DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 13 2008

William C. Bertrand, Jr.
Senior Vice President and General Counsel
MedImmune Oncology, Inc.
One MedImmune Way
Gaithersburg, MD 20878

Re: Docket No. 2006P-0410/CP1

Dear Mr. Bertrand:

This responds to the citizen petition submitted to the Food and Drug Administration (FDA or the Agency) by MedImmune Oncology, Inc. (MedImmune), a subsidiary of MedImmune, Inc., on October 10, 2006 (Petition). The petition requests that we not approve any abbreviated new drug application (ANDA) for an amifostine product with labeling that omits dosage, administration, and other information related to the use of the drug to reduce the incidence of xerostomia in head and neck cancer patients treated with radiotherapy. The petition contends that an ANDA that does not include information related to the protected head and neck cancer indication will, nonetheless, be used in patients with head and neck cancer and would expose such patients to unnecessary health risks.

We have carefully reviewed the arguments in your petition; the comments concerning your petition submitted by Sun Pharmaceutical Industries Ltd. (Sun) dated December 21, 2006, February 27, 2007, and March 29, 2007; and your reply comments dated January 31, 2007, and April 12, 2007. For the reasons stated below, we deny your request. In accordance with the Federal Food, Drug, and Cosmetic Act (the Act), FDA regulations, and case law, the Agency may approve an ANDA for an amifostine product whose labeling omits information relating to use of the drug to reduce the incidence of xerostomia in head and neck cancer patients undergoing radiation.

I. BACKGROUND

A. Ethyol

In 1995, FDA approved the new drug application (NDA) for MedImmune's amifostine product, Ethyol, for the reduction of cumulative renal toxicity associated with the repeated administration of cisplatin in patients with advanced ovarian cancer.[1] This indication received 7 years of orphan drug exclusivity, which expired on December 8, 2002. In 1999, we approved Ethyol for the reduction of the incidence of moderate to severe xerostomia in patients undergoing postoperative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands.

[1] U.S. Bioscience submitted NDA 20-221 for Ethyol. MedImmune acquired U.S. Bioscience in 1999 and purchased the full U.S. rights to Ethyol from ALZA Corporation in 2001. For ease of reference, this response refers to MedImmune as the sponsor of NDA 20-221.

Use of amifostine for this indication is protected by U.S. Pat. No. 5,994,409 (the '409 patent), which is due to expire on December 8, 2017.[2] Ethyol has two additional listed patents: U.S. Pat. No. 5,424,471 (the '471 patent) and U.S. Pat. No. 5,591,731 (the '731 patent), both of which are due to expire July 31, 2012.

Ethyol is approved for intravenous administration and supplied as a sterile lyophilized powder. It is packaged in cartons that contain three single-use vials, each containing 500 milligrams (mg) of amifostine (anhydrous). When Ethyol is used as a single dose for the reduction of renal toxicity associated with cisplatin use for advanced ovarian cancer, the approved recommended starting dose is 910 mg/m^2 administered once daily. When used for reducing the incidence of xerostomia in head and neck cancer patients, the approved recommended dose is 200 mg/m^2 administered once daily.

B. Sun's Amifostine Product

Sun submitted an ANDA for amifostine on April 1, 2004, citing Ethyol as its reference listed drug. Sun filed paragraph IV certifications to the '471, '731, and '409 patents, which, as explained more fully below, challenged the validity of the listed patents (or indicated Sun's belief that its ANDA did not infringe the patents) and indicated Sun's intent to seek approval of its ANDA before these patents expired. FDA received Sun's notice of paragraph IV certification on July 6, 2004. MedImmune sued Sun for patent infringement within the statutorily prescribed 45-pay period. Under section 505(j)(5)(B)(iii) of the Act (21 U.S.C. 355(j)(5)(B)(iii)), this timely suit triggered a "30-month stay of approval" which precluded FDA from approving Sun's ANDA for amifostine for 30 months or until a court ruled that the patents in question were invalid or not infringed.[3]

FDA granted tentative approval to Sun's ANDA for amifostine on October 16, 2006, indicating the technical requirements for approval had been met and the only remaining barrier to approval was the patent litigation. The 30-month stay of approval expired on January 6, 2007, thus removing the last patent barrier to Sun's amifostine approval. We approved Sun's amifostine ANDA on the date of this response.

C. Patent Protection for NDAs and Labeling Differences for ANDAs

Before addressing the arguments you make in your petition, it is appropriate to summarize the statutory and regulatory provisions relevant to the approval of a generic drug product whose labeling omits an indication that is protected by a patent.

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[2] Orphan drug exclusivity for the head and neck cancer indication expired on June 24, 2006.

[3] The court in the patent litigation entered a stipulated order of dismissal of the claims against Sun for infringement of the '409 patent on March 22, 2006, when it learned that Sun was not seeking approval for the xerostomia indication claimed by that patent. Sun subsequently filed a "section viii statement" to the '409 patent which, as explained in greater detail below, indicated that Sun was not seeking approval for the xerostomia indication but was, instead, seeking to carve out this indication from its ANDA labeling. Litigation regarding alleged infringement of the remaining patents is still pending.

The Act and FDA regulations require that a sponsor seeking to market an innovator drug submit an NDA. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. The Act and FDA regulations also require that a sponsor of an NDA submit to FDA a list of patents claiming the approved drug substance, drug product, or approved method of using the drug product described in the NDA. Specifically, section 505(b)(1) of the 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).[4] FDA is required to publish patent information for drugs approved under section 505(c) and does so in its *Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book" (sections 505(b)(1), (c)(2), and (j)(7) of the Act and 21 CFR 314.53(e)).

A drug product with an effective approval under section 505(c) is known as a *listed drug*.[5] Under provisions added to the Act by the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments), Public Law No. 98-417, 98 Stat. 1585, the Act permits submission of ANDAs for approval of generic versions of listed drugs (see section 505(j) of the Act). The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to independently demonstrate the safety and effectiveness of its proposed drug. To rely on such a finding, the ANDA applicant must show that its proposed drug product is the same as the listed drug in many respects (including active ingredient, dosage form, strength, and route of administration), and that its product is bioequivalent to the listed drug.

Each ANDA applicant must identify the listed drug on which it seeks to rely for approval. As described in more detail below, the timing of ANDA approval depends on, among other things, the intellectual property protections for the listed drug the ANDA references and whether the ANDA applicant challenges those protections (see section 505(b), (c), (j)(2)(A)(vii), and (j)(5)(B) of the Act).[6] In general, an ANDA may not obtain final

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

[5] Under 21 CFR 314.3(b), "[*l*]*isted drug* means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." A listed drug is identified as having an effective approval in the Orange Book, which includes patent information for each approved drug (§ 314.53(e)).

[6] Relevant intellectual property protections affecting the timing of ANDA approval include marketing exclusivity and listed patent protection for the listed drug. Because MedImmune's orphan drug marketing exclusivity for Ethyol has expired and MedImmune currently has no other marketing exclusivity for

approval until listed patents and marketing exclusivity have expired or until NDA holders and patent owners have had the opportunity to defend relevant patent rights in court.

Specifically, with respect to each patent submitted by the sponsor for the listed drug and listed in the Orange Book, the ANDA applicant generally must submit to FDA one of four specified certifications under section 505(j)(2)(A)(vii) of the Act. The certification must state one of the following:

(I) that the required patent information relating to such patent has not been filed (Paragraph I certification);
(II) that such patent has expired (Paragraph II certification);
(III) that the patent will expire on a particular date (Paragraph III certification);
(IV) that such patent is invalid or will not be infringed by the drug for which approval is being sought (Paragraph IV certification).

The purpose of these certifications is "to give notice, if necessary, to the patent holder so that any legal disputes regarding the scope of the patent and the possibility of infringement can be resolved as quickly as possible" (*Torpharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003)).

If an applicant files a paragraph I or II certification, the patent in question will not delay ANDA approval. If an applicant files a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking full effective approval of its ANDA.

If, however, an applicant wishes to seek approval of its ANDA before a listed patent has expired by challenging the validity of a patent or claiming that a patent would not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification to FDA. The applicant filing a paragraph IV certification must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal bases for the applicant's opinion that the patent is invalid or not infringed (see section 505(b)(2)(B) and (j)(2)(B) of the Act).

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)). If the patent owner or NDA holder brings a patent infringement suit against the ANDA applicant within 45 days of the date it received notice of the paragraph IV certification, the approval of the ANDA will be stayed for 30 months from the date of such receipt by the patent owner and NDA holder, unless a court decision is reached earlier in the patent case or the patent court otherwise orders a longer or shorter period (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the Act). When the 30 months have expired, the patent ceases to be a barrier to final ANDA approval, even if the patent litigation is ongoing. Similarly if the NDA holder and patent owner receive notice of a paragraph IV

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amifostine, this response does not address the effect of exclusivity on ANDA approval but focuses, instead, on relevant patent protection.

certification and decline to sue within 45 days of receipt of notice, the patent will not be a barrier to ANDA approval.

These four certifications are not the only manner in which an ANDA applicant may address all relevant patents. An ANDA applicant seeking to omit an approved method of use covered by a listed patent need not file a paragraph I-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 Act). Specifically, section 505(j)(2)(A)(viii) of the Act provides that "if with respect to the listed drug referred to in [section 505(j)(2)(A)(i)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a statement that the method of use patent does not claim such a use." Such a statement requires the ANDA applicant to omit from its labeling information pertaining to the protected use (21 CFR 314.92(a)(1) and 314.94(a)(12)(iii)). 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.[7]

FDA implementing regulations at § 314.94(a)(12)(iii) describe the applicability of the section viii statement. Section 314.94(a)(12)(iii) 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] The Agency's interpretation of the plain language of the 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.

[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 where "the labeling for the applicant's proposed drug product does not include any indications that are covered by the use patent," the ANDA applicant would submit a section

Accordingly, FDA regulations also expressly recognize that by submitting a section viii statement, an ANDA applicant may omit from the proposed labeling a method of use protected by a listed patent, and therefore need not seek approval for that use.[9]

The 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. Thus, in *Purepac Pharmaceutical Company v. Thompson*, 354 F.3d 877 (D.C. Cir. 2004), the D.C. Circuit stated 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" (id. at 880). Similarly, in *Torpharm*, 260 F. Supp. 2d at 73, the D.C. District Court stated 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." These courts have upheld the Agency's interpretation that an ANDA applicant may choose not to seek approval for a method of use protected by a listed patent and, under those circumstances, that patent will not be a barrier to ANDA approval.

Thus, under the procedures established in the Hatch-Waxman Amendments, an ANDA will not be approved until all listed patents have (1) expired, (2) been successfully challenged, (3) been subject to a paragraph IV certification pursuant to which the patent owner or NDA holder has declined to sue within 45 days, (4) been subject to a paragraph IV certification that led to a lawsuit and a 30-month stay that has since expired, or (5) are subject to a section viii statement and a corresponding labeling carve-out.

D. Requirements Regarding ANDA Labeling

Section 505(j)(2)(A)(i) of the 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 the 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 reference listed drug 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

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viii statement rather than a paragraph IV certification (54 FR 28872 at 28886 (July 10, 1989)).

[9] See also the final rule titled *Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed*, 68 FR 36676 (June 18, 2003). In the preamble to this final rule, we stated that the section viii statement permits an ANDA applicant to "avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent" (68 FR 36676 at 36682). We stated, "[o]ur position has been that, for an ANDA applicant to file a section viii statement, it must 'carve-out' from the proposed ANDA labeling, the labeling protected by the listed patent" (id.).

drug, except that "conditions of use for which approval cannot be granted because of . . . an existing *patent* may be omitted" (emphasis added).

The 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) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers" (section 505(j)(2)(A)(v) of the Act). A parallel provision appears in section 505(j)(4)(G) of the Act.[10]

Similarly, the regulations at § 314.94(a)(8)(iv) require the following:

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 [21 CFR 314.93] or because the drug product and the reference listed drug are produced or distributed by different manufacturers.

Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and reference listed drug 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)(4)(D) of the Act.[11]

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 non-protected conditions of use."

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*

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[10] Section 505(j)(4)(G) of the 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 same as the labeling approved for [the reference listed drug] 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."

[11] We note that, due to a series of amendments to the Act, the reference in § 314.94(a)(8)(iv) to section 505(j)(4)(D) of the Act corresponds to current section 505(j)(5)(F) of the Act.

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 Pharmaceuticals, 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 due to difference in manufacturer.

Thus, under the statute, regulations, and applicable case law, the carve-out of patent-protected labeling is generally permitted as a permissible difference due to 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.

II. ANALYSIS

You acknowledge that we have the authority under the Act and governing regulations to approve generic drug products whose labeling omits indications or other information that is protected by patent or marketing exclusivity from the labeling of the reference listed drug (Petition at 8). However, you make several arguments why we should nevertheless refuse to approve any ANDA for amifostine that omits the indication of reducing the incidence of xerostomia in head and neck cancer patients undergoing radiation.

In our April 6, 2004, response to the citizen petition in Docket No. 2003P-0321/CP1,[12] we affirmed our authority to approve generic ribavirin drug products with labeling that omits protected information and rejected arguments similar to the ones you are making here. In rejecting your arguments as discussed below, we reaffirm our authority to approve generic drug products with carved-out labeling and deny your specific request that we not approve any ANDA for amifostine whose labeling omits information on the use of the drug in head and neck cancer patients.

A. The Possibility That Generic Amifostine Could Pose Safety Concerns When Used for the Carved-Out Indication Does Not Bar Approval Under the Act and FDA Regulations.

You do not directly challenge our authority to permit ANDA applicants to carve out protected indications or other protected conditions of use under the Act and §§ 314.94(a)(8)(iv) and 314.127(a)(7). Moreover, you acknowledge that the courts have recognized this authority in such cases as *Bristol-Myers Squibb Co.*, *Sigma-Tau Pharmaceuticals, Inc.*, and *Torpharm* (Petition at 8 and footnote 11). More specifically, you do not claim that a carve-out of the head and neck cancer indication would render a generic amifostine product less safe and effective than Ethyol in treating ovarian cancer patients (the remaining nonprotected indication for amifostine). Nevertheless, you maintain that approving a generic amifostine product with the head and neck cancer

[12] April 6, 2004, letter from Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, to David M. Fox, Docket No. 2003P-0321/CP1.

indication carved out would unnecessarily expose patients to significant health risks, thereby making the drug unsafe. You further state that the risk to patients posed by approving an amifostine product with the head and neck cancer indication carved out could not be addressed by providing a warning about the risks associated with uses other than for ovarian cancer (or even affirmatively stating that the product is not approved for any other use) because such an addition would not fall within a permissible exception to the same labeling requirement under the Act and FDA regulations (Petition at 8-9).

You maintain that we should not approve a generic amifostine product without the carved-out indication ". . . given the certainty that a generic product will in fact be used that way. . ." (Petition at 9). Thus, you appear to be suggesting that we are obligated to look beyond the approved labeling for the generic product and consider how the product is likely to be used off-label by physicians.

As you acknowledge, the Act and FDA regulations give us the authority to approve a generic drug product whose labeling carves out an indication of the reference listed drug, and the courts have recognized this authority. Given that fact, the relevant question with respect to the carve-out of the head and neck cancer indication is whether the omission would render a generic amifostine product less safe or effective than Ethyol for the nonprotected, ovarian cancer indication under § 314.127(a)(7). We have concluded that it does not; moreover, you do not assert that it would. Thus, an ANDA applicant's decision to carve out the head and neck cancer indication from its amifostine product labeling is fully in accord with the Act and FDA regulations and provides no basis for refusing to approve the ANDA.

Moreover, the Fourth Circuit in *Sigma-Tau* rejected a "foreseeable use" argument as a bar to generic drug approvals. In *Sigma-Tau,* the innovator (Sigma-Tau) challenged FDA approval of generic versions of Carnitor (levocarnitine) by arguing that the generic levocarnitine drugs were intended for use in the treatment of both the orphan-protected (end stage renal disease (ESRD)) and unprotected (inborn metabolic disorders) indications for Carnitor—despite the fact that the generic levocarnitine drug labeling omitted the orphan-protected, ESRD indication. Sigma-Tau maintained that if we had properly applied our intended use regulation at 21 CFR 201.128, we would have concluded that the generic levocarnitine products were intended for treatment of ESRD patients. Sigma-Tau argued that the court should consider "'compelling, readily available, objective evidence of the generics' intended use,' such as market data for Carnitor [levocarnitine], dosage forms, and federal drug reimbursement policies . . ." (288 F.3d at 145).

The court stated that the intended-use inquiry urged by Sigma-Tau might evolve into a foreseeable use test, which could mean that once we approve an orphan drug for a protected indication, "generic competitors might be prohibited from entering the market for almost any use" (288 F.3d at 147). The court further stated that Sigma-Tau's argument might extend exclusivity beyond what Congress intended and "frustrate the longstanding practice of Congress, the FDA, and the courts not to interfere with physicians' judgments and their prescription of drugs for off-label uses" (id. at 147

(citations omitted)). The court asserted that a "foreseeable off-label use [theory] to bar the approval of generic drugs, even for unprotected indications . . . [would add] a huge evidentiary hurdle to the generic drug approval process [and] would be profoundly anticompetitive" (id. at 147). Accordingly, the court concluded that the statutory scheme permitted an ANDA applicant to carve out a protected indication even when it is likely that the generic drug, once approved, will be used off-label for that indication.

Our approval of an ANDA with the carved-out head and neck cancer indication also is consistent with our approvals of other generic drug products with carved-out indications and conditions of use. For example, in *Bristol-Myers Squibb*, the innovator (Bristol-Myers Squibb) marketed the reference listed drug Capoten (captopril), which was approved and labeled with four indications. The ANDA applicant submitted an ANDA for a generic captopril drug product and referenced Capoten as the listed drug. We approved the ANDA with labeling that excluded two protected indications and corresponding protected, indication-specific dosing information. We did so even though the dosing and administration for the approved generic use was twice as high as the dosing for the carved-out indication. The D.C. Circuit held that omission of the indications protected by exclusivity was a difference in labeling "required . . . because the drug and the listed drug are produced or distributed by different manufacturers" within the meaning of the Act (91 F.3d at 1500). We also approved generic tramadol products with labeling that excluded a protected, slower titration schedule but included information on the unprotected faster titration schedule also appearing in the labeling of the innovator product.

Similarly, the possibility that a generic amifostine product might be used primarily off-label in head and neck cancer patients provides no basis for denying approval of an ANDA for amifostine with the head and neck cancer indication carved out. Requiring FDA to consider the safety and efficacy of a generic amifostine product in the treatment of head and neck cancer patients 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.

B. A Generic Drug Product With an Indication Carved Out in Accordance With the Act and FDA Regulations Is Not Misbranded Because Its Labeling Lacks the Carved-Out Indication.

You state that although section 505(j)(2)(A)(v) of the Act may permit an ANDA applicant to carve out protected labeling and to nonetheless comply with the "same labeling" requirement, it does not excuse compliance with other requirements under the Act. You state that section 502(a) of the Act (21 U.S.C. 352(a)), which states that a drug is misbranded if its labeling is misleading, is applicable to all drugs, including generic drugs with carved-out indications. Further, you state that under section 201(n) of the Act (21 U.S.C. 321(n)), which is equally broadly applicable, a product's labeling is misleading if it lacks information that is material with respect to consequences that may

result from the use of a product under such conditions of use as are customary or usual. You also state that customary or usual use is not the same as intended use, whether intended use is limited to uses claimed by the manufacturer[13] or broadened to include uses for which the product is not labeled or promoted but which are known to the manufacturer.[14] You contend that because the majority of patients who are prescribed Ethyol—and many patients who would be dispensed a generic amifostine product—are patients with head and neck cancer who are receiving radiation therapy and are being given amifostine to reduce the incidence of xerostomia, treating head and neck cancer patients is the most "customary or usual" condition of use for amifostine. Thus, you maintain that any generic amifostine product would be misbranded under sections 502(a) and 201(n) of the Act if it lacked information about use in head and neck cancer patients (Petition at 10-11).

Your interpretation of the misbranding provisions in sections 502(a) and 201(n) of the Act cannot be reconciled with a reading of the Act as a whole. To interpret these provisions as you do would be to read section 505(j)(2)(A)(viii) (permitting the ANDA applicant to decline to seek approval for one or more patented conditions of use) out of the statute. Such a reading would be contrary to the fundamental canon that an individual statutory provision should be construed in the context of the statutory scheme in which it appears.[15] As stated in section I.C of this response, in authorizing the submission of a section viii statement, the Act allows an ANDA applicant to carve out from labeling a method of use claimed by a patent. Although the Act requires that an ANDA contain information showing that the proposed conditions of use have been previously approved for the listed drug, the Act does not require that an ANDA be approved for each indication for which the reference listed drug is approved. And though the Act requires that the labeling of a generic drug be the same as the labeling approved for the listed drug, it provides an exception for changes resulting from the fact that the generic drug and the listed drug are produced or distributed by different manufacturers.

You argue that you do not challenge our general authority to permit carve-outs for protected indications in generic drug products, only our authority to do so in this case. However, your conclusion—that the labeling for a generic amifostine product with the carved-out indication is misleading under sections 502(a) and 201(n) of the Act because the drug will be prescribed off label for patients with head and neck cancer—would effectively nullify the provisions in the Act that permit the approval of a generic drug with a carved-out indication.

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[13] Petition at 11, citing *Sigma-Tau*, 288 F.3d at 147.

[14] Petition at 11, citing § 201.128.

[15] *See United Savings Ass'n v. Timbers of Inwood Forest Associates*, 484 U.S. 365, 371 (1988); *Gustafson v. Alloyd Co.*, 513 U.S. 561, 568 (1995).

Conversely, our interpretation—that a generic drug product is not misbranded if its labeling omits an indication protected by patent—is consistent with the Act's provisions on ANDA patent certifications and sameness of conditions of use and labeling for generic products, yet still gives effect to statutory provisions regarding misbranding and adequate directions for use (in circumstances where the law does not specifically permit omission of protected information).

Moreover, unlike your interpretation of the misbranding provisions, our interpretation is consistent with the underlying goals of the Hatch-Waxman Amendments. The Hatch-Waxman Amendments provided sponsors of innovator drugs with marketing exclusivity and patent listing provisions as a quid pro quo for an approval mechanism allowing sponsors of generic drugs to rely on the Agency's findings of safety and effectiveness for innovator drugs. The Amendments thus strike a balance between encouraging the research and development of new drugs and enabling the marketing of lower-cost, generic versions of those drugs. Under your interpretation of the misbranding provisions, the existence of patent protection for Ethyol's head and neck cancer indication would prohibit the approval of a generic amifostine product for any indication for the duration of the patent, thereby completely eliminating the opportunity for consumers to benefit from the existence of a lower-cost generic product during this period. On the other hand, our interpretation allows innovators to enjoy the benefits associated with their efforts to develop new indications (including patent protection and exclusivity) while promoting competition with respect to indications for which innovators are not entitled to protection (either because they have not conducted research that entitles them to protection earned previously or because any applicable protection has expired).

C. Omission of the Protected Indication Does Not Render Amifostine Less Safe and Effective for the Remaining, NonProtected Conditions of Use.

You state that omitting the head and neck cancer indication from the labeling for an amifostine ANDA would require removal of significant portions of the labeling that are necessary for the safe and effective use of Ethyol in head and neck cancer patients receiving radiation. You state that the deleted sections would, among other things, disclose potential risks for physicians to consider in making risk/benefit determinations, identify ways to minimize these risks, and include instructions concerning calculation of the dosage and administration of the drug. You maintain that without this labeling information, an amifostine product could not be safely used to reduce the incidence of xerostomia in head and neck cancer patients receiving radiation therapy (Petition at 4-5).

You argue that any approved generic amifostine product will be used overwhelmingly to reduce xerostomia in head and neck cancer patients rather than the approved indication associated with treating ovarian cancer (Petition at 1, 3, and 5-6). You state that this presents a risk of medication error because the product will be labeled only for use with a significantly higher dose (more than 4½ times greater than the daily dose approved for reducing the incidence of xerostomia in head and neck cancer patients), different

requirements for preparing the patient to receive the therapy, and different warnings. You state that healthcare professionals prescribing, dispensing, or administering amifostine for reducing the incidence of xerostomia who rely on the generic amifostine labeling will implement a dosage of the drug that is nearly three times the maximum daily dose for those patients (Petition at 6).

You maintain that there is a particular risk of medication errors in the radiology setting as well as with infusion products administered in the clinic or hospital setting where there are multiple points of contact and multiple opportunities for mistake. You state that without the information on the head and neck cancer indication, a practitioner reviewing the labeling of a generic amifostine product could mistakenly administer the drug at an improper dose. You claim that the potential for error is heightened because the drug is dispensed in cartons of three vials containing an aggregate of 1,500 mg of amifostine, which is close to the typical dose administered to chemotherapy patients. You state that an overdose of amifostine could lead a patient to become toxic (Petition at 7-8).

As explained in section II.A of this response, under the Act and our regulations, the fundamental question with regard to the safety of a generic amifostine product with the head and neck cancer indication carved out is whether the product is less safe than Ethyol for the nonprotected, ovarian cancer indication. You do not claim that the head and neck cancer carve-out will make a generic amifostine product any less safe than Ethyol for the ovarian cancer indication.

It is possible that some generic amifostine will be used to reduce xerostomia in head and neck cancer patients rather than for the approved indication of reducing renal toxicity associated with the administration of cisplatin to treat ovarian cancer. However, as stated in section II.A of this response, FDA's long-standing policy is not to interfere with the practice of medicine, including physicians' decisions regarding when and how to prescribe approved drug products.[16]

To the extent that you contend that in the absence of labeling regarding the head and neck cancer indication healthcare professionals might administer 910 mg/m^2 of generic amifostine intravenously over *3 minutes* (the length of time indicated for the infusion for

[16] Even if generic amifostine is used off-label for the head and neck cancer indication, healthcare professionals relying on the generic labeling are unlikely to confuse the dosing schedules for the ovarian cancer and head and neck cancer indications. The generic labeling specifically states that it applies only to the ovarian cancer indication use in conjunction with chemotherapy and makes no mention of the head and neck cancer use in conjunction with radiation. Healthcare professionals who treat cancer have general familiarity with the differences between chemotherapy and radiation therapy uses of drugs and are unlikely to assume, without further investigation, that the dosing information will be the same for both uses. Moreover, even in the event that a radiotherapy (head and neck cancer) patient would accidentally be given the dose of amifostine labeled for chemotherapy (ovarian cancer) use, it is unlikely that the patient would be harmed. A single infusion of 910 mg/m^2 administered intravenously over 15 minutes (the chemotherapy dosage) would not pose a severe risk for radiotherapy patients, as we have already approved this dose for chemotherapy patients. In any event, because the procedures for administering amifostine, whether for radiotherapy or chemotherapy, call for close monitoring of vital signs, such as blood pressure, this would increase the likelihood that any adverse change will be observed, investigated, and corrected.

the head and neck cancer indication) instead of 15 minutes (the length of time indicated for the infusion for the ovarian cancer for which the generic will be approved), it is difficult to see why this would occur, as the labeling for a generic amifostine makes no mention of such an infusion. This error seems more likely to occur with Ethyol, which *does* mention a 3-minute infusion in conjunction with the head and neck cancer indication. Similarly, because generic amifostine will only be labeled for use in conjunction with the cisplatin chemotherapy regimen, it seems unlikely that a practitioner will be misled by the labeling and administer the generic at its approved dose more frequently than is indicated for the ovarian cancer indication (and more frequently than the cisplatin is administered).

D. The Fact That Some State Generic Substitution Laws May Require Substitution of Generic Amifostine for Ethyol Provides No Basis for Denying Approval of a Generic Amifostine With the Protected Indication Carved Out.

You maintain that state generic substitution laws would require that prescriptions for Ethyol in head and neck cancer patients be filled with a generic amifostine product. You state that this is so because under the Orange Book, when FDA approves a generic drug product with a labeling carve-out and gives it an "A" rating indicating therapeutic equivalence, the Orange Book does not disclose the fact that the generic product is approved for less than all of the innovator product's indications. You state that at least 12 states have adopted mandatory generic drug substitution laws that require pharmacists to dispense an A-rated generic drug in response to a prescription written for a brand-name drug (unless the prescriber specifically directs that there be no substitution) and every other state permits such substitution. You further state that 18 state laws specifically rely on the Orange Book to determine what drugs are substituted, while other states rely on the Orange Book ratings indirectly. You also state that more than 30 state Medicaid programs have mandatory generic drug substitution policies that, with certain exceptions, limit reimbursement and/or access to brand-name drugs when an FDA A-rated generic drug is available. Consequently, you state that pharmacists relying on an A rating to substitute generic amifostine for Ethyol would dispense a generic product for all uses of the drug, including the use carved out in the generic labeling (Petition at 6-7).

The existence of state generic drug substitution laws, which might require the substitution of a generic amifostine for Ethyol, provides no basis for refusing to approve an amifostine ANDA. We acknowledge that in some states a generic amifostine product might be substituted for Ethyol even when the drug is intended for reducing xerostomia in head and neck cancer patients, but we have no control over the operation of these substitution laws. In *Bristol-Myers Squibb*, the D.C. Circuit recognized that the existence of "some state laws and health insurers that mandate substitution of generic drugs" could diminish the value of marketing protection given to the manufacturers of pioneer drugs under the Act (91 F.3d at 1500). Despite this, the court upheld FDA's interpretation of the Act and implementing regulations (e.g., §§ 314.94(a)(8)(iv) and 314.127(a)(7)) as permitting the Agency to approve an ANDA for a generic drug with labeling that omitted exclusivity-protected indications (and corresponding indication-specific dosing

information) for which the innovator drug was approved. The court stated that the potential diminution in marketing protection was "not a sufficient basis upon which to conclude that the Congress intended to confer upon the manufacturers of pioneer drugs the much broader protection" which would be conferred if we could not approve generic drug products with carved-out indications (id.). Thus, the fact that state substitution laws may result in the dispensing of generic amifostine for the protected head and neck cancer indication provides no basis for denying approval of an amifostine ANDA.

III. CONCLUSION

We have reviewed your petition, the submitted comments, and other relevant information available to us. For the reasons stated above, we deny your request that we refuse to approve any ANDA for an amifostine product with labeling that omits dosage, administration, and other information related to use of the drug to reduce the incidence of xerostomia in head and neck cancer patients being treated with radiotherapy.

Sincerely,

/s/ for J. Woodcock

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