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MedImmune

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BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**Re: Docket 2006P-0410/CP1
Response to Comments of Sun Pharmaceutical Industries Ltd.**

Dear Sir or Madam:

MedImmune Oncology, Inc. ("MedImmune"), a subsidiary of MedImmune, Inc., submits these comments to address issues raised by Sun Pharmaceutical Industries Ltd. ("Sun") in its December 21, 2006 submission in opposition to MedImmune's petition (2006P-0410/C2) ("Sun Comments").

The MedImmune petition identifies the risk of improper dosing associated with proposed amifostine products that would omit from their labeling all information relating to use of the drug to reduce the incidence of xerostomia in head and neck cancer patients. Sun's opposition to the petition is based on a startling assertion by the company: *That the labeling for this generic drug is irrelevant to how the product is dosed or administered.*

This eviscerates the effect of any labeling carve-out, and undermines Sun's argument that the only relevant question is whether a generic amifostine with a labeling "carve-out" will be safe or effective for the labeled use. That position cannot stand in the face of Sun's medical expert's assertion that, as a matter of fact, healthcare professionals will not read or rely on the generic product's labeling, and will frequently administer the product for a use that is not in the labeling, at a dose not in the labeling, and by a route of administration not in the labeling.

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Further, as discussed below, Sun's comments misconstrue the relevant law and mischaracterize MedImmune's legal arguments.

A. Sun's answer to the safety risk posed by the proposed labeling of a generic amifostine is to assert that the labeling is irrelevant.

MedImmune's petition asks the agency to take action based on the risk that head and neck cancer patients may receive massive overdoses of generic amifostine, because the only dosing information in the product's "carved out" labeling would direct a dose that is more than four times that approved for head and neck cancer patients. Sun's response is that there is no risk associated with the proposed generic product, because healthcare professionals will not read or rely on the labeling that accompanies it.

According to Dr. Jeanne Quivey, whose expert medical opinion was submitted on Sun's behalf, the generic product's labeling is irrelevant. The risk of medication error because of labeling omissions does not exist, because "health professionals who administer amifostine rely on their knowledge and experience, not the particular labeling on a generic drug to determine its proper dosage for a particular indication." Sun Comments, Exh. 1 at 2. Moreover, Dr. Quivey explains, if a professional did have questions about dosing of the generic, he or she would look *not* to that product's approved labeling for information, but to the labeling for Ethyol®. *Id.* at 3-4 and Exh. 1-B.

Dr. Quivey further explains that the proposed labeling is irrelevant not just with regard to the dosage, but also the route of administration:

In fact, while the FDA-approved indications for amifostine are for administering the drug only by i.v. (intravenous) infusion, based on my knowledge of amifostine use in the clinical radiation oncology setting, physicians frequently elect to administer 500 mcg subcutaneously, a dosage which provides approximately 67% of the area under the curve (AUC) of the FDA-approved dosage values of the active metabolite of amifostine (WR-1065) to minimize the acute toxicity.

Id. According to Dr. Quivey, the subcutaneous injection of a higher dose than approved, offset by reduced bioavailability, is "particularly favored." *Id.*

These facts, entered into the record by Sun, expose the fallacy of Sun's initial argument. According to Sun, FDA should concern itself only with the labeled indication and dose, and not what may happen in actual practice. "[T]he only 'relevant question,'" Sun says, "is whether generic amifostine, when labeled to exclude protected information . . . , will be rendered less safe or effective for the labeled, non-protected use . . ." Sun Comments at 3. But the statement of Sun's expert makes clear precisely why that is not true.

Dr. Quivey, on behalf of Sun, has acknowledged Sun's expectation that its product will be used to treat head and neck cancer patients, administered subcutaneously, and at a 500 mcg dose. Accordingly, it is appropriate for the agency, in evaluating the safety of Sun's proposed product, to consider the uses that Sun says will occur. This is especially true here, where the proposed labeled indication accounts for no more than 2% of the drug's use, and there is a risk of medication error with serious consequences.

B. Sun's argument that a "customary or usual" use must be off-label makes no sense and has no support.

The central argument of our petition is that a generic amifostine with a labeling "carve-out" that excludes all information related to the drug's use in head and neck cancer patients should not be approved because it would be unsafe. Although in most circumstances it may be appropriate to ask only whether the generic drug is less safe or effective for the use that is not carved out, that is not the case here, where (1) the labeled indication would account for only 200 or so patients a year, (2) the majority of patients are prescribed the drug for the omitted indication, and (3) the huge dose differential between the two uses (the labeled dose would be more than four times the dose for the primary indication) presents a real risk to patients.

The petition also explains that, because the generic product labeling would omit information that is material with regard to a customary or usual use of the product, *i.e.*, to reduce xerostomia in head and neck cancer patients, the labeling would be misleading and the drug would be misbranded. Petition at 10-11. Sun claims that this is the "fatal flaw" in the petition, because a drug's use can be considered "customary or usual" only if the use is off-label. Sun Comments at 7. To make this argument, Sun creates a legal construct that requires an illogical reading of the statute, is not supported by the cited authority, and does not comport with the facts.

Under section 201(n) of the Food, Drug, and Cosmetic Act (FDCA), a drug's labeling can be misleading (and the drug misbranded) if it omits information that is "material with respect to consequences which may result from the use of the article . . . under the conditions of use prescribed in the labeling . . . or under such conditions of use as are customary or usual." 21 USC 321(n). With no authority (Sun simply cites to the statute), Sun asserts that "[t]he term 'customary or usual' use in the context of FDCA § 201(n) applies only to *off-label* uses of a drug that become commonplace." Sun Comments at 10 (emphasis in original). But there is nothing in the statute that supports that interpretation; the word "or" to join two categories of use is intended to broaden the application of the provision, and in no way suggests that a use cannot fall into both categories.¹ Moreover, Sun's position ignores the fact that, for a generic amifostine with

¹ Nor does the court's decision in *Association of American Physicians and Surgeons, Inc. v. FDA*, 226 F.Supp.2d 204 (D.D.C. 2002), affirm Sun's interpretation of the statute. The court merely concluded that an off-label use can become so common as to be a "customary or usual" use. Nothing in the decision suggests that a "customary or usual" use must be an off-label use.

the proposed labeling “carve-out,” use of the drug for head and neck cancer patients is off-label.²

C. Sun has not addressed MedImmune’s arguments.

Sun insists that “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.” Sun Comments at 12. But that is not MedImmune’s argument. Sun cites to FDA’s response to the Ribavirin Petition and the Fourth Circuit’s decision in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, each of which involved questions not at issue here. See MedImmune Petition at 10-11 and footnote 14. In its response to the Ribavirin Petition, FDA determined that off-label uses that may be intended uses were not relevant to determining whether a proposed generic drug was a “pharmaceutical equivalent” to the reference listed product. Apr. 6, 2004, Letter from Steven K. Galson, M.D., Docket No. 2003P-321/PDN1 at 28. Similarly, *Sigma-Tau* involved whether the agency must consider foreseeable off-label use as evidence of intended use in determining whether a product should be approved in the face of orphan drug exclusivity. See *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 146-47 (4th Cir. 2002). Moreover, in *Sigma-Tau*, the agency maintained that the only evidence it had from the company regarding the drug’s use was the proposed labeling. Here, by contrast, Sun has provided a statement from its expert, made on the company’s behalf, regarding use of the product.

Because the petition does not involve intended use, pharmaceutical equivalence determinations, or orphan drug exclusivity, the cited decisions are inapposite. There are present here circumstances that are rare, if not unique. The proposed labeling will carry an indication relevant to only 1% or 2% of patients; the “carved-out” indication is what the drug is prescribed for in a majority of instances; and state substitution laws guarantee that any approved generic will be dispensed for the “carved-out” indication, with labeling that calls for a dosage level more than three times the maximum tolerated dose for those patients.³ In these circumstances, FDA must recognize that a generic amifostine with the proposed labeling “carve-out” will lack information that is material to a “customary or usual” use. Whether or not treatment of head and neck cancer patients is an intended use is beside the point.⁴

² Sun also says that for a use to be off-label – and therefore possibly “customary or usual” – it must be off-label not only for the drug at issue, but for any other drug that might be the reference product, as well. Sun Comments at 7 (A use “that appears on the brand’s label cannot, as a matter of law, be deemed ‘usual and customary’ under the FDCA.”). Sun cites no authority for this position.

³ Moreover, Sun’s expert’s opinion makes clear that Sun anticipates significant prescriptions for the “carved-out” indication. Sun Comments at 2 (regarding how doctors “frequently” use the product).

⁴ Sun is similarly mistaken in arguing that MedImmune “ignores an FDA rule on point,” *i.e.*, 21 CFR 201.5. Sun Comments at 11. MedImmune has ignored the rule, but that is because it is not at all on point. That regulation provides that the requirement for drug labeling to include “adequate directions for use” does not require directions for uses that are by prescription only. That is because “adequate directions for

D. Conclusion

MedImmune has raised an important safety issue, driven by omissions in the labeling of proposed generic amifostine products. In response, Sun has asserted that the product labeling is irrelevant, because healthcare professionals will not rely on it. Beyond that, Sun has made specious legal arguments and mischaracterized MedImmune's position. The risks identified in the petition are real. By granting the petition, FDA can prevent those risks now, rather than waiting until any patients are harmed. We urge you to do so.

Respectfully submitted,



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cc: Paul Seligman
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use" are by definition directions for the layman. 21 CFR 201.5. Prescription drugs are exempt from that requirement, but only if the labeling contains "adequate information" for the drug's safe and effective use by healthcare practitioners. 21 CFR 201.100(c)(1). Moreover, MedImmune's position involves whether the product labeling is misleading, and the product misbranded under FDCA § 502(a). Whether a drug is misbranded for lacking adequate directions for use is a separate inquiry under FDCA § 502(f)(1).