DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Ave
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AUG 0 1 2013

Gretchen Trout
Head NA Policy & FDA Liaison
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Re: Docket No. FDA-2013-P-0247

Dear Ms. Trout:

This response addresses the petition submitted to the Food and Drug Administration (FDA or the Agency) by Novartis Pharmaceuticals Corporation (Novartis) dated March 1, 2013 (Petition). The Petition requested that FDA not approve any abbreviated new drug application (ANDA) referencing Novartis's new drug application (NDA) for Reclast (zoledronic acid) injection, 5 milligrams (mg)/100 milliliters (mL) (NDA 021817), which seeks approval based on omitting protected information in Reclast labeling. The Petition further requested that FDA only approve an ANDA for a zoledronic acid product whose labeling includes adequate safety information, including all protected information in Reclast labeling relating to the osteoporosis indications (Petition at 1-2).[1]

FDA has carefully reviewed the information in your Petition. For the reasons set forth below, FDA concluded that the Agency can approve ANDAs for a zoledronic acid product whose labeling omits information related to the osteoporosis indications, and we approved two ANDAs referencing Reclast on March 29, 2013. Thus, your Petition is denied.

I. BACKGROUND

A. Reclast

On April 16, 2007, FDA approved Novartis's NDA 021817 for Reclast. The NDA was approved for treatment of Paget's disease of bone in men and women (Paget's disease). Reclast is

[1] Novartis is also the NDA holder of another zoledronic acid injection drug product, Zometa (NDA 021223). Zometa is indicated for the treatment of hypercalcemia of malignancy and for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Currently, Zometa is being supplied as a 4 mg/100 mL, single-use ready-to-use bottle and a 4 mg/5 mL, single-use vial of concentrate. References to "generic zoledronic acid" in this response mean generic zoledronic acid injection, 5 mg/100 mL, products (i.e., a generic version of Reclast (zoledronic acid) injection, 5 mg/100 mL).

available in a liquid form that is diluted in standard buffer media and ready to administer (Petition at 2). At the time of the NDA approval in 2007, one patent (U.S. Patent No. 4,939,130) (the '130 patent)) was listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). This patent expired on September 2, 2012, and its associated period of pediatric exclusivity expired March 2, 2013.

On October 16, 2006, while FDA was reviewing NDA 021817, Novartis submitted NDA 022080 for Reclast for the treatment of osteoporosis in postmenopausal women.[2] FDA approved NDA 022080 on August 17, 2007. Subsequently, Novartis submitted and received approval of four supplements to NDA 021817: (1) on June 3, 2008, FDA approved a supplement to include information on the safety and efficacy of Reclast in patients with recent low-trauma hip fracture; (2) on December 19, 2008, FDA approved a supplement for treatment to increase bone mass in men with osteoporosis; (3) on March 13, 2009, FDA approved a supplement for the treatment and prevention of glucocorticoid-induced osteoporosis in patients expected to be on glucocorticoids for at least 12 months; and (4) on May 29, 2009, FDA approved a supplement for prevention of osteoporosis in postmenopausal women.[3]

Novartis listed two additional patents for Reclast in the Orange Book: U.S. Patent numbers 7,932,241 (the '241 patent) and 8,052,987 (the '987 patent). According to the Petition, the '241 patent is titled *Pharmaceutical products comprising bisphosphonates* and covers a plastic-coated vial able to hold zoledronic acid for extended periods (Petition at 2-3). The '241 patent was not listed as a method of use patent and thus does not have an associated patent use code in the Orange Book. Therefore, the '241 patent is not related to the carve-out issues.

The '987 patent was issued on November 8, 2011. According to the Petition, the patent is titled *Method of administering bisphosphonates* and "is directed to the discovery that Reclast could be effective when administered once per year, or even less frequently" (Petition at 3). Novartis submitted Form 3542 to its NDA on December 6, 2011, to list the '987 patent in the Orange Book. The patent was subsequently listed in the Orange Book with use code U-1199 (treatment and prevention of postmenopausal or glucocorticoid-induced osteoporosis and treatment to increase bone mass in men with osteoporosis). The expiration date of the '987 patent is March 19, 2024. Novartis asserts that all osteoporosis-related information in Reclast labeling is protected information (Petition at 2).

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[2] After submission of an NDA, a pending original or supplemental application cannot be amended to add a new indication or claim (21 CFR 314.60(b)(6)). Consequently, Novartis submitted NDA 022080 for Reclast for the treatment of osteoporosis in postmenopausal women, while FDA was reviewing NDA 021817 for Paget's disease.

[3] In this response, the four indications for Reclast approved after the initial approval for Paget's disease in men and women are collectively referred to as the "osteoporosis indications."

B. Abbreviated Approval Pathway for Generic Drugs

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)). The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.[4] Section 505(j) of the FD&C Act established an abbreviated approval pathway for a drug product that is the same as a previously approved drug (the reference listed drug or RLD) with respect to active ingredient, dosage form, route of administration, strength, and, with certain exceptions, labeling and conditions of use, among other characteristics. An ANDA applicant also must demonstrate that its proposed product is bioequivalent to the RLD. An applicant that meets the requirements under section 505(j) for approval may reference the Agency's finding of safety and effectiveness for the RLD and need not repeat the extensive nonclinical and clinical investigations required for approval of a stand-alone NDA submitted under section 505(b)(1) of the FD&C Act.

An ANDA applicant is subject to applicable periods of marketing exclusivity granted to the RLD and is required to submit an appropriate patent certification or statement for each patent that claims the RLD or a method of using the RLD for which the applicant is seeking approval and for which information is required to be filed under section 505(b)(1) or 505(c)(2) of the FD&C Act (see section 505(j)(2)(A)(vii)-(viii) of the FD&C Act).[5]

C. Patent Listing Requirements and Patent Certification Requirements

Section 505(b)(1) of the FD&C Act requires NDA applicants to file as part of the NDA "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or *which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" (emphasis added).[6] FDA is required to publish the patent information provided by the NDA holder for drugs approved under 505(c) and does so in the Orange Book (section 505(b)(1), (c)(2), and (j)(7) of the FD&C Act, and 21 CFR 314.53(e)).

For each unexpired patent listed in the Orange Book, the ANDA applicant must submit either a

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[4] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[5] Marketing exclusivity is not at issue here, so this response does not address the effect of exclusivity on ANDA approval but focuses, instead, on relevant patent protection.

[6] Section 505(c)(2) of the FD&C Act imposes an additional patent submission requirement on holders of approved NDAs when those NDA holders subsequently obtain new patent information that could not have been submitted with the NDA.

paragraph III certification (delaying approval until the date on which such patent will expire), a paragraph IV certification (certifying that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted), or, with respect to a method of use patent, a statement that the patent does not claim a use for which the ANDA applicant is seeking approval (section 505(j)(2)(A)(vii)-(viii) of the FD&C Act).

An applicant submitting a paragraph IV certification is required to give notice of the patent challenge to the holder of the NDA for the RLD and each owner of the patent that is the subject of the certification. Notice of a paragraph IV certification is intended to provide an opportunity for "any legal disputes regarding the scope of the patent and the possibility of infringement [to] be resolved as quickly as possible" (*Torpharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003)). The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of patent infringement (35 U.S.C. 271(e)(2)(A)). In most cases, if the NDA holder or patent owner initiates a patent infringement action within 45 days after receiving notice of the paragraph IV certification, there will be a statutory 30-month stay of approval of the ANDA while the patent infringement litigation is pending (section 505(j)(5)(B)(iii) of the Act).[7]

An ANDA applicant seeking to omit an approved method of use covered by a listed patent need not file a paragraph III or IV certification for that patent. Instead, the applicant may submit a "section viii statement" acknowledging that a given method of use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval (see section 505(j)(2)(A)(viii) of the FD&C Act). Such a statement requires the ANDA applicant to omit or "carve out" from its labeling information pertaining to the protected use (21 CFR 314.92(a)(1) and 314.94(a)(12)(iii)(A)). Section 314.94(a)(12)(iii)(A) states that:

> If patent information is submitted under section 505(b) or (c) of the [A]ct and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications.[8]

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[7] However, if patent information for the RLD is submitted by the NDA holder after the date on which an ANDA is submitted (so long as FDA later determines that the ANDA is substantially complete), a 30-month stay is not available (see section 505(j)(5)(B)(iii) of the FD&C Act).

[8] FDA regulations implementing this statutory provision use the term "indications" to refer to information an ANDA applicant omits from its labeling in the context of submitting a statement that a protected use of a drug is not claimed in a listed patent (§ 314.94(a)(12)(iii)). However, the preambles for the proposed rule and final rule on patent and exclusivity provisions related to ANDA approval express no intent to distinguish between method of use and indication, using the terms interchangeably (see, e.g., 59 FR 50338 at 50347 (October 3, 1994)). Moreover, the preamble to the final rule emphasizes that an ANDA applicant does not have the option of choosing between a paragraph IV certification and a section viii statement; where the labeling does not include the indication, only the section viii statement is appropriate (id.). The preamble to the proposed rule states that if "the labeling for the

If an ANDA applicant files a section viii statement, the patent claiming the protected method of use will not serve as a barrier to ANDA approval.[9] This right to file a section viii statement and carve out from labeling method-of-use information protected by a patent has been upheld by the courts.[10]

D. Labeling Requirements for Products Approved as ANDAs

Section 505(j)(2)(A)(i) of the FD&C Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." This language reflects Congress' intent that a generic drug be safe and effective for each "condition of use" prescribed, recommended, or suggested in the generic drug labeling. However, it does not require that an ANDA be approved for each condition of use for which the RLD is approved. In § 314.92(a)(1), FDA has explicitly stated that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted."

The FD&C Act also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug. . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C)] or because the new drug and the listed drug are produced or distributed by different manufacturers" (section 505(j)(2)(A)(v) of the FD&C Act; see also § 314.94(a)(8)(iv)). A parallel provision appears in section 505(j)(4)(G) of the FD&C Act.[11] Section 314.94(a)(8)(iv)

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applicant's proposed drug product does not include any indications that are covered by the use patent," then the ANDA applicant would submit a section viii statement rather than a paragraph IV certification (54 FR 28872 at 28886 (July 10, 1989)).

[9] The Agency's interpretation of the plain language of the FD&C Act is further supported by Congressional intent as evidenced by the passage below:

> . . .The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

H.R. Rep. No. 857 (Part I), 98th Cong., 2d sess. 21.

[10] See *Purepac Pharmaceutical Company v. Thompson*, 354 F.3d 877, 880 (D.C. Cir. 2004) (stating that a "section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent"); *Torpharm*, 260 F. Supp. 2d at 73 (stating that a section viii statement "avers that the patent in question has been listed, but does not claim a use for which the applicant seeks FDA approval").

[11] Section 505(j)(4)(G) of the FD&C Act provides that FDA must approve an ANDA unless, among other things, "the information submitted in the application is insufficient to show that the labeling proposed for the drug is the

sets forth examples of permissible differences in labeling that may result because the generic drug product and RLD are produced or distributed by different manufacturers. These differences include the following:

> . . . differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or *omission of an indication or other aspect of labeling protected by patent* [emphasis added] or accorded exclusivity under section 505(j)(5)(F) of the [FD&C A]ct.

The regulations at 21 CFR 314.127(a)(7) further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent* [emphasis added]," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use." FDA has affirmed its authority to approve generic drug products with labeling that omits protected information on many occasions.[12]

Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement. For example, in *Bristol Myers Squibb* v. *Shalala*, F.3d 1493, 1500 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for the use of the pioneer is a matter of indifference." Similarly, in *Sigma-Tau Pharmaceutical, Inc.* v. *Schwetz*, 288 F.3d 141, 148, fn. 3 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible difference because of a difference in manufacturer.

Thus, the statute, regulations, and applicable case law permit the omission of an indication or other aspect of labeling protected by a listed patent (patent-protected labeling) as an acceptable difference between an ANDA and the RLD because of a difference in manufacturer if the omission does not render the proposed drug product less safe or effective for the conditions of use that remain in the labeling.

E. ANDAs

Dr. Reddy's Laboratories Ltd.'s (DRL's) ANDA 091363 for zoledronic acid, 5 mg/100 mL, 100 mL vials, was received by FDA on March 25, 2009. The ANDA included a paragraph IV certification to the '241 patent and a section viii statement for the '987 patent. DRL's labeling

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same as the labeling approved for [the RLD] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

[12] See, e.g., July 30, 2010, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Stephen Auten, Docket No. FDA-2010-P-0087.

carved out protected information specific to the osteoporosis indications and includes information only for the treatment of Paget's disease. DRL was not sued in response to its notice of paragraph IV certification. DRL received tentative approval on November 29, 2011, for its ANDA. DRL's ANDA was approved on March 29, 2013.

Emcure Pharmaceuticals Ltd.'s (Emcure's) ANDA 201801 for zoledronic acid, 5 mg/100 mL, 100 mL vials, was received by FDA on May 17, 2010. The ANDA included a paragraph IV certification to the '241 patent and a section viii statement to the '987 patent. Emcure's labeling carves out protected information specific to the osteoporosis indications and includes information regarding the treatment of Paget's disease. Emcure was not sued in response to its notice of paragraph IV certification. Emcure received tentative approval on July 10, 2012, for its ANDA. Emcure's ANDA was approved on March 29, 2013.

II. ANALYSIS

Novartis requests that FDA not approve any ANDA referencing NDA 021817 for Reclast injection, 5 mg/100 mL, which seeks approval based on omitting protected information in Reclast labeling. Novartis further requests that FDA only approve an ANDA for a zoledronic acid product whose labeling includes adequate safety information, including all protected information in Reclast labeling relating to the osteoporosis indications (Petition at 1-2). In support of the Petition, Novartis asserts that the Reclast labeling uniquely consists of efficacy and safety data relating primarily to its use in the osteoporosis indications, and that "carving out" the protected osteoporosis information from generic drug labeling would result in omission of most information relating to the safe use of the product, including information relevant to its safe use in Paget's disease (Petition at 2, 4). We address the statements you have made in support of your request below.

A. Omission of Protected Information Regarding the Osteoporosis Indications Does Not Render Zoledronic Acid Less Safe or Effective for the Treatment of Paget's Disease.

Novartis maintains that data from clinical trials evaluating use in the osteoporosis indications are essential to the safe and effective use of Reclast in all patients (Petition at 2). Specifically, Novartis contends that some of the protected information is essential to the safe use of zoledronic acid in Paget's disease, and "its inclusion is necessary to raise the awareness of physicians and other health-care professionals of the risks of treating Paget's disease patients with zoledronic acid" (Petition at 2). Novartis asserts that an ANDA applicant seeking to carve out protected information would be required to delete data or information that is necessary for the safe and effective use of a generic zoledronic acid product for the treatment of Paget's disease, rendering the product less safe than Reclast when Reclast is used to treat Paget's disease (Petition at 4).

FDA has concluded that omission of information regarding the osteoporosis indications from product labeling does not render a generic zoledronic acid product less safe or effective for the remaining nonprotected conditions of use, i.e., Paget's disease.

As a preliminary matter, FDA notes that Reclast was initially approved and adequately labeled for Paget's disease on April 16, 2007, prior to approval of the osteoporosis indications. Since the approval for Paget's disease, there have been no new labeled safety findings based on the osteoporosis data that are pertinent to the Paget's disease indication. Although FDA agrees that a significant amount of information would need to be carved out of the zoledronic acid product labeling by an ANDA applicant who submitted a section viii statement, including but not limited to certain warning and precautions and adverse reactions associated with the use of zoledronic acid for osteoporosis,[13] this omitted information relates to use in osteoporosis and is not necessary for the safe or effective use of zoledronic acid for the treatment of Paget's disease. As discussed below, the sections of Reclast labeling identified by Novartis as safety-related information related to the method of using the drug product for the osteoporosis indications may be omitted from product labeling for a generic zoledronic acid product seeking approval for Paget's disease without rendering the generic product less safe or effective than Reclast for the treatment of Paget's disease.

1. Adverse Reactions

Novartis asserts that a generic zoledronic acid injection product that carves out the osteoporosis indications would need to exclude information on the osteoporosis trials in the Adverse Events section (section 6.1),[14] which discusses rates of atrial fibrillation and injection site reactions, neither of which is discussed in the Paget's disease subsection.

The atrial fibrillation information highlighted by Novartis pertains to an imbalance in reports of atrial fibrillation in Reclast-treated subjects relative to placebo in one of two osteoporosis trials. FDA was aware of this safety finding during the Agency's review for the Paget's disease indication. The atrial fibrillation data did not preclude the approval of Reclast for treatment of Paget's disease, nor did FDA require labeling for atrial fibrillation. Furthermore, since marketing approval, no postmarketing cases of atrial fibrillation have been reported in the FDA Adverse Event Reporting System (FAERS) database for zoledronic acid in connection with use in Paget's disease. Therefore, FDA concluded that labeling for a generic zoledronic acid product that does not describe atrial fibrillation can provide for safe use for treatment of Paget's disease.

No injection site reactions were reported in any of the clinical trials for Reclast to support

[13] Novartis states that "references to osteoporosis would need to be omitted from the Pediatric Use, Geriatric Use, Pharmacokinetics, and Patient Counseling Information sections (8.4, 8.5, 12.3, and 17), and the Medication Guide" (Petition at 4, footnote 2). As discussed above, under § 314.94(a)(8)(iv), differences in the labeling of a generic drug product as compared to the RLD are permissible to prevent disclosure of aspects of the RLD labeling that are protected information. The differences may include omissions of words or phrases from the RLD's labeling. FDA agrees that references to osteoporosis in these sections need to be omitted from the labeling of generic zoledronic acid products that do not seek approval for the osteoporosis indications.

[14] Reclast (zoledronic acid) package insert.

approval of the Paget's disease indication.[15] In addition, in the postmarketing period, there have been no reports of injection site reactions specific to zoledronic acid use for treatment of Paget's disease. Therefore, FDA also has concluded that labeling for zoledronic acid that does not describe injection site reactions can provide for safe use for treatment of Paget's disease.

2. Warnings and Precautions

Novartis states that section 5.5 of the Reclast labeling,[16] regarding the warnings and precautions of atypical subtrochanteric and diaphyseal femoral fractures, must be omitted at least in part, if not in its entirety, for the labeling of zoledronic acid for the treatment of Paget's disease (Petition at 5). Section 5.5 of Reclast labeling states the following:

> **5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fractures**
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> Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.
>
> Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g., prednisone) at the time of fracture.
>
> Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

FDA disagrees that the entire section must be removed from the labeling of an ANDA with the osteoporosis indications carved out. As discussed above, under § 314.94(a)(8)(iv), differences in the labeling of a generic drug product as compared to the RLD are permissible to prevent disclosure of aspects of the RLD labeling that are protected by patents or exclusivity. The differences may include omissions of words or phrases from the RLD's labeling and minor

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[15] Based on findings with Zometa, the initial labeling for Reclast for treatment of Paget's disease included the following statement, "Local reactions at the infusion site such as redness, swelling and/or pain has been observed infrequently following the administration of zoledronic acid." This statement was removed when the Reclast label was revised to the physician's labeling rule (PLR) format, because FDA concluded that this statement did not convey information that was pertinent to the Paget's disease trials.

[16] See supra footnote 14.

attendant changes to ensure that the language of the labeling reads properly.[17]

Complete removal of section 5.5 of the Reclast labeling is not necessary to ensure that the protected osteoporosis indications are not disclosed. Rather, selective deletions of the references to the osteoporosis indications, consistent with § 314.94(a)(8)(iv), can adequately ensure that the necessary safety information is conveyed without disclosing the patent-protected indications. For example, the third sentences in the first and second paragraphs in section 5.5 are patent-protected language, and therefore, these two sentences would need to be omitted from the labeling for a generic zoledronic acid product that carves out the osteoporosis indications.

As modified, the language reflects minor changes in the form of the deletion of two sentences, consistent with § 314.94(a)(8)(iv), and adequately conveys the necessary safety information without disclosing the patent-protected indication. The remaining language is considered class labeling for drug products containing bisphosphonates,[18] and therefore, is not patent-protected language.

3. Pharmacodynamics

Novartis asserts that the entire Pharmacodynamics section of the Reclast labeling (section 12.2)[19] would need to be omitted because it is based on the osteoporosis treatment trial and on bone turnover markers compared to the "pre-menopausal range" (Petition at 5-6). Novartis contends that section 12.2 is the only "labeled pharmacodynamics information available" in the Reclast labeling (Petition at 6).

FDA agrees that section 12.2 is the only "labeled" pharmacodynamics information and should be omitted from the labeling of zoledronic acid for the treatment of Paget's disease. Notably, the pharmacodynamics information for use of Reclast in Paget's disease (serum alkaline phosphatase (SAP), total procollagen type 1 N-terminal propeptide (P1NP), and urinary or serum collagen type 1 cross-linked C-telopeptide (CTX)) is found in the Clinical Studies section (section 14.5) of the Reclast labeling. In addition, the information from the mechanism of action/ pharmacodynamics section of the original labeling of Reclast for the treatment of Paget's disease is captured under section 12.1 of the Reclast labeling (Mechanism of Action).[20] Therefore, FDA concludes that removal of section 12.2 would not affect a practitioner's ability to safely use generic zoledronic acid for treatment of Paget's disease.

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[17] See, e.g., Feb. 24, 2011, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Robert Trainor, Docket No. FDA-2010-P-0545.

[18] FDA Drug Safety Communication: Safety update for osteoporosis drugs, bisphosphonates, and atypical fractures, Oct. 13, 2010, available at http://www.fda.gov/Drugs/DrugSafety/ucm229009.htm.

[19] See supra footnote 14.

[20] See supra footnote 14.

B. Approval of Zoledronic Acid ANDAs That Omit Protected Information Regarding the Osteoporosis Indications Is Consistent With Agency Precedent

Novartis contends that in comparable labeling circumstances, FDA has determined it cannot approve ANDAs that omit protected information (Petition at 6). Novartis cites two citizen petition responses for this proposition. We find that neither case is supportive of Novartis's position for the reasons discussed below.

With reference to the first cited petition response, Novartis states that FDA determined that ANDA approvals omitting the protected information for Rapamune (sirolimus) was inappropriate "because this labeling is necessary to enable physicians to adequately assess the risks and benefits" of the product for the entire labeled population, including those patients not discussed in the protected labeling (Petition at 16).[21] Rapamune was approved as an immunosuppressive agent for the prophylaxis of organ rejection in patients receiving renal transplants and was originally for use in a regimen including cyclosporine and corticosteroids. However, Rapamune and cyclosporine were found to be associated with increased renal function impairment. Wyeth conducted a clinical study that showed the benefits of a cyclosporine withdrawal regimen outweighed the risks in patients with low to moderate risk of immune system reactions. Based on this study, FDA approved efficacy supplements for Rapamune that provided for cyclosporine withdrawal procedures in patients at low to moderate risk for rejection, and Wyeth received 3-year exclusivity under section 505(c)(3)(D)(iv) of the FD&C Act.[22] In granting Wyeth's petition, FDA concluded that "the protected labeling in question contains extensive, critical prescribing information . . . that any physician should receive to appropriately determine treatment *for all indications* for sirolimus," (emphasis added).[23] FDA determined that the protected information was necessary for safe use, even in the remaining unprotected population (i.e., patients at high risk of immune system reactions), because patients who were classified at high-risk because of their baseline characteristics may later be reclassified as low to moderate risk and conceivably could benefit from a cyclosporine-sparing regimen. The Agency concluded that the protected information regarding the cyclosporine withdrawal regimen was necessary to adequately assess the risks and benefits of sirolimus for the general population of renal transplant patients. Here, by contrast, as discussed in detail above, the Agency has concluded that the protected information in the Reclast labeling regarding the osteoporosis indications is not necessary to make a generic zoledronic acid product safe and effective for the nonprotected conditions of use, i.e., Paget's disease.

The second petition response cited by Novartis focused on drug-drug interaction information,

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[21] Sept. 20, 2004, letter from Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, to Michael S. Labson and Elizabeth M. Walsh, Docket No. 2003P-0518/CP1.

[22] See supra footnote 21, at 1-2.

[23] See supra footnote 21, at 4.

which is not relevant to the present case.[24] There are no corresponding issues related to drug-drug interactions in the current Reclast labeling that were not identified in the first Reclast labeling for the Paget's disease indication alone.

Finally, Novartis suggests the possibility that a generic zoledronic acid product might be used off-label for one of the osteoporosis indications (Petition at 3). Requiring FDA to consider the safety and efficacy of a generic zoledronic acid product for the carved-out osteoporosis indications would effectively create new approval requirements beyond those established by Congress and the Agency. In addition, it would be inconsistent with our long-standing policy of not interfering with the practice of medicine, in particular, with physicians' ability to prescribe approved drug products for their patients for any purpose deemed appropriate in their professional judgment.

III. MISUSE OF PETITION PROCESS

This Petition represents a particularly egregious misuse of the FDA citizen petition process for what appears to be the purpose of delaying generic competition. Novartis first submitted an incomplete version of this Petition on Thursday, February 28, 2013, and submitted the corrected version on Friday, March 1, 2013, just one day before the pediatric exclusivity attaching to the '130 patent expired, which would have allowed approval of tentatively approved ANDAs on Monday, March 4, 2013.

FDA carefully evaluates assertions that the approval of a drug will put patients at risk, and Novartis's claims required consultation with experts within the Agency. That process resulted in some minor changes to the proposed labeling of the generic products, but, as this Petition response demonstrates, the assertions in the Petition were found to be without merit. We note that the 25-day delay in approval of the ANDAs was entirely the result of the timing of Novartis's Petition, rather than its merits. Had the Petition been filed, for example, even one month before the date on which pediatric exclusivity associated with the '130 patent expired, these issues would have been resolved in time for approval of the ANDAs on that date. Moreover, according to the certification to the Petition, the information on which the Petition was based became known to Novartis on or about November 8, 2011 (Petition at 7). Had the Petition been submitted within a reasonable time after that date, the Agency could have considered its merits and taken final agency action within the time period contemplated under section 505(q) of the FD&C Act, and resolved the matter before ANDAs were eligible for approval.

IV. CONCLUSION

For the reasons described above, FDA concludes that omission of information in Reclast product

[24] See May 25, 2011, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Gary L. Veron, Docket No. FDA-2010-P-0614.

labeling related to the osteoporosis indications does not render a generic zoledronic acid product less safe or effective than Reclast for treatment of Paget's disease. Accordingly, we deny your Petition.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research