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July 30, 2003

VIA FACSIMILE AND FEDERAL EXPRESS

Docket Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA Docket No. CP1 2003P-0321 (Petition of ICN Pharmaceuticals, Inc. And Ribapharm Inc. Regarding Approval Of Generic Ribavirin)

On behalf of Geneva Pharmaceuticals, Inc. ("Geneva"), we submit the following comments to the Citizen Petition submitted by ICN Pharmaceuticals, Inc. and Ribapharm Inc. (collectively "ICN").

First and foremost, ICN's petition should be put into proper context. ICN neglects to inform the FDA that it is the owner of three U.S. patents covering the administration of ribavirin to treat disease. ICN has licensed those patents to Schering Corporation ("Schering"), the NDA holder for the drugs Rebetron® and Rebetol®. ICN's petition was apparently prompted by a recent decision by the United States District Court for the Central District of California holding that ICN's patents do not cover the administration of ribavirin at dosages of 1000 or 1200 mg/day and, therefore, Geneva's proposed labeling (which is directed to dosages of 1000 or 1200 mg/day) does not infringe ICN's patents. Spurned by the courts, ICN has now turned to the FDA asking it to ignore established law permitting a generic company to carve out from its labeling information that is still patent-protected, and to compel a change in the labeling of generic ribavirin so that the drug falls within the coverage of ICN's patents. ICN's petition, therefore, should be seen for what it is: a last-ditch attempt to keep generic competition off the market to protect ICN's revenue stream.

Geneva's generic ribavirin product ("Geneva's product") is indicated for use in combination with standard interferon alpha-2b, which is sold by Schering under the brand name Intron® A. Geneva's product is not indicated for use with peg-interferon alpha-2b, which is sold

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under the brand name PEG-Intron®. As originally filed, Geneva's labeling was based on the approved labeling for Rebetron®, the combination product of ribavirin capsules and Intron® A which was the only FDA-approved labeling for ribavirin capsules when Geneva filed its ANDA on June 22, 2001. The labeling for Rebetron® contains dosage instructions of 1000 or 1200 mg/day ribavirin in combination with standard interferon. Subsequent to the filing of Geneva's ANDA, on July 25, 2001, Schering obtained approval for Rebetol® (ribavirin) as a stand-alone product, which was approved only at a dosage of 1000 or 1200 mg/day in combination with Intron® A. Subsequently, Schering obtained approval for a new dosage regimen of 800 mg/day ribavirin in combination with a different interferon product, PEG-Intron®, and amended the labeling for Rebetol® so that it included both the original indication of Rebetol® with a dosage of 1000 or 1200 mg/day in combination with Intron® A and the new indication of Rebetol® with a dosage of 800 mg/day in combination with PEG-Intron®. That new indication is the subject of Schering's U.S. Patent No. 6,177,074 (the "'074 patent") which claims a method of treating hepatitis C patients "comprising administering to the patient, in combination, (i) a conjugate comprising PEG_{12000} and interferon alpha-2b [peg-interferon] . . . and (ii) ribavirin."

Geneva and two other generic manufacturers, Three Rivers Pharmaceuticals LLC and Teva Pharmaceuticals USA, have carved out from their ribavirin labeling the indication for use in combination with PEG-Intron® because that indication is arguably protected by the '074 patent. Because the '074 patent claims a use for which Geneva is not seeking approval, the FDA permitted Geneva to file a "section (viii)" statement with respect to the '074 patent consistent with 21 U.S.C. § 355(j)(2)(A)(viii). In so doing, and in allowing the generic manufacturers to carve-out the protected information from their labeling, and for the reasons set forth below, the FDA has correctly applied its own regulations consistent with its statutory mandate.

A. The FDA Has Authority To Approve An ANDA That Omits Labeling Protected By Patents

As ICN correctly states, it is settled that the labeling for a proposed generic drug product may exclude, or carve out, indications or other aspects of labeling protected by patent. ICN Citizen Petition dated July 16, 2003 ("Petition") at 7. That right is found in the Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), which provides that a generic manufacturer's labeling must be "the same as the labeling approved for the listed drug . . . except for changes required . . . because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v); see Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1499-1501 (D.C. Cir. 1996) (upholding FDA's interpretation of § 355(j)(2)(A)(v) to permit omission of an indication or other aspect of labeling protected by patent or exclusivity). As the legislative history of the FDCA makes clear, Congress intended this section to permit a generic company to carve out from its labeling the portions of the innovator's labeling that remain patent-protected:

> The Applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the application could seek approval for only the angina pectoris indication.

H.R. Rep. No. 857 (Part I), 98th Cong., 2d Sess. at 21, reprinted in 1984 U.S.C.C.A.N. 2654-55.

This view has been codified in the FDA's rules, which provide in relevant part:

> Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

21 C.F.R. § 314.94(a)(8)(iv) (emphasis added). Differences in generic and listed drug labels are permitted where "aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such 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 C.F.R. § 314.127(a)(7). Moreover, the Act and pertinent regulations also permit an ANDA applicant to submit a "section (viii)" statement to the FDA whenever a patent listed in the FDA's Orange Book claims a method of using the listed drug and the applicant is not seeking approval for that claimed use. See 21 U.S.C. § 355(j)(2)(A)(viii).

The FDA's interpretation of the Act to permit a generic company to carve out the protected portion of the innovator's labeling has been expressly approved by the courts. In Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1499-1501 (D.C. Cir. 1996), the D.C. Circuit held that, under 21 U.S.C. § 355(j)(2)(A)(v), a generic manufacturer's labeling may exclude indications that appear on the innovator's label.[1] The Court reasoned that this interpretation is not only consistent with the other parts of the statute and with legislative intent, but is also necessary to prevent abuse of the statute by innovator drug companies which could otherwise delay approval of an ANDA simply by amending their labeling to include new protected indications. Id. at 1500.

[1] A copy of this decision is attached hereto as Tab 1.

Thus, there can be no question that Geneva is permitted to carve out labeling protected by patents. The only remaining question is whether excluding use in combination with PEG-Intron® renders the Geneva's product "less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 C.F.R. § 314.127(a)(7) (emphasis added). In a closely analogous case regarding generic forms of the pain medication Ultram®, the FDA determined that carving out a protected dosage regimen does not render the non-protected dosage regimen less safe or effective. See FDA letter, dated June 11, 2002, re Docket Nos. 01P-0495/CP1, 02P-0919/CP1 and 02P-0252/CP1, a copy of which is attached at Tab 2. In that case, three generic manufacturers sought approval to market generic Ultram® (tramadol hydrochloride) labeled with dosage instructions to administer 50 to 100 mg every 4 to 6 hours as needed for pain relief, not to exceed 400 mg per day, the same dosing regimen for Ultram® when it was originally approved in 1995. In 1998, the NDA holder, R.W. Johnson Pharmaceutical Research Institute ("Johnson"), received approval for a new dosing schedule, one that provided for a 10-day titration with a starting dose of 50 mg/day. Id. at 2. In 1999, Johnson received approval for a second, longer titration schedule with a starting dose of 25 mg/day that is increased over a 16-day period. Johnson claimed patent protection over this 16-day, 25 mg titration dosing regimen. Id. at 3. In addition, Johnson was granted 3-year marketing exclusivity for both titration dosing schedules, although at the time of its citizen petition, Johnson's exclusivity for the 10-day, 50 mg schedule had expired. Id.

The three generic manufacturers sought approval for labeling that contained only the dosing regimen in the Ultram® label as originally approved, having carved out the 16 day, 25 mg titration dosing schedule to avoid Johnson's patents and exclusivity. The FDA first determined that it had ample authority to approve ANDAs that omit labeling protected by patents or exclusivity. Id. at 5-6. The only remaining question for the FDA, therefore, was whether excluding the 16-day, 15 mg titration dosing regimen rendered the generics less safe or effective than the listed drug "for all remaining non-protected conditions of use" under 21 C.F.R. 314.127(a)(7) (emphasis added). Id. at 6. The agency concluded it did not. Id. at 8. In addition, the FDA concluded that because the shorter 10-day, 50 mg titration schedule was not protected by patent or exclusivity, the generic label can and should include that titration schedule. Id. at 7.

There, as here, the omission of a protected dosing schedule from a generic label is not treated any differently under the statute or the regulations from any other carve-out of protected labeling. It is a fully permissible carve-out and does not render the remaining non-protected dosing schedules any less safe or effective. Consequently, ICN's assertion that Geneva's proposed labeling must be amended to include dosing instructions for ribavirin's use in combination with PEG-Intron® is simply wrong and disingenuous. As ICN is well aware, ICN's licensee Schering owns the '074 patent directed to the combination of PEG-Intron® and ribavirin. Under 21 C.F.R. § 314.94(a)(8)(iv) and the holding of Bristol-Myers, and consistent with the FDA's determination concerning generic Ultram®, Geneva may properly exclude instructions from their labeling relating to PEG-Intron® in light of that patent. According to the reasoning of

Bristol-Myers, approval of Geneva's product should not be blocked because the innovator added an indication to its labeling (ribavirin in combination with pegylated interferon) that is outside the scope of Geneva's ANDA (limited to the original indication of ribavirin in combination with standard interferon).

B. The Exclusion Of Use With PEG-Intron® Does Not Render Geneva's Product "Misbranded"

Under the FDCA, "[a] drug or device shall be deemed to be misbranded . . . if its labeling is false or misleading in any particular." 21 U.S.C. § 502(a). A drug may also be deemed misbranded "[u]nless its labeling bears (1) adequate directions for use . . . ." 21 U.S.C. § 352(f). There is simply nothing false or misleading about the proposed labeling for Geneva's product. The proposed labeling states that it is approved for use with interferon alpha-2b at dosages of 1000 or 1200 mg/day, depending on the patient's weight, and at a reduced dosage of 600 mg/day for patients with anemia. That is the same labeling that was approved for the listed drug product, Rebetol® in combination with Intron® A, which the FDA has already determined contains "adequate directions for use."

Merely excluding one indication from the proposed labeling does not render that labeling misbranded. If it did, a generic manufacturer could never carve out a protected indication because every new indication would be grounds for exclusivity and, potentially, further patent protection. Thus, an innovator company could keep generic competition out of the market indefinitely by obtaining approvals for new indications or new combinations with other drugs.

1. Geneva's Product Is Not Labeled For Use With PEG-Intron®

At the core of ICN's argument that the proposed labeling for Geneva's product is misbranded lies ICN's assertion that Geneva's product is "intended for use with PEG-Intron." See Petition at 10-11. That assertion is incorrect. An "intended use" is defined as the "objective intent of the persons legally responsible for labeling the drugs." 21 C.F.R. § 201.128. "The intent is determined by such persons' expressions [i.e., product labeling] or may be shown by the circumstances surrounding the distribution of the article." Id. When determining the intended use of a generic product that is the subject of an ANDA, the FDA looks to the generic manufacturer's proposed labeling. Sigma-Tau Pharm., Inc. v. Schwetz, 288 F.3d 141, 146-47 (4th Cir. 2002) (holding FDA properly determined the intended use for generic drugs by relying primarily upon the proposed labeling provided by the companies). Indeed, "no court has ever found that a product is 'intended for use' or 'intended to affect' within the meaning of the [FDCA] absent manufacturer claims as to that product's use." Id. (quoting Brown & Williamson Tobacco Corp. v. FDA, 153 F.3d 155, 163 (4th Cir. 1998) (internal quotation omitted), aff'd 529 U.S. 120 (2000)).

Here, Geneva's proposed labeling makes no mention whatsoever of PEG-Intron®. Thus, Geneva's product is clearly not intended for use with PEG-Intron®. ICN's argument that *Rebetol®* is intended for use with PEG-Intron® because *Rebetol®'s* labeling repeatedly refers to PEG-Intron® is a non-sequitur. At issue here is the intended use of Geneva's ribavirin product, not Rebetol®. Although ICN urges that the labeling of the generic and innovator drugs must be the same with regard to the drug's intended use, as discussed above, the Act, FDA regulations, the federal courts and the FDA say otherwise. Simply, a generic drug manufacturer is permitted to carve out a use covered by patent or exclusivity. Indeed, the very nature of a carve-out means that the generic drug will be intended for fewer uses than that of the listed drug.

On point is Sigma-Tau Pharm., Inc., 288 F.3d 141, 146-47 (4th Cir. 2002), in which the Fourth Circuit upheld the FDA's approval of generic versions of the drug levocarnitine to treat a rare condition known as carnitine deficiency in people with inborn metabolic disorders. Because the plaintiff's seven-year exclusivity for that disease under the Orphan Drug Act had expired, the FDA approved the ANDAs of two generic manufacturers to market and sell the drug for the unprotected indication. The plaintiff, however, still maintained orphan-exclusivity for a second disease, ESRD. The plaintiff challenged the approvals, arguing that generic levocarnitine was "intended for use" to treat both the protected (ESRD) and unprotected (inborn metabolic disorders) diseases. The Fourth Circuit upheld the FDA's determination that the generic drug was intended for use for the unprotected disease alone because the labeling was restricted to the unprotected disease. The court rejected plaintiff's contention that the FDA was obligated to look beyond the labeling. The court reasoned that to require the FDA to consider market factors in addition to labeling content would create "formidable problems" for the agency and might result in "extensions of exclusivity periods that Congress never intended." Id. at 147.

Geneva's generic ribavirin product is manifestly intended for use only with Intron® A in dosages of 1000 or 1200 mg/day. If ICN were permitted to graft *Rebetol®'s* intended use onto the proposed labeling of every ANDA filer for generic ribavirin, the launch of generic ribavirin could be postponed time and again. Under ICN's theory, every time Rebetol® is approved for a new indication protected by patent or exclusivity, generic manufacturers would be required to include the new indication for Rebetol®, effectively preventing the generic manufacturer from carving-out that indication and entering the market, a result plainly at odds with the Act.

2. Geneva's Product And PEG-Intron® Are Not A "Combination Product"

ICN also argues that generic ribavirin and PEG-Intron® are a combination product within the meaning of the FDCA. Again, ICN is incorrect. As defined in 21 C.F.R. § 3.2(e), the term combination product includes ". . . [a] drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product

the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose . . . ." 21 C.F.R. § 3.2(e) (emphasis added).

As discussed above, Geneva's product is not labeled for use with PEG-Intron® and, therefore, it is not a combination product with PEG-Intron®. Moreover, the approval of Geneva's product would not require a change in the proposed labeling of Intron® A, the only product with which Geneva's product is approved to be used.

3. Any FDA Concerns Regarding Patient Safety May Be Addressed In The Medication Guide

The FDA has already determined that Geneva's product should be distributed with an approved Medication Guide. The purpose of a Medication Guide is to provide plain-English instructions to patients taking prescription drugs on an outpatient basis without direct supervision by a health care professional. 21 C.F.R. § 208.1(a). By regulation, Medication Guides are to include a section entitled "How should I take (name of drug)?" followed by information on the proper use of the drug product, such as "[a] statement stressing the importance of adhering to the dosing instructions, if this is particularly important." 21 C.F.R. 208.20(b)(5). Thus, the Medication Guide provides ample opportunity to address any concerns the FDA may have regarding the required dosing regimen of Geneva's product.

C. The FDA Need Not Issue A "Guidance Document"

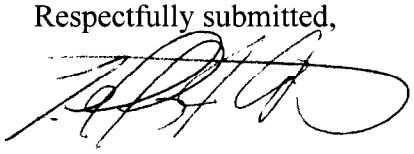
ICN's assertion that the FDA must provide the public with an opportunity for comment under the agency's "good guidance practice" regulations is also incorrect. The agency's "good guidance" rules do not apply to communications directed to individual persons or firms. 21 C.F.R. § 10.115(b)(3). Moreover, guidance documents are only required where the agency is communicating "new or different regulatory expectations to a broad public audience for the first time" or where "regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public audience." 21 C.F.R. § 10.115(e).

Here, there has been no change in agency regulations or policy; the FDA is merely adhering to a well-established and court-approved interpretation of the Act and clear agency regulations. As ICN admits, a generic manufacturer's right to carve out patent protected information from its labeling is "settled." Petition at 7. There is nothing novel or unique about the application of these settled rules to the present situation; the FDA has permitted similar carve-outs in the Ultram case and others. Therefore, no public process is necessary. Indeed, under ICN's unduly broad view of the FDA's good guidance practice regulations, nearly every FDA action in which it applies established FDA regulations to the particular facts of an individual ANDA would require a guidance document. This cannot be the case, and ICN's assertion that the FDA must issue a guidance document should be rejected.

D. Conclusion

ICN's citizen petition improperly seeks to compel Geneva and other generic manufacturers of ribavirin to include the protected subsequent indication of Rebetol® in combination with PEG-Intron® as a means of postponing indefinitely the entry of generic ribavirin. Geneva's proposed labeling of its ribavirin product is limited to the original and still approved indication of ribavirin in combination with Intron® A. Consistent with the Act, Congressional intent, FDA regulations and federal court decisions, Geneva has properly carved out the protected indication of ribavirin in combination with PEG-Intron®. Geneva respectfully submits that, for the foregoing reasons, the FDA should promptly approve Geneva's ribavirin ANDA as submitted.

Respectfully submitted,



Jeffrey J. Oelke

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Enclosures