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COMMENTS TO CITIZEN PETITION DOCKET 2006P-0410/CP1

EXPEDITED RESPONSE REQUESTED

Sun Pharmaceutical Industries, Ltd. acknowledges MedImmune Oncology, Inc.'s January 31, 2007 submission. That submission provides nothing new. Nevertheless, Sun addresses below several misstatements by MedImmune to clarify the record.

First, MedImmune distorts Dr. Quivey's statement when stating: "Dr. Quivey, on behalf of Sun has acknowledged Sun's expectation that its product will be used to treat head and neck cancer." Dr. Quivey's expert statement, which speaks for itself, makes no such assertion about Sun's expectations concerning generic amifostine. Sun intends to market its generic amifostine only for its labeled use (and not for the radiotherapy indication), and there is no dispute that the proposed label is safe for that use. That ends the inquiry.

It appears that MedImmune's distortion may be designed to suggest that Sun's ANDA can be denied based on a foreseeable use of the product. The FDA, however, already has rejected this argument. *See* Docket No. 2003P-0321/CP1, FDA Decision, at 28 (Apr. 6, 2004) (holding that the foreseeable use theory is not a bar to generic drug approvals). And so have the Fourth and District of Columbia Circuits. *See Sigma-Tau Pharm., Inc. v. Schwetz*, 288 F.3d 141, 147 (4th Cir. 2002) (rejecting the foreseeable use theory, and holding that such a theory would create "formidable problems" for the agency and "would be profoundly anti-competitive");

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Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1500 (D.C. Cir. 1996) (holding “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 use of the pioneer is a matter of indifference”).¹

Second, MedImmune continues to disregard FDA precedent and regulations as well as decisions by the federal courts – all of which expressly permit “carve-outs” in drug labeling and provide that a generic product that is admittedly safe and effective for its *labeled* indication must be approved.² As clearly discussed in Sun’s December 21, 2006 submission, MedImmune’s statutory interpretation conflicts directly with this authority. A protected use that appears on the brand’s label (i.e., the radiotherapy indication in this case) cannot, as MedImmune asserts, be deemed a “usual and customary” use under FDCA § 201(n). MedImmune’s baseless arguments about safety issues for a different, *unlabeled* use – a carve-out expressly permitted by regulation – should not and cannot delay Sun’s final approval as a matter of law.

Third, MedImmune distorts Sun’s challenge to MedImmune’s factual assertion that health professionals will be confused by the proposed label for generic amifostine. According to MedImmune, “Sun’s response [to the petition] is that there is no risk [of confusion] associated with the proposed generic product, because healthcare professionals will not read or rely on the labeling that accompanies it.” This grossly mischaracterizes and oversimplifies Sun’s response.

In its December 21 submission, Sun argued that health professionals using generic amifostine for reducing renal toxicity in ovarian cancer patients receiving chemotherapy (the use described on Sun’s proposed label) would consult and follow the label. Sun further argued, however, that health professionals prescribing the drug for off-label uses would not *blindly* rely on that labeling for other uses too, and merely assume that the same dose should be applied to patients receiving amifostine in the radiotherapy setting. To support this position, Sun submitted the expert statement of Dr. Jeanne M. Quivey, M.D., F.A.C.R., which demonstrated that health professionals will not be confused by the proposed label for generic amifostine because, among other reasons: (1) health professionals who use amifostine are trained in how to administer the drug for labeled and off-label uses, thus showing that they will not blindly apply the proposed labeled amifostine dosage for the chemotherapy indication to radiotherapy patients; (2) at least three health professionals will have the opportunity to review the dosage regimen for each instance of prescribed amifostine, thus providing checks to eliminate confusion; (3) health professionals who provide cancer care fully appreciate the differences in chemotherapy and radiation therapy dosing schedules and thus will not blindly assume that a chemotherapy dosage applies to a radiotherapy dosage; (4) health professionals generally understand that a dosage

¹ MedImmune’s distortion also may reflect a baseless effort to lay the foundation for another attempt by MedImmune to delay Sun’s entry into market – this time, by suggesting that Sun will implicate MedImmune’s ‘409 patent, which claims certain methods for using the drug product. Again, however, Sun intends to market its generic amifostine only for its labeled use, which was first approved and published more than one year before the ‘409 patent’s priority date. Thus, any effort by MedImmune to establish that Sun implicates MedImmune’s ‘409 patent would fail.

² Docket No. 2003P-0321/CP1, FDA Decision, at 14 (Apr. 6, 2004); *see also* 21 CFR 314.127(a)(7); *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 147 (4th Cir. 2002).

pertaining to one indication of a drug does not necessarily apply to a second indication; and (5) no reasonable physician who had a question about the proper dose would risk the patient's health by merely assuming that the dosage for one indication applies to another indication. (Dr. Quivey Statement at 2-4.)

Fourth, MedImmune still provides no support whatsoever for its argument that Sun's proposed label raises "a risk of medication with serious consequences" because "head and neck cancer patients may receive massive overdoses of generic amifostine."³ Because MedImmune does not even specifically define what it means by "massive doses," Sun has addressed all the possibilities below. As Dr. Quivey's statement demonstrated, the result clearly is that MedImmune's factual assertions concerning the safety of Sun's proposed label for generic amifostine are unsupported and incredible.

MedImmune apparently argues that patients receiving radiation therapy for head and neck cancer are at risk if a health professional administers on a single occasion a dose of $910\text{mg}/\text{m}^2$ over 15 minutes. Dr. Quivey explained that the exact opposite is true – *i.e.*, patients "would not be harmed if this same dosage regimen ($910\text{ mg}/\text{m}^2$ administered as a 15-minute i.v. infusion) were mistakenly administered to a patient prior to receiving radiation therapy." (Dr. Quivey Statement at 4.) When a dose of $910\text{mg}/\text{m}^2$ over 15 minutes is given, a health professional monitors the blood pressure periodically, and it is clear from Dr. Quivey's statement that amifostine would be safe if administered at this dose in patients receiving cisplatin for ovarian cancer.

To the extent MedImmune argues that health professionals may administer a dose of $910\text{mg}/\text{m}^2$ over 3 minutes (instead of the 15 minutes mentioned on the proposed label), this argument makes no sense. The proposed label makes no mention of a 3-minute i.v. infusion. Therefore, MedImmune's argument presumes that health physicians will commit severe malpractice – an argument that has no basis whatsoever in reality or common sense. In fact, such a dosage error would be more likely to occur with Ethyol® itself – which, unlike Sun's proposed label, *does* mention a 3-minute i.v. infusion.

To the extent MedImmune argues that health professionals will read $910\text{mg}/\text{m}^2$ over 15 minutes from the ovarian cancer indication, and administer the same dose to head and neck cancer patients not just once, but daily for 4-5 days in a week for 3-6 weeks, such an argument also would be based on wild speculation and defy logic. As Dr. Quivey made clear, given the significantly different dosing schedules for chemotherapy treatment versus radiation treatment, there would be no reason for health professional to assume arbitrarily that the dosing information for chemotherapy patients would apply to patients undergoing radiation treatment for head and neck cancer. (Dr. Quivey Statement at 3.)

MedImmune's argument about the risk of "massive overdoses" also ignores the different settings and personnel involved in the different therapies. The $910\text{mg}/\text{m}^2$ over 15 minutes infusion is given in a different hospital ward by a different health professional than the $200\text{mg}/\text{m}^2$ over 3 minutes infusion. Further, any suggestion that health professionals will

³ MedImmune fails to dispute any of Dr. Quivey's expertise or her opinions regarding the safety of the proposed labeling for generic amifostine. Dr. Quivey's statement makes clear there are no safety risks for generic amifostine.

continue to make the same error over several weeks (again, an assertion that is unsupported) ignores the reality that, as Dr. Quivey explained, at least three health professionals will have the opportunity to review the dosage regimen for each instance of prescribed amifostine. MedImmune thus asks FDA to assume that not just one – but three – health professionals will commit severe medical malpractice when administering generic amifostine.

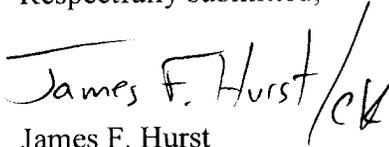
Even putting aside the obvious factual flaws in MedImmune's "massive overdoses" argument based on a "dose differential," as discussed in Sun's December 21 submission, that argument is barred by FDA's own precedent. *See* Docket No. 2003P-0321/CP1, FDA Decision, at 20 (Apr. 6, 2004); Docket Nos. 02P-0252/PRC1, 02P-0191/PRC1, & 01P-0495/PRC1, FDA Decision, at 1 (May 31, 2003). MedImmune's safety concerns amount to an argument that physicians cannot be trusted to prescribe medication for indications that do not appear on the drug's label before them. This argument runs afoul of "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." *Sigma-Tau Pharm.*, 288 F.3d at 147 (emphasis added).

Finally, MedImmune still provides no support for its summary and irrelevant assertion that "the labeled indication would account for only 200 or so patients a year" – *i.e.*, "no more than 2% of the drug's use." Sun is not aware of any evidence to support such statistics, and MedImmune has submitted no such evidence. To the contrary, as noted in footnote 18 on page 12 of Sun's December 21 submission, cisplatin use has *increased* in recent years and, therefore, there is a significant need for Sun's generic amifostine to benefit patients for the labeled chemotherapy indication. Sun anticipates that once generic amifostine becomes available at a price much less costly than MedImmune's Ethyol, the use of amifostine to reduce cisplatin side-effects will increase.

In sum, the motivation behind MedImmune's citizen petition and January 31, 2007 submission remains clear – this is yet another improper effort by a brand name company to delay entry into the market of a generic drug manufactured by a competitor. Ethyol® is many times costlier than generic amifostine, and MedImmune's citizen petition is an effort to extend its own monopolistic profits, *not* to promote public safety. Now that the 180-day period has expired, Sun again urges an expeditious resolution of MedImmune's petition to avoid any unwarranted delay in the availability of a generic version of amifostine.

Thank you for your consideration of this matter.

Respectfully submitted,


James F. Hurst

cc: Elizabeth Dickenson, Food and Drug Administration
William C. Bertrand, Jr., MedImmune Oncology, Inc.

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