



MedImmune

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Food and Drug Administration
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CITIZEN PETITION

MedImmune Oncology, Inc., (MedImmune), a subsidiary of MedImmune, Inc., submits this petition under 21 CFR 10.30 and Section 505 of the Food, Drug, and Cosmetic Act (FDCA), among other provisions of law, to ask the Commissioner of Food and Drugs (the Commissioner) to refuse to approve any abbreviated new drug application (ANDA) for an amifostine product with labeling that omits dosage, administration, and other information related to the consequences of using the drug to reduce the incidence of xerostomia in head and neck cancer patients being treated with radiotherapy.

This indication, for which MedImmune's Ethyol® (amifostine) for Injection is approved, is the most prevalent use of the drug. MedImmune is aware of at least one amifostine ANDA submitted to FDA that identifies Ethyol® as its reference listed drug (RLD) and has proposed labeling that omits information concerning use of the drug to reduce the incidence of xerostomia in head and neck cancer patients undergoing radiation. In this instance, the omission of labeling from the generic product will lead to serious medication errors.

The indication for which such a generic amifostine would be approved involves an unusually limited set of chemotherapy patients. The ovarian cancer indication accounts for no more than 2% of the drug's use, and would be applicable to only 200 or so patients in a given year. The chemotherapy use, however, requires *more than four times the dose* compared to the radiotherapy indication. The proposed generic product would include dosing and administration

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labeling that only describes the high dose; no mention will be made of the fact that the majority of patients require a much lower dose.

At the same time, it is certain – as a matter of law – that a generic product would be substituted in place of Ethyol® for use in treating radiotherapy patients. As a result, in nearly every instance in which the product would be used for the approved radiotherapy indication, the end user will be presented with a set of instructions that directs the use of an incorrect and potentially dangerous dose of the drug.

The dose differential between the two approved uses of the drug, the extreme difference between the number of chemotherapy patients and the number of radiotherapy patients for whom the drug is indicated, and the serious toxicity (including precipitous hypotension) potentially associated with overdosing of the drug that may occur, lead to a necessary conclusion: It would be unsafe to approve a generic version of Ethyol®, yet allow the product to contain instructions on a dose that is simply incorrect for most patients for whom the drug is indicated. For these reasons, MedImmune is compelled to seek the relief requested below.

A. ACTION REQUESTED

MedImmune respectfully requests that the Commissioner not approve any ANDA for a generic amifostine product with labeling that omits information concerning the dosage, administration, and risk information related to use of the drug to reduce the incidence of moderate to severe xerostomia in patients receiving radiation therapy for head and neck cancer.

B. STATEMENT OF GROUNDS

1. Background

Ethyol® (amifostine) is a selective cytoprotective agent used to reduce toxicities associated with certain cancer chemotherapy and radiotherapy. U.S. Bioscience submitted NDA 20-221 for Ethyol® (amifostine) for Injection, which FDA approved in December 1995.¹ The product was initially approved for the reduction of cumulative renal toxicity associated with the repeated administration of cisplatin in patients with advanced ovarian cancer. In June 1999, FDA approved Ethyol® to reduce the incidence of moderate to severe xerostomia, or dry mouth, in patients undergoing post-operative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands.²

¹ MedImmune, Inc., acquired U.S. Bioscience in 1999 and purchased the full U.S. rights to Ethyol® from ALZA Corporation in 2001.

² U.S. Bioscience also received accelerated approval for use of Ethyol® to reduce cumulative renal toxicity associated with repeated administration of cisplatin in patients with non-small cell lung cancer (NSCLC). MedImmune voluntarily removed that indication late last year, however, because it was not feasible to complete the additional clinical trial in NSCLC that had been required as a condition of accelerated approval.

In the decade since the approval of Ethyol®, the use of cisplatin to treat ovarian cancer has diminished precipitously, which has led to a corresponding drop in the use of Ethyol® in ovarian cancer patients. In fact, data from 2004 and 2005 indicate that only 1 or 2% of Ethyol® patients are ovarian cancer patients undergoing chemotherapy. By comparison, more than half of Ethyol® patients are receiving radiation therapy for head and neck cancer, and are being given Ethyol® to reduce the incidence of xerostomia.³ Projections for 2006 are similar.

For both indications, Ethyol® is approved for intravenous administration. The product is supplied as a sterile lyophilized powder, and is packaged in cartons that contain three 10 mL single-use vials, each with 500 mg of amifostine on the anhydrous basis. The vials are reconstituted with 9.7 mL of sterile 0.9% Sodium Chloride Injection, USP, and the drug is dosed on the basis of the surface area of the patient's body, which is calculated from the patient's height and weight. The approved dosage for each indication is very different, however.

The dosing and administration of intravenous drugs generally are more complex than for medications with other routes of administration. This is particularly so with drugs such as Ethyol®, which is intended for use by cancer patients who are undergoing what often are very debilitating treatments. There are a number of critical elements in the dosing and administration of Ethyol®, including the pre-administration workup (*i.e.*, hydration and antiemetic medication), dosage, frequency of administration, duration of infusion, and timing of administration in relation to the cancer treatment. These parameters, which are crucial to safe and effective use of Ethyol®, are very different for the drug's two indications.

Of these differences, the most significant is the recommended dosing and schedule. When Ethyol® is used as a single dose to reduce renal toxicity in ovarian cancer patients, the approved dose is 910 mg/m². That is *more than four and a half times greater* than the 200 mg/m² daily dose approved for reducing the incidence of xerostomia in head and neck cancer patients. *See* Approved Labeling for Ethyol®, "Dosage and Administration" section. This reflects the fact that cisplatin treatments for ovarian cancer are typically given once every three weeks for six courses (six doses over 18 weeks), while head and neck cancer patients generally receive radiation four or five days a week for three to six weeks (up to 30 doses over six weeks).

The magnitude – and potential impact – of the different dosages is highlighted by the fact that the recommended dose for an ovarian cancer patient (910 mg/m²) is nearly *three times* the reported maximum tolerated dose (MTD) for radiotherapy patients. *See* M. M. Kligerman, *et al.*, "Final Report on Phase I Trial of WR-2721 Before Protracted Fractionated Radiation Therapy," 14 *International Journal of Radiation Oncology*Biophysics* 1119, 1122 (1988).⁴ Study investigators concluded that the MTD of amifostine, without concomitant administration of antiemetic medication, was 340mg/m² when administered four days a week for five weeks. *See id.* at 1121. Dose-limiting toxicities included nausea, vomiting, hypotension,

³ The remaining prescriptions evidently are for off-label, cancer-related uses.

⁴ This study, which is discussed in Section 8.C.3 of supplement 012 to the Ethyol® NDA, is attached at Tab A.

rash, fever, and malaise. *See id.* at 1121-22. Moreover, the report concluded that the effects of exceeding the MTD are severe: “All patients at 450mg/m² were severely toxic, and only one patient of the four assigned [to this dose] completed all 20 doses, but with an unacceptable degree of hypotension.” *See id.* at 1121.

On June 29, 2004, Sun Pharmaceutical Industries Limited (Sun) sent MedImmune notification that Sun had submitted ANDA 77-126, which relies on Ethyol® as the reference listed drug. In the notification, Sun indicated that its ANDA includes proposed labeling for Sun’s drug product that includes only the ovarian cancer and non-small cell lung cancer indications, and “carves out” the head and neck cancer indication.⁵

Within 45 days of receiving Sun’s notification, MedImmune filed suit against the company for patent infringement. *See MedImmune Oncology, Inc. v. Sun Pharmaceutical Industries Ltd.*, Civil Docket No. 1:04-CV-02612-MJG (D.Md. filed Aug. 10, 2004). In accordance with FDCA § 505(j)(5)(B)(iii), this precluded FDA’s approving the Sun ANDA for 30 months. Although this patent litigation is ongoing, the 30-month stay expires December 29, 2006.

2. The Ethyol® Labeling Contains Critical Information Concerning the Consequences of Using Amifostine to Reduce the Incidence of Xerostomia in Head and Neck Cancer Patients.

As noted above, Sun’s notification says the company has proposed labeling that is limited to the ovarian cancer indication and dosing regimen. This presumably means the proposed labeling for Sun’s product does not include the information that was added to the Ethyol® labeling with approval of the NDA supplement containing the head and neck cancer indication. Not surprisingly, such a labeling “carve-out” 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. Among other things, the deleted sections disclose potential risks for doctors to consider in making risk/benefit determinations, identify ways to minimize these risks, and include instructions concerning calculation of the dosage and proper administration of the drug. Among the portions of the labeling that would likely be excised are:

- *Clinical Studies*: Summarizes the data from a Phase III trial evaluating use of amifostine to reduce the incidence of certain types of xerostomia in patients receiving radiotherapy for head and neck cancer.
- *Dosage and Administration*: Describes recommended dosing and administration instructions for amifostine for use in head and neck cancer

⁵ As noted above, MedImmune voluntarily removed the NSCLC indication. Accordingly, if Sun seeks to include that indication in the labeling of the proposed generic amifostine, the company must submit a petition seeking a determination by FDA that the indication was not withdrawn for reasons of safety or effectiveness. 21 USC 355(j)(4)(I). MedImmune is not aware that Sun has submitted any such petition, and therefore assumes that Sun is seeking approval for only the ovarian cancer indication.

patients undergoing radiotherapy. Instructs healthcare professionals to ensure that patients are properly hydrated prior to infusion, and to monitor patient blood pressure at least before and immediately after infusion. Instructs administration of antiemetic medications prior to and in conjunction with amifostine and recommends a specific class of antiemetic medications that have been used effectively in combination with amifostine in the radiotherapy setting.

- *Warnings:* Warns that amifostine should *not* be administered to patients receiving definitive radiotherapy. Discloses that the effects of amifostine on the incidence of xerostomia and on toxicity in the setting of combined chemotherapy and radiotherapy, accelerated, and hyperfractional therapy have not been systemically studied. Regarding the potential for hypotension, the labeling advises that for infusion durations of less than five minutes, blood pressure should be monitored at least before and immediately after the infusion. Specifically notes that certain, potentially serious adverse events have been reported more frequently when Ethyol® is used as a radioprotectant.
- *Precautions:* Advises that amifostine be administered as a three-minute infusion prior to radiation therapy and that patient blood pressure should be monitored.
- *Adverse Reactions:* Describes the safety results of the Phase III trial supporting the approval for xerostomia in head and neck cancer patients, noting that 17% of patients in the study discontinued amifostine due to adverse events, 15% of the patients experienced hypotension, and 3% experienced grade three or higher hypotension.

See Approved Labeling for Ethyol®. Without this information, an amifostine product could not be safely used to reduce the incidence of xerostomia in head and neck cancer patients receiving radiation therapy.

3. A Generic Amifostine Without Labeling on Use to Reduce the Incidence of Xerostomia in Head and Neck Cancer Patients Would Be Unsafe.

As noted above, use of Ethyol® with ovarian cancer patients undergoing chemotherapy – the only use for which a generic amifostine with Sun’s proposed “carve-out” would be labeled – accounts for only 1% or 2% of the drug’s use. The prevalent use of Ethyol® – accounting for the majority of Ethyol® patients – is with radiation therapy for head and neck cancer. There is every reason to believe that the prescribing patterns of a generic amifostine will be similar to those of Ethyol®; the most frequent use of the product will be in head and neck

cancer patients receiving radiation therapy. This presents a very real risk of medication error,⁶ because the product will be labeled only for a use with a significantly higher dose, different requirements for preparing the patient to receive the therapy, and different warnings, among other things. 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 MTD for those patients. The generic drug will present a risk profile that is unacceptable and, more importantly, completely avoidable. The risks should be addressed preemptively, rather than after adverse events occur. Further, because the product will not be labeled for safe and effective use in the most prominent use, its labeling will be misleading, and the product will be misbranded.

a. Generic Amifostine Will Be Prescribed for Head and Neck Cancer.

Notwithstanding any “carve-out” in the labeling, a generic amifostine product will frequently be dispensed for use in head and neck cancer patients undergoing radiation therapy. This is not speculation or a prediction based on doctors’ past prescribing habits with Ethyol®. It is known with a certainty because of state laws that will require prescriptions for Ethyol® in head and neck cancer patients to be filled with a generic amifostine.

FDA lists generic drugs approved under FDCA § 505(j) in the *Orange Book*, which is updated regularly and made available to the public. *See Orange Book* (26th ed. 2006), at Preface 1.1. In doing so, the agency supplies each generic drug with a therapeutic equivalence code. *See id.* at Preface 1.2. The therapeutic equivalence code essentially collapses into a letter-based designation the agency’s findings on pharmaceutical equivalence and bioequivalence, both of which are required for ANDA approval. *See id.* The therapeutic equivalence code is a shorthand way of communicating FDA’s medical and scientific conclusions about a given generic product to patients and the healthcare system (including State Boards of Pharmacy, pharmacists, formularies, and physicians). A therapeutic equivalence “A rating” signifies that the generic is therapeutically equivalent to other pharmaceutically equivalent products. *See id.* at Preface 1.7. A therapeutic equivalence “B rating” suggests that FDA does not consider the product to be therapeutically equivalent to other pharmaceutically equivalent products. *See id.*

But there is an important gap between the findings made in approving an ANDA and the therapeutic equivalence listing in the *Orange Book*. There is nothing in the *Orange Book* that reflects or reports any labeling “carve-out” that was a condition of approval. Accordingly, when a generic product with a labeling “carve-out” is approved and given an “A rating” as therapeutically equivalent, the fact that the generic product is approved for less than all of the innovator product’s indications is not disclosed in the *Orange Book*.

⁶ A “medication error” is defined by FDA as “preventable event that may cause or lead to inappropriate medication use or patient harm while the medicine is in the control of a health care professional, patient, or consumer.” 68 Fed. Reg. 12406 (May 14, 2003).

This has important and undeniable implications in practice. At least 12 states have adopted mandatory generic drug substitution laws, which require a pharmacist to dispense an “A rated” generic in response to a prescription written for the brand-name drug, unless the prescriber specifically directs that there be no substitution.⁷ See National Association of Boards of Pharmacy, 2006 Survey of Pharmacy Law (NABP Survey), 65-67 (2005) (attached as Tab B). Every other state at least permits such substitution.⁸ *Id.* Eighteen of the state laws specifically rely on the *Orange Book* as the basis for determining what drugs are substituted; other states rely on FDA’s therapeutic equivalence ratings indirectly.⁹ In addition, more than 30 state Medicaid programs have mandatory generic drug substitution policies that, with certain exceptions, limit reimbursement and/or access of brand name drugs when an FDA “A rated” generic is available.

Accordingly, because the *Orange Book* does not reflect labeling “carve-outs,” pharmacists relying on an “A rating” to substitute generic amifostine for Ethyol® will be dispensing the generic product for all uses of the drug, including those for which the generic product is not approved, and for which it is not labeled.

b. There is a Real Risk of Medication Errors With Serious Consequences.

The American Hospital Association reports that errors due to “unavailable drug information” are one of the top five types of medication errors. See CDER, “Medication Errors” (updated Jun. 14, 2006), available at <http://www.fda.gov/cder/drug/MedErrors/default.htm>. Dosing errors also represent a substantial portion of medication errors. An FDA analysis of medication errors reported over a five-year period concludes that 41% of these errors involved administering an improper dose. See Arthur E. Wharton, “CE: Oh no! Not another medication error!,” *Drug Topics* (Nov. 22, 2004) (attached as Tab G). Data suggest there is a particular risk of medication errors in the radiology setting. The USP Center for the Advancement of Patient Safety reviewed medication errors reported between 2000 and 2004, and concluded that the number of “harmful” medication errors occurring in radiological service areas is seven times that

⁷ States with mandatory substitution laws are Florida, Hawaii, Kentucky, Massachusetts, Minnesota, Mississippi, New Jersey, New York, Pennsylvania, Rhode Island, Washington, and West Virginia. NABP Survey at 65-67. Even where any harm arguably is caused by operation of state pharmacy law, an improper ANDA approval cannot stand. See *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1499 (D.C. Cir. 1996) (“If BMS is correct [that FDA acted improperly], then it is no answer to say that the FDA is merely permitting a competitive product to enter the market and leaving the purchasing decision to the consumer” under state substitution laws).

⁸ Some states have additional requirements or limitations on substitution, whether mandatory or permissive. See, e.g., Haw. Rev. Stat. Ann. 328-92(a) (requiring patient consent to substitution) (attached at Tab C).

⁹ For example, Pennsylvania law states that a “pharmacist shall substitute a less expensive generically equivalent drug” and defines “generically equivalent drug” as a “drug product that the Commissioner of Food and Drugs of the United States Food and Drug Administration has . . . determined to be therapeutically equivalent, as listed in ‘The Approved Drug Products with Therapeutic Equivalence Evaluations.’” Pa. Stat. Ann. Tit. 35, 960.3 (attached at Tab D); *id.* at 960.2 (attached at Tab E). In Washington, pharmacists have the discretion to determine therapeutic equivalence and may rely on several sources in making their decisions, including the *Orange Book*. See Wash. Admin. Code 246-899-030 (attached at Tab F).

of other areas. See John P. Santell, "USP Drug Safety News: Medication errors in radiological services," *Drug Topics Health-System Edition* (Feb. 20, 2006) (attached as Tab H).¹⁰

The risk of medication errors is particularly high with infusion products administered in the clinic or hospital setting where there are multiple points of contact and multiple opportunities for mistake. Without the appropriate dosing, administration, and risk information in the labeling, any one of the individuals involved in prescribing, dispensing, or administering the drug could review the labeling enclosed in the generic amifostine package and mistakenly administer the drug at a dose that is nearly three times the MTD for radiotherapy patients and four times the recommended dose. The potential for this error is heightened because the drug is dispensed in cartons of three vials, containing an aggregate of 1,500 mg of amifostine – close to the typical dose administered to chemotherapy patients.

The potential impact of such an overdose is significant. Particularly over a course of radiation therapy, it could easily lead the patient to become toxic. And if the overdosage caused hypotension and the healthcare professional again sought direction from the generic product's labeling, he or she would be instructed to reduce the dose only to 740 mg/m² for subsequent cycles, which is still more than three times the approved dose and more than twice the MTD.

c. Labeling With the Omitted Information Renders the Product Unsafe.

As a general rule, an ANDA applicant must "show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug." 21 USC 355(j)(2)(A)(v); 21 CFR 314.94(a)(8)(iv). The FDCA contains two exceptions to this requirement: changes to the labeling that reflect product differences approved in a suitability petition, and labeling differences required because the products are produced or distributed by different manufacturers. *Id.* FDA has by regulation expanded the second exception to permit the omission or "carve out" of an indication or other aspect of labeling in certain circumstances, as long as the omission does not make the generic product "less safe or effective than the listed drug for all remaining, non-protected" indications. 21 CFR 314.127(a)(7); see also 21 CFR 314.94(a)(8)(iv). MedImmune does not challenge here the agency's general authority to permit these "carve-outs," which the courts have recognized.¹¹ We also do not assert that a "carve-out" would render a generic amifostine less safe or effective than Ethyol® in treating ovarian cancer patients.

¹⁰ Recent reports of deaths from heparin overdoses in children mistakenly given an adult dose of the drug demonstrate both the potentially serious risks of improper dosing and the ease with which such mistakes can occur, even when the proper dosing instructions are available. See, e.g., Tom Davies, "Fatal Drug Mix-Up Exposes Hospital Flaws," Associated Press (Sept. 22, 2006), available at <http://www.washingtonpost.com/wp-dyn/content/article/2006/09/22/AR2006092200815.html> (attached as Tab D).

¹¹ See, e.g., *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002); *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996); *Torpharm, Inc. v. Purepac Pharmaceutical Co.*, 260 F.Supp.2d 69 (D.D.C. 2003). By filing this petition, MedImmune is not taking a position, except as expressly set forth herein, as to whether a "carve-out" of information related to the xerostomia indication is permissible under the statute and implementing regulations.

Nonetheless, the safety issue here is too compelling to ignore, and too serious to permit waiting until adverse events occur. Given that no more than 2% of patients prescribed amifostine would be using a generic product for its approved use, given the risk of serious overdose if a generic product were used to treat head and neck cancer patients, and given the certainty that a generic product will in fact be used in that way, the approval of a generic amifostine with the head and neck indication "carved out" would unnecessarily expose patients to significant health risks, making the drug unsafe.

Nor could this be addressed by a warning in the labeling as to the risks associated with uses other than for ovarian cancer patients, or even affirmatively stating that the product is not approved for any other use. Such an addition to the labeling falls outside the exceptions to the "same labeling" requirement. As FDA has explained:

The agency will not accept ANDA's for products with significant changes in labeling (such as new warnings or precautions) intended to address newly introduced safety or effectiveness problems not presented by the listed drug. . . . Moreover, FDA does not believe that it would be consistent with the purpose of section 505(j) of the act, which is to assure the marketing of generic drugs that are as safe and effective as their brand-name counterparts, to interpret section 505(j)(2)(A)(v) of the act as permitting the marketing of generic drugs with diminished safety or effectiveness and concomitantly heightened labeled warnings.

54 Fed. Reg. 28872, 28884 (Jul. 10, 1989).¹² Cf. *Zeneca v. Shalala*, 213 F.3d 161, 169-170 (4th Cir. 2000) (permitting addition of specific warning in ANDA labeling concerning sulfites, where required by FDA regulation).

FDA has the information necessary to conclude that a generic amifostine that is not labeled for reducing the incidence of xerostomia in head and neck cancer patients would be unacceptably unsafe. The putative benefits of a generic amifostine are not worth the risks to which cancer patients would be exposed.

¹² An applicant might propose to take steps to ameliorate the risks associated with an amifostine product that is not labeled for use in head and neck cancer patients. These might include use of a bolded warning or other labeling changes to make clear that the drug is not approved for that use; dissemination of materials alerting healthcare professionals that the product is not labeled for use in head and neck cancer patients and should not be used for that purpose; conducting training of those involved in administering the drug to ensure proper dosing and use for the approved indication only; and adding a note to section 1.8 of the *Orange Book* addressing the situation. Even if an applicant were able to devise a risk management program that adequately prevented the risk to patients, such a program could not be adopted within the context of an ANDA, but would require the applicant to pursue approval in accordance with FDCA § 505(b)(2).

d. Labeling With the Omitted Information Renders the Product Misbranded.

Although FDCA § 505(j)(2)(A)(v) may permit FDA to exempt generic drugs from the “same labeling” requirement by means of a “carve-out,” it does not excuse compliance with other obligations under the FDCA. FDCA § 502(a) is applicable to all drugs – innovator and generic, “carve-out” or not – and it states that a drug is misbranded if its labeling is misleading. 21 USC 352(a). And FDCA § 201(n), which is equally broadly applicable, explains that a product’s labeling is misleading if it lacks information that is “material with respect to consequences which may result from the use of the [product] . . . under such conditions of use as are customary or usual.” 21 USC 321(n).

A generic amifostine that is labeled only for reducing renal toxicity in ovarian cancer patients undergoing chemotherapy would be labeled for only 1% or 2% of the patients for whom the drug is prescribed, most likely no more than 200 or so patients a year. The majority of patients who are prescribed Ethyol® – and many patients who would be dispensed a generic amifostine – are patients with head and neck cancer who are receiving radiation therapy and being given the drug to reduce the incidence of xerostomia. In this regard, treating head and neck cancer patients is the most “customary or usual” condition of use, and a generic amifostine that lacks information for the safe and effective use for that indication is misbranded.

FDCA § 201(n) provides an objective standard; one need only determine whether the use is “customary or usual” and then consider whether the labeling lacks material information about the consequences of that use. FDA has recognized that a product’s “customary or usual” use can be based on evidence of how a drug is “routinely used.” 62 Fed. Reg. 43900, 43908 (Aug. 15, 1997). Moreover, where a product is “widely used” in a population, that use may be considered “customary,” such that failure to provide information on that use in the labeling “could render the product misbranded, even where the manufacturer does not promote the product for that subpopulation.”¹³ *Id.*

Importantly, the statute distinguishes between “customary or usual” use and the use for which the drug is labeled. The statute speaks in alternatives; labeling is misleading if it lacks information material to the possible consequences of use “under the conditions of use prescribed in the labeling . . . or under such conditions of use as are customary or usual.” 21 USC 321(n) (emphasis added). Similarly, the “customary or usual” use is not the same as the

¹³ FDA made these findings in promulgating the Pediatric Rule. Although the rule was invalidated, *Association of American Physicians and Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002), the court did *not* determine that FDA lacks authority to declare a drug misbranded for material omissions related to the consequences of usual or customary use. To the contrary; the court noted the “extensive evidence demonstrating that at least some drugs are ‘commonly’ or ‘usually’ used by children, despite the absence of pediatric labeling.” *Id.* at 213. The court merely held that FDA’s authority under FDCA § 201(n) did not support the Pediatric Rule because, among other things, the rule applied to newly approved products, “which do not yet have any ‘customary or usual’ use.” *Id.* Here, by contrast, the customary or usual use of amifostine is already known. For the reasons discussed above, there can be no doubt that a “customary or usual” use of a generic amifostine product would be to reduce the incidence of xerostomia in head and neck cancer patients receiving radiotherapy.

intended use, whether “intended use” is limited to those uses claimed by the manufacturer, *see, e.g., Sigma-Tau Pharmaceuticals*, 288 F.3d at 147, or expanded to include uses for which the product is not labeled or promoted, but which are known to the manufacturer. *See* 21 CFR 201.128. “Customary or usual” use is not defined by a product’s labeling, nor is it a function of the manufacturer’s intent or knowledge.

That is why the agency’s previous decisions regarding the interplay of FDCA §§ 201(n) and 505(j) in the context of labeling “carve-outs,” which concerned intended use, are inapposite. *See* Apr. 6, 2004 Letter from Steven K. Galson, M.D., Docket No. 2003P-321/PDN1, at 27-29 (Ribavirin Petition Response) (rejecting “any assertions about the ANDA applicant’s post-approval intended use”); *Sigma-Tau Pharmaceuticals*, 288 F.3d 141 (upholding FDA’s refusal to consider “foreseeable off-label use” as evidence of intended use, because 21 CFR 201.128 (defining “intended use”) “grants the agency discretion to decide what evidence of intent it will examine”). As discussed above, (1) at issue in this instance is usual or customary use, not the sponsor’s intended use, and (2) the operation of state law will mandate the dispensing of generic amifostine for treating head and neck cancer patients, and such use therefore is not speculative.¹⁴

Reducing the incidence of xerostomia in head and neck cancer patients receiving radiation therapy is the most prescribed use of amifostine. A generic amifostine that lacks dosing, administration, and other safety and effectiveness information for that use contains material omissions regarding the consequences of that “usual and customary” use, and therefore is misbranded.

4. Conclusion

A generic amifostine undoubtedly will be used to treat head and neck cancer patients receiving radiotherapy. If the product’s labeling omits dosing, administration and other information for that use – and instead directs healthcare providers to administer a dose that is more than four times the approved radiotherapy dose and three times the maximum tolerated dose for these patients – there will be medication errors. Given the huge difference in dose, the severity of the resultant adverse effects, and fact that the labeled dose will be approved for no more than 2% of patients, while putting the majority of amifostine patients at risk – the drug would be unsafe and should not be approved.

¹⁴ Moreover, contrary to the agency’s assertion, *see* Ribavirin Petition Response at 21, 26-27, the court in *Bristol-Myers Squibb Co.* did not reject any misbranding argument. The court never even addressed any misbranding argument, because none was raised by Bristol-Myers Squibb. As the court stated, “[t]he crux of the dispute” was whether the “same labeling” requirement precluded approval of an ANDA with a labeling “carve-out.” 91 F.3d at 1499. The court conducted a straightforward (and brief) *Chevron* analysis, noting that Bristol-Myers Squibb “rest[ed] its case squarely upon the first step” under *Chevron*, *i.e.*, “whether the Congress has directly addressed the issue now in dispute.” *Id.* Bristol-Myers Squibb argued that Congress had addressed the issue with the same labeling requirement, which contained two exceptions, neither of which was applicable. The court rejected that argument, agreeing with FDA that a “carve-out” fell within the exception for labeling differences “required . . . because the new drug and the listed drug are produced or distributed by different manufacturers.” *Id.* at 1500.

This is not a question of broad policy; MedImmune does not question FDA's general authority to approve generic drugs that "carve out" an indication approved for the reference listed drug. In this particular instance, however, the risk to patients is too great. A generic amifostine that lacks labeling for reducing the incidence of xerostomia in head and neck cancer patients receiving radiotherapy – its prevalent use – would be unsafe and misbranded, and should not be approved.

C. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusions under 21 CFR 25.31.

D. ECONOMIC IMPACT

Information on the economic impact of this proposal will be provided upon request by the Commissioner.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully Submitted,



William C. Bertrand, Jr.
Senior Vice President & General Counsel

cc: Mr. Paul Seligman
Office of Drug Safety

Attachments