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COMMENTS TO CITIZEN PETITION
DOCKET 2006P-0410/CP1

EXPEDITED RESPONSE REQUESTED

Sun Pharmaceutical Industries, Ltd. ("Sun"), by counsel, urgently submits the following comments to Citizen Petition Docket 2006P-0410/CP1 ("Petition" or "Pet.") submitted by MedImmune Oncology, Inc. ("MedImmune"). The Petition asks the Food and Drug Administration ("FDA") to refrain from approving any abbreviated new drug application ("ANDA") for an amifostine product that carves-out information in the labeling on the use of the drug to reduce the incidence of xerostomia in head and neck cancer patients being treated with radiotherapy. As demonstrated below, the Petition should be denied expeditiously.

I. Introduction

MedImmune filed the Petition for the sole purpose of extending the company's monopolistic profits on its star product (Ethyol®) by delaying FDA approval of a generic amifostine competitor—*not* to promote public safety. Since the Petition was "submitted very close to the date of patent or exclusivity expiration [and was] based on information that was

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readily available well before the petition[] was filed," it reflects an improper "blocking petition" evidencing "anti-competitive behavior."[1]

Last year alone, MedImmune booked almost $100 million in worldwide Ethyol® sales, an increase from the prior year. In the hope of continuing this trend and improving its bottom-line, the company has initiated a campaign of raising the price of Ethyol® while, at the same time, abusing the citizen petition process to prevent the public from having access to a lower-priced, generic amifostine.[2] Although MedImmune had sufficient information to file the Petition almost two and a half years ago, it strategically timed its filing to frustrate final approval of Sun's ANDA by waiting until just before the 30-month stay of FDA approval expires on December 29, 2006. MedImmune makes no effort to explain this delay because it is inexplicable. To be sure, this delay was intentional and reflects an improper effort to exploit the citizen petition process and postpone approval of a generic drug that will benefit the public. This true purpose of the Petition is further confirmed by its complete lack of merit.

First, the Petition is legally meritless because it merely rehashes arguments that have been rejected repeatedly by the FDA and federal courts and mischaracterizes the pertinent facts. Significantly, the FDA can, and should, deny the Petition based solely on MedImmune's two critical concessions:

1. "FDA . . . permit[s] 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." Pet. at 8 (citing 21 CFR 314.127(a)(7) & 21 CFR 314.94(a)(8)(iv)) (emphasis added).

2. MedImmune does "not assert that a 'carve-out' would render a generic amifostine less safe or effective than Ethyol® in treating ovarian cancer patients," *id.*—the sole "non-protected" indication at issue in Sun's ANDA.

MedImmune's own words confirm what the FDA and federal courts have firmly established—namely, that the "FDA will approve an ANDA for a listed drug with three years of exclusivity as long as omission of the labeling protected by exclusivity does not render the generic drug less safe or effective as the listed drug *for the remaining, non-protected conditions of use*."[3]

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[1] Report to House and Senate Committee on Appropriations: Citizen Petition Process Improvement Efforts Within the Food and Drug Administration's Center for Drug Evaluation and Research, at 2 (Apr. 20, 2006) ("FDA Report to Congress") ("[C]itizen petitions, which, based upon the timing of the submission, might reasonably appear to have been filed in an attempt to delay approval of a generic version of a drug that is not yet subject to generic competition, are sometimes referred to informally as 'blocking petitions.'").

[2] MedImmune Oncology, Inc., Annual Report, at 27 (2005) "Worldwide Ethyol® sales increased slightly to $95.0 million . . . *primarily due to an increase in the domestic sales price*[.]" (emphasis added).

[3] Docket No. 2003P-0321/CP1, FDA Decision, at 14 (Apr. 6, 2004) (emphasis added); *see also Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 147 (4th Cir. 2002) (holding that "foreseeable off-label use to bar

Accordingly, the only "relevant question" concerning the FDA's approval of Sun's ANDA is whether generic amifostine, when labeled to exclude protected information (e.g., information on the use of amifostine to reduce the incidence of xerostomia in head and neck cancer patients being treated with radiotherapy), will be rendered less safe or effective for the labeled, non-protected use of reducing renal toxicity in ovarian cancer patients receiving chemotherapy. Docket No. 2003P-0321/CP1, FDA Decision, at 18 (Apr. 6, 2004). Since MedImmune does not even attempt to assert that generic amifostine is misbranded for its non-protected indication, this should end the inquiry under well-established law and procedure.

In fact, as MedImmune no doubt is well-aware, the FDA already has rejected its two primary arguments that: (1) a label can be deemed misbranded or misleading due to foreseeable use of a drug by health care providers, *id.* at 28; and (2) an ANDA can be denied because the dose pertaining to the non-protected use on the generic label is higher than the dose pertaining to the protected use that has been carved-out of the generic label, *id.* at 20. The FDA should decline MedImmune's implicit request to overrule well-established FDA and federal court precedent.

Even putting aside its legal flaws, the Petition also should be denied on the independent ground that it is factually meritless. According to MedImmune, radiotherapy health professionals will see the dosage for the chemotherapy indication on the generic amifostine label and apply that *chemotherapy* dosage to *radiotherapy* patients. MedImmune further argues that such medical errors will cause radiotherapy patients to receive an overdose. As demonstrated in the Statement of Jeanne M. Quivey, M.D., F.A.C.R. (attached hereto as Exhibit 1), however, these arguments improperly assume that health professionals will engage in severe malpractice, and further ignores medical safeguards that would prevent harm to patients even in the event of such extremely unlikely malpractice.

In sum, the Petition should be rejected on both legal and factual grounds. And public policy dictates that such denial of this "blocking petition" be expedited. In fact, the Petition clearly falls within the category of "anti-competitive behavior" that the FDA has indicated it intends to refer to the Federal Trade Commission.[4]

II. The FDA Should Deny The Petition

A. The Petition Is A "Blocking Petition" Improperly Designed To Delay Generic Competition

Expedited consideration of the Petition is necessary to send a clear message to brand-name companies like MedImmune that they cannot abuse the citizen petition process by

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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 anti-competitive").

[4] FDA Report to Congress, *supra* note 1, at 4 ("Where we believe that further investigation into potentially anti-competitive behavior may be warranted, we intend to refer the case to the Federal Trade Commission.").

filing meritless petitions in the hope of delaying entry into the market of a generic drug manufactured by a competitor. This conduct of filing a "blocking petition" is improper and runs afoul of the strong public policy favoring the approval of generic drugs.

Congress passed the Hatch-Waxman Act of 1984 in an effort to promote innovation and competition in the pharmaceutical industry.[5] This Act "emerged from Congress' efforts to balance two conflicting policy objectives: to induce name-brand pharmaceutical firms to make the investments necessary to research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of those drugs to market." *Abbott Labs. v. Young*, 920 F.2d 984, 991 (D.C. Cir. 1990); *see also* H.R. Rep. No. 98-857 (II), at 4 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686. The public's interest in this second policy objective—*i.e.*, the timely approval of safe generic drugs—has intensified as the costs of health care rise to unprecedented levels.[6]

The Petition, like similar meritless citizen petitions filed by brand-name pharmaceutical companies to delay entry of a generic drug into the marketplace, frustrates this laudable policy objective. Unfortunately, as the FDA, Congress,[7] and countless articles[8] have recognized, brand-name pharmaceutical companies frequently resort to abusing the citizen

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[5] Elizabeth Stotland Weiswasser & Scott D. Danzis, *The Hatch-Waxman Act: History, Structure and Legacy*, 71 ANTITRUST L.J. 585, 585 (2003); *see also* H.R. Rep. No. 98-857 (II), at 4 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686.

[6] Delays in the approval of generic drugs has cost consumers hundreds of millions of dollars. For instance, "approval of a generic version of the drug product Arava was delayed by 6 months when the brand company filed a citizen petition just before the generic drug was scheduled to receive approval. The cost to consumers was approximately $110 million. . . . Currently, delays in granting approval to the generic version of Wellbutrin XL pending review of a petition filed by Biovail is costing consumers approximately $36,999,925 per month." Letter from Sens. Debbie Stabenow and Trent Lott to Andrew von Eschenbach, acting FDA Commissioner (June 23, 2006).

[7] Senators Debbie Stabenow and Trent Lott recently raised strong concerns about the abuse of the Citizen Petition process in a letter to acting FDA Commissioner Andrew von Eschenbach, stating, "[t]he filing of strategically-timed petitions is an increasingly common method to delay generic competition." *Id.* Since 2000, there has been proposed legislation to stop the meritless citizen petitions used only to delay entry. *See* H.R. 5247, 106th Cong., 2d Sess. (2000) (proposal to amend 21 U.S.C. § 355(j)(5) to include a provision stating that the filing of a citizen petition "shall not . . . delay review and approval of [an ANDA]" unless the petition demonstrates that approval would pose a threat to public health and safety); H.R. 1862, 107th Cong. § 5 (2002) (proposed legislation would require a petitioner to have a proper purpose before filing a citizen petition).

[8] *See, e.g.*, Justina Molzon, *The Generic Drug Approval Process*, 5 J. Pharmacy & L. 275, 281 (1995) (noting that a citizen petition could severely delay an ANDA approval, and that "most Citizen Petitions are submitted shortly before an innovator product's patent expiration"); Brian Porter, Article, *Stopping the Practice of Authorized Generics: Mylan's Effort to Close the Gaping Black Hole in the Hatch-Waxman Act*, 22 J. Contemp. Health L. & Pol'y 177, 181 (Fall 2005) ("[S]ome brand name manufacturers have used delay tactics, such as filing a citizen petition requesting the FDA not to approve the generic manufacturer's ANDA. This tactic has been effective, because anytime 'a citizen petition is filed, the FDA places a hold on approval of the generic while it investigates the complaint.'"); Alison R. McCabe, Note, *A Precarious Balancing Act—The Role of the FDA as Protector of Public Health and Industry Wealth*, 36 Suffolk U. L. Rev. 787, 807 (2003) ("Seemingly legitimate concerns about the safety of generic drugs often are, behind the 'smokescreens,' another means by which brand-name companies stall generic competition.").

petition process as a means to quash competition. Sheldon Bradshaw, FDA Chief Counsel recently stated in a speech that he has

> already seen several examples of citizen petitions that appear designed not to raise timely concerns with respect to the legality or scientific soundness of approving a drug application but rather to try to delay the approval simply by compelling the agency to take the time to consider arguments raised in the petition whatever their merits and regardless of whether or not the petitioner could have made those very arguments months and months before.[9]

Not surprisingly, therefore, the FDA has rejected the vast majority of citizen petitions filed by brand-name pharmaceutical companies as baseless.[10]

Similarly here, MedImmune repeatedly has attempted to delay Sun's generic amifostine from coming to market. On June 29, 2004, *two and a half years ago*, Sun properly notified MedImmune, in a notice letter, of its submission of ANDA 77-126 that cites to Ethyol® as the reference-listed drug. In this letter, Sun clarified that its proposed ANDA for generic amifostine was intended only for the drug's chemotherapy indication:

> The original indication is to "reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer or non-small cell lung cancer." Approved dosing and administration of the amifostine is as a 15 minute infusion daily, beginning 30 minutes prior to the administration of chemotherapy. *SUN's ANDA reflects the inclusion of this indication alone, and this particular dosing regiment, in its proposed labeling.*

Sun's Notification Pursuant to FDCA § 505(j)92(B)(ii) (21 U.S.C. 355(j)(2)(B)(ii)) & 21 CFR 314.95 at 7 (Jun. 29, 2004) (emphasis added).

Upon receiving this notice, MedImmune filed suit against Sun for patent infringement and to delay Sun's entry into the market.[11] Under 21 U.S.C. § 355(j)(5)(B)(iii),

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[9] FDA Chief Counsel Sheldon Bradshaw, Speech before the Generic Pharmaceutical Association Annual Policy Conference, Sept. 19, 2005. *See also Generic Drugs: The Stalling Game*, CONSUMER REP., at 36-39 (July 2001) ("[m]ost of the time [the brand name pharmaceutical company's] motivation is simply to make it harder for the competition to come to market") (quoting Dale Connor, the director of the Division of Bioequivalence at the FDA).

[10] Elizabeth Powell-Bullock, Article, *Gaming the Hatch-Waxman System: How Pioneer Drug Makers Exploit the Law to Maintain Monopoly Power in the Prescription Drug Market*, 29 J. Legis. 21, 29 n.52 (2002) ("Brand name drug makers also commonly file citizen petitions raising safety questions about a potential competitor, which are often without merit and can delay approval. Between 1990 and 2000, eighty percent of these petitions were substantially rejected by the FDA or were withdrawn.").

[11] *MedImmune Oncology, Inc. v. Sun Pharmaceutical Industries Ltd.*, Civil Docket No. 1:04-CV-02612-MJG (D. Md. filed Aug. 10, 2004). Sun filed for summary judgment against MedImmune's claims of infringement, and that motion is pending.

MedImmune's lawsuit precluded the FDA from approving Sun's ANDA for 30 months. During this stay, on October 16, 2006, Sun received "tentative approval" from the FDA on its proposed ANDA.

With Sun's product close to coming to market, MedImmune now purports to raise safety concerns about matters of which it had notice almost two and a half years ago. Like other baseless petitions, MedImmune waited until the 30-month stay was about to expire to file a Petition that could have been filed years ago. This lengthy delay was intentional and improper. Absent the Petition, final approval from the FDA should come when the 30-month stay expires—*i.e.*, December 29, 2006. It is no secret, therefore, that MedImmune waited to the eleventh hour to take advantage of the 180-day period under 21 CFR 10.30(e)(2) allotted to the FDA to respond to a citizen petition to delay the public's access to generic amifostine.

Significantly, however, the agency has discretion to issue a decision on the Petition before the 180 days elapse. And such expedited consideration is warranted here. By expediting consideration of the Petition, the FDA would make it clear that brand-name companies like MedImmune cannot abuse citizen petitions to deprive the public of less expensive generic drugs. Alternatively, Sun's ANDA should be approved at the end of the 30-month stay notwithstanding the Petition since "there is no requirement that FDA issue a citizen petition response before approving a related ANDA[.]" FDA Report to Congress at 2, *supra* n.1.

B. The Petition Should Be Denied As A Matter Of Law

Any legal analysis of the Petition must appreciate the distinctions among the following three uses of an FDA-approved drug: (1) protected use, (2) non-protected use, and (3) off-label use. Amifostine is a selective cytoprotective agent that has both a protected use and a non-protected use. Both of these uses appear on MedImmune's label for Ethyol®, have been approved by the FDA, and are discussed in the Physicians' Desk Reference®.

The "protected use" is "protected by patent, or by exclusivity." 21 CFR 314.127(a)(7). The protected use of amifostine is to reduce the incidence of xerostomia associated with receiving radiation to treat head and neck cancer. This use is purported by the NDA applicant to be protected by U.S. Patent No. 5,994,409.

The "non-protected use" is not protected by patent, or by exclusivity. *Id.* The non-protected use of amifostine here is to reduce renal toxicity in ovarian cancer patients undergoing chemotherapy.

The third type of use—which, by definition, does not appear on the label of a brand-name drug or a generic drug—is an "off label" use of the drug. The FDA recognizes that "once a [drug] product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling," and that "unapproved or more precisely unlabeled uses may be appropriate and rational in certain circumstances, and may, in fact reflect approaches to drug therapy that have been extensively reported in medical literature." 12 FDA Drug Bulletin 4-5 (1982). An off-label use may become

so popular as to be deemed "customary or usual." *Ass'n of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 213 (D.D.C. 2002).

In the Petition, MedImmune argues that, if approved, a generic amifostine label that carves-out information about the drug's protected use would be misbranded under the Federal Food, Drug, and Cosmetic Act ("FDCA") because the label purportedly would omit material information about the drug's "usual and customary" use. According to MedImmune, amifostine's "usual and customary" use is its protected use (*i.e.*, the radiotherapy indication). It thus follows, according to MedImmune's logic, that generic amifostine is misbranded unless it includes information about the drug's radiotherapy indication.

The fatal flaw in the Petition's legal reasoning is that the term "usual and customary" applies only to off-label uses that do not appear on any label. A protected use that appears on the brand's label cannot, as a matter of law, be deemed "usual and customary" under the FDCA. The Petition thus should be denied based solely on MedImmune's concessions that generic amifostine's label: (1) can carve-out the drug's protected use, and (2) is safe for its non-protected use.

1. MedImmune Does Not Challenge the FDA's General Authority To Permit Generic Drug Labels To "Carve-Out" Protected Uses Of The Drug

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 U.S.C. § 355(j)(2)(A)(v); 21 CFR 314.94(a)(8)(iv). As MedImmune concedes, however, there are two exceptions to this general rule: (1) changes to the labeling that reflect product differences approved in a suitability petition; and (2) labeling differences required because the products are produced or distributed by different manufacturers. Pet. at 8; *see also* 21 U.S.C. 355(j)(2)(A)(v); 21 CFR 314.94(a)(8)(iv). MedImmune, therefore, "does not challenge here the agency's general authority to permit these 'carve-outs'"—*i.e.*, the second exception. Pet. at 8.[12]

2. The Relevant Question Concerning The FDA's Approval Of An ANDA That Carves Out Protected Uses Is Whether The Generic Product Will Be Rendered Less Safe Or Effective For All Remaining, *Non-Protected Conditions Of Use*

[12] Federal courts repeatedly have held that the FDA has authority to permit "carve-outs" in labeling drugs. *See Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 148 n.3 (4th Cir. 2002) (The FDA is entitled to approve a carve-out for a non-patent protected treatment. An argument otherwise "constitutes nothing more than another attempt to obtain market exclusivity for any and all uses of its drug, thereby preventing generic competitors from entering the market for any indication."); *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996) (upholding the FDA's interpretation as permitting the agency to approve an ANDA for a generic drug with labeling that excluded exclusivity-protected indications and corresponding indication-specific dosing information for which the reference-listed drug was approved).

MedImmune recognizes, as it must, that an ANDA applicant's proposed labeling for a generic drug is evidence of the intended use of that product. Pet. at 10-11.[13] Additionally, when a generic drug company proposes a "carve-out" in the labeling of a drug, the FDA has found that, "if an ANDA applicant for [a generic drug] submits proposed labeling with information only [for one particular indication], the proposed labeling would be evidence that the generic . . . drug product is intended for that very use, not for some other use." Docket No. 2003P-0321/CP1, FDA Decision, at 22 (Apr. 6, 2004).

In examining the intended use of a drug, the FDA has found that "the proposed labeling would be the most relevant and compelling, *if not exclusive*, manifestation of the objective intent of the ANDA applicant legally responsible for that proposed generic . . . drug product. *Id.* (emphasis added).[14] Accordingly, the pertinent FDA regulations provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are protected . . . by exclusivity," the agency 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*." 21 CFR 314.127(a)(7) (emphasis added); *see also* Pet. at 8. Under this approach, "the relevant question is whether a generic . . . drug product, when labeled to exclude protected information . . . will be rendered less safe or effective" than the non-protected conditions of use for the listed drug. Docket No. 2003P-0321/CP1, FDA Decision, at 18 (Apr. 6, 2004).

Here, MedImmune does not dispute that Sun's generic label lists only the drug's non-protected use for reducing renal toxicity in ovarian cancer patients undergoing chemotherapy. Accordingly, the FDA cannot assume "some other use" of the generic drug.

3. MedImmune Concedes that Sun's Proposed "Carve-Out" in the Label of Generic Amifostine Would Not Render The Product Less Safe Or Effective For The Remaining, Non-Protected Condition Of Use – *i.e.*, The Chemotherapy Indication

There is no dispute that the chemotherapy indication for generic amifostine is the only remaining, non-protected condition of use. To approve Sun's ANDA for this non-protected use, therefore, the FDA simply must find that Sun's label for generic amifostine does not render that product less safe or effective for reducing renal toxicity in ovarian cancer patients. Significantly, MedImmune does "not assert that a 'carve-out' would render a generic amifostine less safe or effective than Ethyol [brand amifostine] in treating ovarian cancer." Pet. at 8. This answers the only "relevant question" raised in the Petition, which should be denied on this basis alone. Docket No. 2003P-0321/CP1, FDA Decision, at 18 (Apr. 6, 2004).

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[13] *See also Sigma-Tau Pharmaceuticals,* 288 F.3d at 147-48 (holding that it is proper for the FDA to look to the ANDA applicant's proposed generic drug labeling as evidence of the intended use for that generic drug product in the pre-approval context).

[14] *See also* 21 CFR 201.128, which provides, in part, that "intended use" refers to the "objective intent of the person legally responsible for the labeling of drugs."

4. The Legal Arguments Raised By MedImmune In The Petition Conflict With FDA And Federal Court Precedent And Thus Should Be Summarily Rejected

MedImmune raises three legal arguments in a misguided effort to circumvent the well-established precedent discussed above. First, to set the stage for its second and third arguments, MedImmune argues that the FDCA authorizes the FDA to consider the "customary or usual" protected use of amifostine to determine whether the label for generic amifostine is misbranded or misleading. Second, MedImmune argues that Sun's proposed label for generic amifostine would be misbranded or misleading because it is foreseeable that generic amifostine, if approved, would be used more often in radiotherapy treatments of head and neck cancer patients (*i.e.*, the protected use omitted from Sun's proposed label) than for ovarian cancer patients undergoing chemotherapy (*i.e.*, the non-protected use discussed in Sun's proposed label). Finally, MedImmune argues that Sun's proposed label for generic amifostine would be misbranded or misleading because the dosage on the label for generic amifostine pertaining to its use in chemotherapy patients purportedly is higher than the dosage pertaining to the protected use in radiotherapy patients and, therefore, radiotherapy patients receiving generic amifostine might receive an overdose.

None of MedImmune's legal arguments survives scrutiny.

a. MedImmune's Primary Legal Argument Is Based On A Flawed Statutory Analysis And Conflicts With Settled FDA And Federal Court Authority

In a misguided effort to circumvent the FDA and federal authority discussed above in Sections II.B.1.-2., MedImmune relies on two sections of the FDCA and a proposed FDA regulation to argue that generic amifostine would be mislabeled or misbranded if it lacked information on the "customary or usual" use of the product—even if that use is a carved-out protected use.

According to MedImmune, amifostine's "customary or usual" use is for reducing the incidence of xerostomia in head and neck cancer patients being treated with radiotherapy (*i.e.*, amifostine's protected use). It thus follows, under MedImmune's reasoning, that "[a] generic amifostine that lacks dosing, administration, and other safety and effectiveness information for that use contains material omissions regarding consequences of that 'usual and customary' use, and therefore is misbranded." Pet. at 11.

To support this argument, MedImmune cites to FDCA § 502(a), which states that "a drug or device shall be misbranded if its labeling is misleading in any particular." 21 U.S.C. § 352(a). MedImmune then cites to FDCA § 201(n), which states:

> *If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things)* not only representations made or suggested by statement, word,

> design, device, or any combination thereof, but also *the extent to which the labeling or advertising fails to reveal facts material* in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates *under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.*

21 U.S.C. § 321(n) (emphases added).

MedImmune construes this statutory language to mean that a drug is mislabeled or misbranded if it lacks information on the "customary or usual" use of the product protected under the patent laws. MedImmune further relies on a proposed regulation (the so-called "Pediatric Rule") saying that a product's "customary or usual" use can be based on evidence of how a drug is "routinely used." Pet. at 10 (citing 62 Fed. Reg. 43900, 43908).[15] According to MedImmune, these statutes and the Pediatric Rule, when read together, stand for the proposition that Sun's label for generic amifostine is mislabeled if it does not include the purportedly routine use of the drug in radiological treatments of head and neck cancer patients—even if that use is a protected use that appears on MedImmune's label.

MedImmune's statutory interpretation, however, is based on a tortured reading of the FDCA. The term "customary or usual" use in the context of FDCA § 201(n) applies only to *off-label* uses of a drug that become commonplace – *i.e.*, routine uses of the drug that appear on no label. In fact, the express language of this statute distinguishes between "the conditions of use prescribed in the labeling or advertising" and "such conditions of use as are customary or usual." 21 U.S.C. § 321(n). Thus, a protected use that appears on MedImmune's label cannot be deemed a "customary or usual" use under FDCA § 201(n).

The United States District Court for the District of Columbia confirmed this statutory interpretation in *Association of American Physicians and Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002), which concerned a challenge to the Pediatric Rule and declared that rule invalid. In that case, the FDA invoked its authority under FDCA § 201(n) to regulate the labeling of drugs. The court found that, "in determining whether a label is misleading, the [FDA] should look to whether the 'labeling fails to reveal [material] facts . . . under such conditions of use as are *customary or usual*." *Id.* at 213 (emphasis in original). Significantly, however, the court construed the term "customary or usual" use to refer to "drugs [that] are 'commonly' or 'usually' used by children, *despite the absence of pediatric labeling*." *Id.* at 213 (emphasis added). As the court explained, such indications are referred to as off-label uses: "Prescribing adult-approved drugs to children is often referred to as going 'off-label.' An off-label use is the prescription of a drug by a doctor for a condition not indicated on the label or for a dosing regimen or patient population not specified on the label. Off-label use of

[15] The proposed Pediatric Rule would have required drug manufacturers to conduct drug tests on pediatric populations and suggest pediatric doses for drugs when ordered to do so by the FDA. As discussed below, this rule was invalidated in *Association of American Physicians and Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002).

pharmaceuticals appears to be 'generally accepted' in the medical community." 226 F. Supp. 2d 204, 206 (D.D.C. 2002).[16]

Similarly, in the Pediatric Rule itself, the FDA defined a "customary or usual" use as one that developed off-label: "In many cases, the use in pediatric patients of a drug labeled only for adults will increase over time, as physicians become aware of the drug's potential usefulness in children and familiar with the drug's uses and effects. Thus, FDA may conclude that a drug that was appropriately labeled for adult use at the time of approval is, at some later date, no longer appropriately labeled." 62 Fed. Reg. 43900, 43908.[17]

MedImmune cites no authority to support its novel position that the protected use of amifostine for the radiotherapy indication can be deemed a "customary or usual" use of that drug in the context of FDCA § 201(n). Nor could it have done so. MedImmune's statutory interpretation conflicts directly with the FDA and federal court authority discussed above holding that generic drug labels can carve out a protected use and, when deciding whether to approve such a carve-out, the FDA should focus on the safety of the label only as to the "remaining, non-protected conditions of use." 21 CFR 314.127(a)(7); *see also* cases cited in note 12, *supra*.

Even putting aside MedImmune's flawed statutory analysis, the company also ignores an FDA rule on point that exempts certain labeling for drugs used under the supervision of physicians. This rule, 21 CFR 201.5, concerns the adequate directions for use of drugs and states that directions on labels may be inadequate where there are omissions of uses for which a drug "is commonly used." Significantly, however, the FDA has stated that directions for use do not require a statement regarding the common use of a drug where, as here, "*the drug can be safely used only under the supervision of a practitioner licensed by law and for which it is advertised solely to such practitioner.*" 21 CFR 201.5 (emphasis added). Since generic amifostine is administered only by licensed practitioners and advertised only to licensed practitioners, Sun's label for generic amifostine need not address *any* customary or usual uses of the drug. Any argument that Sun's ANDA can be denied for failing to include customary or usual uses of amifostine on the generic drug label should be rejected as a matter of law.

MedImmune's second and third legal arguments are based solely on its flawed analysis of pertinent statutes and regulations. Accordingly, the FDA need not even consider those arguments. Nevertheless, as demonstrated in the following two subsections, the FDA already has rejected them.

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[16] The district court invalidated the Pediatric Rule, finding that the FDA lacked authority to require drug manufacturers to conduct certain drug studies that would have been required under that proposed rule. 226 F. Supp. 2d at 214.

[17] *See also* Final Rule: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632, 66,657 (1998) ("In determining the intended uses of a drug for which it must be adequately labeled, [the] FDA may consider *both* the uses for which it is *expressly* labeled *and* those for which the drug is commonly used.") (emphasis added).

b. The FDA Already Has Rejected MedImmune's Argument That A Label Can Be Deemed Misbranded Or Misleading Due To Foreseeable Decisions By Health Care Providers

The FDA already has rejected MedImmune's argument that a generic label needs to contain information on other uses of the product because state laws that require the substitution of generic drugs make those other uses foreseeable.[18] The brand-name company in the FDA's decision regarding generic ribavirin products took the same position as MedImmune, arguing that at least twelve states had enacted laws mandating the substitution of generic products in place of innovator products and, therefore, "this is not a case in which FDA must speculate about hypothetical or foreseeable uses." Docket No. 2003P-0321/CP1, FDA Decision at 28 (Apr. 6, 2004).

The FDA, however, found this argument to be unpersuasive and confirmed that it will review only those indications specified on the generic product's label. As the agency put it: "[The FDA] considers drug products to be therapeutically equivalent and generally interchangeable only if they are 'pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients *under the conditions specified in the labeling.*'" *Id.* at 28 (emphasis in original); *see also Sigma-Tau Pharm.*, 288 F.3d at 146. The FDA further explained that the D.C. Circuit rejected the argument that generic drugs cannot have carve-outs on labels where state laws mandate the use of generic equivalents. "[The D.C. Circuit] explicitly recognized that there were 'some state laws and health insurers that mandated substitution of generic drugs.' Yet, the court still upheld the agency's interpretation . . . 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." *Id.* at 28 (citing *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996)).

c. The FDA Already Rejected MedImmune's Argument That An ANDA Can Be Denied Because The Dose Of The Non-Protected Use On Generic Amifostine's Label Is Higher Than The Dose Of The Protected Use Omitted From That Label

MedImmune also argues that Sun's proposed label for generic amifostine would be misbranded or misleading because the dosage on the label for generic amifostine pertaining to its use in chemotherapy patients purportedly is higher than the dosage pertaining to the protected use in radiotherapy patients and, therefore, confusion concerning these different doses may result

[18] MedImmune repeatedly states that the use of amifostine for reducing renal toxicity in ovarian cancer patients undergoing chemotherapy would only be used for 1% to 2% of the patients who use amifostine. Pet. at 3, 10. According to MedImmune, the use of cisplatin to treat ovarian cancer has decreased, and this has led to a corresponding decrease in the use of Ethyol® to reduce cisplatin side-effects. Pet. at 3. Notably, however, MedImmune offers no authority to support this argument. Indeed, the use of cisplatin has not decreased but, in fact, has *increased* as shown by 2006 IMS data on kilograms of cisplatin sold (as/in dosage forms). According to 2006 IMS data, the use of cisplatin *in volume* has not decreased but, instead, only dollar sales of cisplatin have decreased because that drug is less expensive than it used to be.

in radiotherapy patients receiving an overdose. The FDA, however, has approved as safe applications carving out the protected lower dose indication on generic drug labels, finding that the carve-out on the label did not render the generic product less safe or effective for its intended use:

- The FDA approved generic versions of Capoten (captopril) that omitted the protected use in diabetic nephropathy, even though the dosing and administration for the approved generic use (hypertension) was twice as high as the recommended dosing for the carve-out indication, diabetic nephropathy (50 mg t.i.d. vs. 25 mg t.i.d). Docket No. 2003P-0321/CP1, FDA Decision, at 20 (Apr. 6, 2004) (citing the FDA's captopril decision).

- The FDA approved generic tramadol products with labeling that omitted a lower-dose dosing schedule (i.e., 25 mg, 16-day titration schedule) and retained information on the higher dose dosing schedule. As the FDA put it: "The agency affirms that generic tramadol products as labeled according to FDA's earlier decision *are no less safe or effective* than the listed drug for the remaining, nonprotected conditions of use. Specifically, tramadol drug products with labeling omitting the protected 25-mg, 16-day titration schedule are no less safe and effective than Ultram for use according to the titrated and nontitrated 50-mg dosing schedules for which they are labeled." Docket Nos. 02P-0252/PRC1, 02P-0191/PRC1, & 01P-0495/PRC1, FDA Decision, at 1 (May 31, 2003) (emphasis added).

C. The Petition Should Be Denied Because MedImmune's Arguments Also Lack Merit From A Medical Standpoint

Even putting aside the fact that the Petition is legally deficient, it should be denied on the alternative and independent ground that MedImmune has provided no evidence that the generic amifostine label, if approved, would be misbranded or misleading. As discussed in the Statement of Jeanne M. Quivey, M.D., F.A.C.R. (attached as Exhibit 1), health professionals will not confuse the chemotherapy and radiotherapy uses of generic amifostine.

Moreover, as Dr. Quivey explains, there would be no risk of harm to the patient even in the extremely unlikely event that a healthcare professional mistakenly assumed that the dose on Sun's label for treating chemotherapy patients also applied to the drug's use for reducing side effects in radiotherapy patients and thus mistakenly administered 910 mg/m^2 of amifostine as a 15-minute i.v. infusion to a patient prior to radiotherapy. To the extent MedImmune argues that a healthcare professional relying on Sun's proposed label would mistakenly administer 910 mg/m^2 of amifostine as a 3-minute i.v. infusion to a patient prior to radiotherapy, that argument makes no sense because Sun's proposed label never mentions a 3-minute i.v. infusion. To be sure, any such error would be more likely to occur under the labeling for Medimmune's Ethyol® because only the Ethyol® label, unlike the proposed generic amifostine label, includes both the 910 mg/m^2 dosage information and the 3-minute infusion schedule. Yet, no such medication

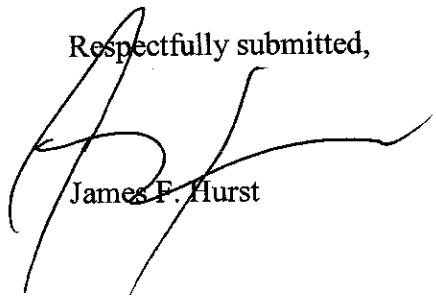
error is known to have been reported for Ethyol® itself. This fact further establishes that no such medication error could occur when administering generic amifostine.

The Petition thus can and should be denied because Sun's proposed label is safe.

III. Conclusion

For all of the following reasons, the Petition should be expeditiously denied, and Sun's ANDA for generic amifostine should be approved.

Respectfully submitted,



James F. Hurst

Enclosure