural formula I

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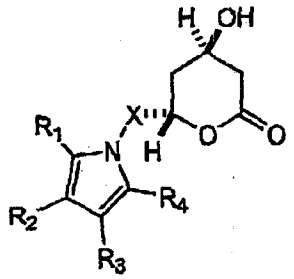
6 Claim 5 claims the racemic lactone of atorvastatin.



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wherein X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH(CH_3)-$.

R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

Either of R_2 or R_3 is $-CONR_5R_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other of R_2 or R_3 is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

R_4 is alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; or trifluoromethyl.

Also contemplated as falling within the scope of the present invention are the hydroxy acids, and pharmaceutically acceptable salts thereof, derived from the opening of the lactone ring of the compounds of structural formula I above.

The '893 patent at 2:3–43.

The stereochemistry of the compounds is discussed at 3:45–54:

The compounds of structural formula I above possess two asymmetric carbon centers, one at the 4-hydroxy position of the pyran-2-one ring, and the other at the 6-position of the pyran-2-one ring where the alkylpyrrole group is attached. This asymmetry gives rise to four possible isomers, two of which are the R-cis- and S-cis-isomers and the other two of which are the R-trans- and S-trans-isomers. This invention contemplates only the trans- form of the compounds of formula I above.

The '893 Patent discloses what is stated to be a synthetic scheme for racemic mixtures of formula I. The '893 patent at 2:44–3:21; *id.* at 4:35–6:68. No asymmetric synthetic scheme is provided. In particular, the only stereogenic step is alleged to produce a product "in which the

product contains a predominance of the desired R*,R* configuration at carbon atoms three and five which bear the hydroxy groups." *Id.* at 6:56–58.

The Prosecution History of the '893 patent

The '867 Application was filed on May 30, 1986, and included no claim to foreign or domestic priority. *See* the prosecution history of the '893 patent, Paper 1 (May 30, 1986).

The '867 Application was filed with 10 claims. Claims 1–7 were directed to a compound, Claim 8 was directed to a pharmaceutical composition comprising the compound, Claim 9 was directed to a method of using the compound, and Claim 10 was directed to a method for preparing the compound. Claim 1 was independent and provided a generic formula. Claims 2–10 were dependent from Claim 1.

The first office action was mailed from the PTO on October 2, 1986. The Applicant filed an Amendment on December 17, 1986, amending Claim 1 to a form identical to issued Claim 1, and addressing the other rejections. A Notice of Allowability was mailed on December 22, 1986 allowing Claims 1–9.

The Patent Term Extension Application

On February 7, 1997, the assignee of record, Warner-Lambert, applied for a 1213-day term extension for the '893 Patent under 35 U.S.C. § 156. Importantly, in the application for extension, Warner-Lambert acknowledged a duty to disclose information material to the determination of the term extension to the PTO and the FDA in accordance with 37 C.F.R. 1.765. Warner-Lambert averred, "Applicant is unaware of any additional information material to this Application for extension."

The FDA confirmed Warner-Lambert's asserted dates for calculating the regulatory review period. From these data, the PTO calculated a term extension of 1,213 days, and a certificate extending the term of the '893 Patent by 1,213 days was issued on July 15, 1998.

U.S. Patent No. 5,273,995

U.S. Patent No. 5,273,995 ("the '995 patent") titled "[R-(R*R*)-2-(4-FLUOROPHENYL)-β,δ-DIHYDROXY-5-(1-METHYLETHYL-3-PHENYL-4[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-HEPTANOIC ACID, ITS LACTONE FORM AND SALTS THEREOF," issued on December 28, 1993 to Bruce D. Roth from application serial number 07/660,976 ("the '976 Application"), filed February 26, 1991. The '995 Patent is a continuation of application serial number 07/384,187, filed July 21, 1989 ("the '187 Application).

The Claims of the '995 Patent

The '995 Patent issued with 12 claims. Claim 1 is independent, reciting the title enantiomerically pure compound, the lactone thereof, and pharmaceutically acceptable salts thereof. Claims 2–10 are dependent on Claim 1 and also recite compounds. Claim 11 refers to Claim 1 and recites a pharmaceutical composition. Claim 12 also refers to Claim 1 and recites a method of use. The claims of the '995 Patent are set forth below.

1. [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; or pharmaceutically acceptable salts thereof.

2. A compound of claim 1 which is [R-(R*R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

3. A compound of claim 1 which is (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

4. The monosodium salt of the compound of claim 2.

5. The monopotassium salt of the compound of claim 2.

6. The hemicalcium salt of the compound of claim 2.

7. The N-methylglucamine salt of the compound of claim 2.

8. The hemimagnesium salt of the compound of claim 2.

9. The hemizinc salt of the compound of claim 2.

10. The 1-deoxy-1-(methylamino)-D-glucitol mixture with the compound of claim 2.

11. A pharmaceutical composition for treating hypercholesterolemia comprising a hypocholesterolemic effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

12. A method of inhibiting cholesterol synthesis in a human suffering from hypercholesterolemia comprising administering a compound of claim 1 in unit dosage form.

The Written Description of the '995 Patent

The '995 Patent states that it "provides for compounds consisting of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-((1-methylethyl) -3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid (compound of formula I), pharmaceutically acceptable salts thereof and (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (the lactone form of the heptanoic acid or compound of formula II)." U.S. Patent No. 5,273,995 at 2:29–38. The specification states that this *R*-enantiomer "provides surprising inhibition of the biosynthesis of cholesterol." *Id.* at 1:23–32.

The '995 Patent states that it provides two routes to the compounds: "(1) resolving the racemate, that is prepared by the process described in U.S. Pat. No. 4,681,893" and (2) asymmetric synthesis. *See id.* at 4:7–14. The resolution is described in Scheme I and Examples 6 and 7 of the '995 Patent. *Id.* at 4:15–6:36, 13:34–14:28. The asymmetric synthesis is described in Scheme 2 and Examples 1–5. *Id.* at 6:37–7:60, 9:40–13:32.

The Prosecution History of the '995 Patent

The '187 Application was filed on July 21, 1989. The '995 patent prosecution history, Paper 1 (Jul. 21, 1989).

The '187 Application was filed with 12 claims. Among other rejections, all claims were rejected under 35 U.S.C. § 102(b) as anticipated by the '893 Patent.

In a response filed on August 6, 1990, the Applicant argued that the § 102(b) rejection over the '893 Patent was inappropriate because the '893 teaches only the racemic mixtures of compounds whereas the claimed compounds are enantiomerically pure.

In the second (and Final) Office Action mailed on November 13, 1990, the Examiner again rejected all claims as anticipated by the '893 Patent, applying the rule in *In re Schaumann*, 197 U.S.P.Q. 5 (C.C.P.A. 1978), wherein a limited genus of similar compounds may anticipate a species.

The Applicant filed a File Wrapper Continuation application on February 26, 1991, to which serial number 07/660,976 was assigned. The Applicant argued that the § 102(b) rejection was improper because *Schaumann* did not apply and under *In re Williams*, 36 C.C.P.A. 756, 171 F.2d 319 (1948), a racemate does not anticipate an enantiomer.

In the first Office Action mailed September 23, 1991, the Examiner again rejected all claims under 35 U.S.C. § 102(b) as anticipated by the '893 Patent. In support of the rejection, the Examiner pointed out the following paragraph from the '893 Patent:

> The compounds of structural formula I above possess two asymmetric carbon centers, one at the 4-hydroxy position of the pyran-2-one ring, and the other at the 6-position of the pyran-2-one ring where the alkylpyrrole group is attached. This asymmetry gives rise to four possible isomers, two of which are the R-cis- and S-cis-isomers and the other two of which are the R-trans- and S-trans-isomers. This invention contemplates only the trans- form of the compounds of formula I above.

U.S. Patent No. 5,273,995 at 3:45–54.[7]

The Examiner found the description provided in this paragraph sufficient description to sustain the § 102(b) rejection. The action was made final because the application was a continuation, all claims were drawn to the same invention as the earlier application, and all claims could have been rejected on the grounds or art of record in the earlier application.

The Applicant's attorney interviewed the Examiner on November 4, 1991 and the Examiner maintained the § 102(b) rejection.

The Applicant appealed to the Board of Patent Appeals and Interferences ("the Board") on December 20, 1991. In the Appeal Brief, the Applicant's position was that the '893 Patent did not anticipate the appealed claims, arguing that the specification of the '893 Patent teaches the existence of four isomers (two diastereomers and their enantiomers) and identifies the preferred diastereomeric pair of compounds, and arguing further that the '893 Patent does not teach which enantiomer is preferred or how to synthesize either pure enantiomer. The Applicant further argued that although the '893 Patent suggested the existence of the enantiomers, it did not enable one of ordinary skill to practice the invention because the '893 Patent does not teach one how to separate the enantiomers to determine which is preferred. Finally, the Applicant argued that under *Williams*, a racemate does not anticipate an enantiomer.

After an oral hearing on August 11, 1992, the Board reversed the § 102(b) rejection. The Board found that the appealed claims were directed to "the *R* isomer which is essentially free of any of the *S* isomer also present in the trans racemate." The Board agreed with the Applicant that the '893 Patent, "at best, only describes the trans racemate containing the R-trans and the S-trans isomers in admixture. Nowhere does Roth [the '893 Patent] state or suggest which optical isomer is preferred and, moreover, does not specifically mention how one skilled in the art could make the pure optical isomer separately." Following *Williams*, the Board affirmed that a racemate does not anticipate an enantiomer, and recommended the Examiner analyze the claims under 35 U.S.C. § 103. Despite this recommendation and without making a § 103 rejection, the Examiner mailed the Notice of Allowability on July 6, 1993. The '995 Patent issued on December 28, 1993.

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7 The Examiner mistakenly cited this passage as 4:45–54.

The Term Extension of the '893 Patent is Invalid

A patent is ineligible for term extension unless it claims a product that was subject to a regulatory review period. As stated above, under *Hoechst-Roussel Pharms., Inc. v. Lehman*, 109 F.3d 756 (Fed. Cir. 1997), a patent does not claim a product unless the product is described in a valid claim of the patent. In *Hoechst*, Hoechst applied for a patent term extension for the patent claiming 1-hydroxy-tacrine. The product subject to regulatory review was tacrine hydrochloride. The Court of Appeals found that because the Hoechst patent did not claim tacrine hydrochloride, it was not eligible for term extension.

In the present case, atorvastatin calcium was subject to regulatory review. Warner-Lambert applied for a term extension for the '893 Patent. The '893 Patent does not claim atorvastatin calcium. Accordingly, the term extension for the '893 Patent is invalid.

The Applicant for the '995 Patent admitted that the '893 Patent *does not* and *cannot* claim atorvastatin calcium. Per the Applicant, atorvastatin calcium is an enantiomerically pure compound. Per the Applicant, the claims of the '995 Patent are directed to enantiomerically pure compounds. Claim 6 of the '995 Patent claims atorvastatin calcium specifically. In the prosecution of the '995 Patent, the Examiner repeatedly rejected all claims under 35 U.S.C. § 102(b) as anticipated by the '893 Patent. The Applicant consistently argued that the '893 Patent taught only racemic mixture of compounds.

Eventually, the Applicant appealed to the Board of Patent Appeals and Interferences. In the Appeal Brief, the Appellant-Applicant argued:

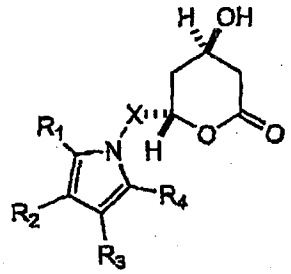
> It is well established patent law that a prior art reference does not anticipate unless its disclosure is enabling in that it describes in full, clear and exact terms as to enable any person skilled in the art to practice the invention. The mere suggestion of isomers in the Roth patent, U.S. 4,681, 893, *is not enabling* and therefore is not anticipatory. (emphasis added)

By the Applicant's own admission in the prosecution of the '995 Patent, the '893 Patent does not enable the enantiomerically pure compounds. Per the Applicant, because atorvastatin is an enantiomerically pure compound, the '893 Patent cannot claim atorvastatin. Accordingly, the '893 Patent is not eligible for patent term extension under § 156(a), and the term extension is invalid.

In the application for patent term extension for the '893 Patent, Warner-Lambert asserted that atorvastatin calcium is claimed as a new chemical entity in Claims 1–4, as a pharmaceutical composition in Claim 8, and in a methods of use in Claim 9. However, per the Applicant, atorvastatin calcium is an enantiomerically pure compound. The critical question is whether Claim 1 claims the precise stereoisomer that is atorvastatin calcium. Claims 2–4, 8, and 9 are all dependent on Claim 1. If Claim 1 does not claim atorvastatin calcium, none of these claims can claim it absent limitations indicating the appropriate absolute configuration. None of the

dependent claims include such limitations. Accordingly, if atorvastatin calcium is not claimed in Claim 1, it cannot be claimed in Claims 2–3, 8, and 9.

Claim 1 provides structural formula I:



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As stated before, the '893 Patent discusses the absolute stereochemistry only in the paragraph cited by the examiner in the prosecution of the '995 Patent:

> The compounds of structural formula I above possess two asymmetric carbon centers, one at the 4-hydroxy position of the pyran-2-one ring, and the other at the 6-position of the pyran-2-one ring where the alkylpyrrole group is attached. This asymmetry gives rise to four possible isomers, two of which are the R-cis- and S-cis-isomers and the other two of which are the R-trans- and S-trans-isomers. This invention contemplates only the trans- form of the compounds of formula I above.

The '893 patent at 3:45–54.

The paragraph from the '893 patent reproduced on page 6 above discloses the existence of the lactone with the absolute configuration of atorvastatin calcium (the "R-trans-isomer"). It also discloses the existence of the enantiomeric lactone (the S-trans-isomer"), however. This paragraph does not specify which enantiomer has hypocholesterolemic activity. Neither does this paragraph teach one how to make either enantiomer. It teaches only that the novel compounds have trans-stereochemistry, which consists of two enantiomers. In other words, the compounds are racemic mixtures.

Summary

Accordingly, the drug product for which RLL is seeking approval to market in ANDA No. 76-477 does not infringe any valid claim of the '893 patent as of the date of expiration of the originally issued, unextended patent.

Very truly yours,

Jay R. Deshmukh
Vice President – Intellectual Property