HOGAN & HARTSON
L.L.P.

DAVID M. FOX
PARTNER
(202) 637-5678
DMFOX@HHLAW.COM

COLUMBIA SQUARE
555 THIRTEENTH STREET, NW
WASHINGTON, DC 20004-1109
TEL (202) 637-5600
FAX (202) 637-5910
WWW.HHLAW.COM

October 3, 2003

VIA HAND DELIVERY

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

Re: *Citizen Petition, Reply to Opposing Comments*
Docket Number 2003P-0321

Dear Sir or Madam:

On July 16, 2003, we submitted the above-referenced petition on behalf of ICN Pharmaceuticals, Inc., and Ribapharm Inc. ("ICN/Ribapharm") challenging the proposed marketing of generic versions of Rebetol® (ribavirin, USP) that lack approval or labeling for use with PEG-Intron® (peginterferon alfa-2b) (the "Petition"). On July 29, 2003, we submitted supplemental information in support of our petition (the "Supplement").

We now submit the following response to comments submitted in opposition to the Petition by Geneva Pharmaceuticals, Inc. ("Geneva"), dated July 30 and August 26, 2003, and Three Rivers Pharmaceuticals, LLC and Par Pharmaceutical, Inc. ("Three Rivers/Par"), dated July 25 and August 21, 2003. These comments make one thing absolutely clear: The law and the facts require that the Petition be granted in full.

I. The Comments Fail to Rebut the Conclusion that the Labeling of PEG-Intron Describes and Defines Intended Uses for the Proposed Generic Products

As shown in the Petition, the labeling of PEG-Intron establishes that Rebetol is intended for use in combination with PEG-Intron. *See*

ICN/Ribapharm Petition at 10-11. As a matter of law and fact, generic versions of Rebetol must be approved and labeled for each use for which they are intended, including the use of Rebetol in combination with PEG-Intron. Otherwise, such products will be misbranded under section 502 of the Food, Drug, and Cosmetic Act (the "FDCA"), and unapproved under section 505 of the FDCA. 21 USC 352(a) and (f); 21 USC 355(a).

Geneva and Three Rivers/Par, at bottom, have only one response to the Petition. As captured by Geneva, they argue that the "proposed labeling makes no mention whatsoever of PEG-Intron®. Thus, Geneva's product *is clearly not intended for use with PEG-Intron®*." Geneva Comments (July 30, 2003) at 6 (emphasis added); *accord* Three Rivers/Par Comments (July 25, 2003) at 3. That is, by sanitizing their own labeling, they avoid having to seek approval for the use of generic Rebetol with PEG-Intron.

Their argument, in the purest sense, is too clever by half. Rebetol is not a stand-alone product; rather, it is one-half of an approved combination product. As such, the intended use of Rebetol is defined not only by the labeling for Rebetol, but also by the labeling of the companion product, PEG-Intron. By carving out from their labeling all references to PEG-Intron, the generics have not changed the intended use of their products. Instead, they have rendered their products unlawful as a matter of basic food and drug law.

A. The Labeling of PEG-Intron Establishes that Generic Rebetol is Intended for Use with PEG-Intron

The "intended use" of a drug product is defined by labeling claims and by the circumstances surrounding the distribution of the product. *See* 21 CFR 201.128. Where a person knows that his product is being offered for a use for which the product lacks adequate labeling, he is required *as a matter of law* to label his product for that use. *Id.* That is,

> if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide

> adequate labeling for such a drug which accords with such other uses to which the article is to be put.

Id.

Here, the labeling of PEG-Intron establishes beyond any doubt that Rebetol is intended for use in combination with PEG-Intron. *See ICN/Ribapharm Petition,* Tab 3 (PEG-Intron labeling). The package insert for PEG-Intron contains more than one hundred references to the use of PEG-Intron with "ribavirin" and "Rebetol." *See id.* The package insert also includes more than thirty references to the "combination" use of PEG-Intron with "ribavirin" and "Rebetol." *Id.* Even the black box warning at the beginning of the labeling states: "**Use with ribavirin**." *Id.* at 1 (emphasis in original).

Added to this is the fact that PEG-Intron is distributed with mandatory patient labeling, in the form of a Medication Guide, that contains more than fifty references to "ribavirin," "Rebetol," and the combination use of PEG-Intron with Rebetol (ribavirin). *See ICN/Ribapharm Petition,* Tab 6 (PEG-Intron MedGuide). And, as shown in the Petition, the package insert and Medication Guide for PEG-Intron repeatedly direct the reader to the companion package insert and Medication Guide for Rebetol. *See, e.g., id. at* 1 ("**If you are taking PEG-Intron/REBETOL combination therapy, also read the Medication Guide for REBETOL (ribavirin, USP) Capsules**") (emphasis in original). In short, the two products are inextricably knotted together through labeling, through regulatory approval and, to date, through joint marketing by a single sponsor.

Geneva and Three Rivers/Par appear not to grasp the fact that they are seeking to market a generic version of a product that is approved only for use as part of a combination product. Geneva, for example, believes that ICN/Ribapharm is arguing "that *Rebetol*® is intended for use with PEG-Intron® because *Rebetol*®'s labeling repeatedly refers to PEG-Intron® . . . ." Geneva Comments (July 30, 2003) at 6 (emphasis in original). They have it completely wrong. It is the repeated references to Rebetol *in the labeling of PEG-Intron* that is the focus of ICN/Ribapharm's Petition.

Geneva even argues that its generic Rebetol product and PEG-Intron would not be considered a "combination product" under 21 CFR 3.2, because "Geneva's product is not labeled for use with PEG-Intron® . . . ." Geneva Comments (July 30, 2003) at 7. Again, Geneva fails to grasp the significance of the PEG-Intron labeling and approval. So long as PEG-Intron is specifically labeled and approved for use with Rebetol, equal weight must be given to the labeling of PEG-Intron. The labeling of PEG-Intron clearly establishes that PEG-Intron and Rebetol is a combination product within the meaning of 21 CFR 3.2, as well as section 503(g)(1) of the FDCA. 21 USC 353(g)(1) (establishing standards for products that constitute a combination of a drug, device, or biological product). Try as they might, the generics simply cannot avoid the text of the labeling of PEG-Intron.

Finally, this is not a case in which FDA must speculate about hypothetical or foreseeable uses; nor is it a case in which there is an absence of express labeling claims. *Cf. Sigma–Tau Pharmaceuticals, Inc. v. Schwetz,* 288 F.3d 141 (4th Cir. 2002) and *Bristol-Myers Squibb Co. v. Shalala,* 91 F.3d 1493 (D.C. Cir. 1996). Here, the intended use of the proposed generic Rebetol products is established by the labeling of PEG-Intron. Any patient or healthcare provider who reads the approved labeling of PEG-Intron is told – clearly and repeatedly – that PEG-Intron and Rebetol (ribavirin, USP) are intended to be used together.

B. The Licensing Agreements Between the Generic Sponsors and Schering Leaves No Doubt that Generic Rebetol Products Must be Labeled and Approved for Use with PEG-Intron

On July 29, 2003, we submitted a supplement to the Petition, to include information (as reported to the press) on the licensing agreements between the generic applicants and the sponsor of PEG-Intron, Schering-Plough Corporation ("Schering"). The supplement showed that three generic applicants (Geneva, Three Rivers, and Teva Pharmaceuticals USA, Inc. ("Teva")) had entered into contracts with Schering under which Schering will receive a royalty payment for sales of generic Rebetol products. In return, the generic sponsors received permission to use the inventions claimed in Schering's patents – including patents on the use of ribavirin in combination with PEG-Intron.

The agreements leave no doubt that the labeling of PEG-Intron bears directly on the intended uses of the proposed generics. As we suggested in our supplement, the generic sponsors will be paying Schering a royalty on all sales of generic Rebetol, including payments for the use of generic Rebetol in combination with PEG-Intron. When given the opportunity, neither Geneva nor Three Rivers/Par denied that the royalty payments under the agreements include payments based on the sale of generic Rebetol for use with PEG-Intron.1/ In fact, Three Rivers/Par conceded that its licensing agreement with Schering covers "the use of ribavirin in combination with either interferon *or peginterferon*." Three Rivers/Par Comments (Aug. 21, 2003) at 1 (emphasis added). Thus, while the labeling of the proposed generics may purport to carve out use with PEG-Intron, the licensing agreements do not. *See FDA Warning Letter to Global Pharm. Corp.* (July 20, 1998) (methyltestosterone product labeled for human use was nevertheless intended for veterinary use based on sales agreement to distribute the product for use in dogs).

With these agreements, Geneva, Three Rivers/Par, and Teva have expressly and knowingly tied their products to the labeling and marketing of PEG-Intron. Beyond the textual relationship described above, the generic sponsors have fully integrated the marketing of their products with the marketing of PEG-Intron. In this way, the generic sponsors are simply paying Schering to do what the generics themselves are prohibited by law from doing: namely, labeling and marketing their products for use with PEG-Intron. Under these circumstances, and given the undeniable textual relationship between the products, FDA must consider the labeling of PEG-Intron as directly relevant to the intended uses of the proposed generic Rebetol products.

The only discernible point raised by Geneva and Three Rivers/Par with respect to the agreements is that Schering has retained the three-year exclusive labeling rights under the Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Act") to the Rebetol/PEG-Intron combination. *See* Geneva Comments (Aug. 26, 2003) at 2; Three Rivers/Par Comments (Aug. 21, 2003) at 1-2. That is, while Geneva and Three Rivers/Par bargained for the rights to Schering's patents on the Rebetol/PEG-Intron combination – to ensure that they would not be liable for

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1/ Teva has failed to file any comments to this proceeding.

infringement of Schering's patents – they did not bargain for the Hatch-Waxman exclusivity rights.

Once again, this proves nothing. In fact, with Schering marketing PEG-Intron for use with Rebetol, the generics have absolutely no need for the labeling rights to the combination product. All the labeling that is needed to promote the use of generic Rebetol with PEG-Intron is found in the labeling of PEG-Intron.

II. The Labeling Carve Out Rule Does Not Trump the Statutory Prohibition Against Marketing Misbranded and Unapproved New Drugs

Geneva and Three Rivers/Par argue that FDA has a regulation, 21 CFR 314.94(a)(8)(iv), that allows for the omission from labeling of information that is protected by patent. They insist that with a simple "labeling carve out" under 21 CFR 314.94(a)(8)(iv), they can sever the link between their generic Rebetol products and the labeling of PEG-Intron.

The regulation, however, does not trump the unqualified statutory prohibition against the marketing of misbranded and unapproved new drugs. 21 USC 331(a) and (d), 502(a) and (f), and 505(a); *see, e.g., Atlantic City Electric Co. v. Federal Energy Regulatory Commission*, 295 F.3d 1, 11 (D.C. Cir. 2002) (statutory rights must prevail over principles memorialized in a regulation); *Robbins v. Bentsen*, 41 F.3d 1195, 1198 (7th Cir. 1994) (regulations "cannot trump the plain language of statutes" and, instead, must be read in a way that makes the regulation compatible with the statute).

Here, the generics fail to recognize that the agency's regulation is, properly so, permissive and not mandatory. *See* 21 CFR 314.94(a)(8)(iv) (stating that the labeling of a generic product "may include differences" because an aspect of the labeling is protected by patent). In a case such as this, where the omission of information renders the product misbranded under section 502 of the FDCA, there is no entitlement to use carved-out labeling.

Finally, Geneva argues that if the mere exclusion of one indication from a proposed generic product were to render the product

misbranded, "a generic manufacturer could never carve out a protected indication, because every new indication would be grounds for exclusivity and, potentially, further patent protection." Geneva Comments (July 30, 2003) at 5. This, of course, proves too much. For a single entity drug (*i.e.*, a monotherapy), in which the generic sponsor controls all of the labeling that accompanies the product, the deletion of an indication is not likely to render the product misbranded. There is no other labeling that dictates the sale and use of the product. However, where two products are specifically approved for use in combination, a labeling carve out becomes much more difficult; unless the carve out can be accomplished in a mutually conforming way – affecting the labeling of both products in the combination – it renders at least one of the products misbranded.[2]/

In short, Geneva and Three Rivers/Par insist that after carving-out an indication from their labeling, to avoid a patent, the only question is whether the remaining labeling describes a safe use. *See* Three Rivers/Par Comments (July 25, 2003) at 2 and Geneva Comments (July 30, 2003) at 4. We disagree. Nothing in the statute or regulations exempts a generic drug sponsor from compliance with the fundamental aspects of the FDCA, including sections 301(a) and 502 (prohibiting the marketing of misbranded drugs) and sections 301(d) and 505 (prohibiting the marketing of unapproved new drugs). While in most cases the omission of an indication allows for the product to be approved, in this instance the omission causes the product to be misbranded and ineligible for approval.[3]/

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[2]/ Geneva argues at length that the agency's approach to the labeling of generic versions of Ultram® (tramadol) is "closely analogous" to PEG-Intron/Rebetol because Ultram® involved carving-out protected dosing instructions. Geneva Comments (July 30, 2003) at 4. Ultram®, however, is approved as a monotherapy and, as such, there was no labeling for a companion product – an existing, approved product used in combination with the reference drug – that would continue to bear the information that had been carved-out of the proposed generic label.

[3]/ Even if the generic products were to state that they are "not intended for use with PEG-Intron," that would not solve the problem. The labeling of PEG-Intron, along with the licensing agreement, creates an intended use for the generic products that cannot be disclaimed. Objective evidence of intended use, including the labeling at issue here, cannot be negated by subjective claims of intent. *See FDA Citizen Petition Response to William B. Schultz et al.* (July 1, 2002), Docket No. 01P-0573 (citing numerous cases showing that "subjective claims of intent" are not determinative of intended use) (emphasis in original).

III. The Proposed Generic Products Present a High Risk of Medication Error

Geneva and Three Rivers/Par insist that a generic Rebetol product, labeled for use with Intron-A®, is perfectly safe. *See* Three Rivers/Par Comments (July 25, 2003) at 2; Geneva Comments (July 30, 2003) at 4. In fact, because of the cross-labeling issues described above, and the proposed use of a Medication Guide that omits key dosing information, the generic sponsors are well on the way to creating the ideal conditions for serious medication error. *See* 68 FR 12406, 12472 (Mar. 14, 2003) (defining "medication error" to include any "preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer").

As shown in the Petition, the approved daily dose of ribavirin for use in combination with Intron-A is 1000 to 1200 mg per day, based on the patient's body weight. *See ICN/Ribapharm Petition*, Tab 1 at 19 (Rebetol labeling). And, patients are advised that they may take the drug with or without food. *Id.* In contrast, the recommended daily dose of ribavirin for use in combination with PEG-Intron is 800 mg per day regardless of body weight, *id.* at 19-20, and patients are specifically directed to take the drug only *with* food. *Id.* at 20. Thus, patients using PEG-Intron in combination with ribavirin use 20 to 33 percent less ribavirin *each day* under different conditions.[4]

According to Three Rivers/Par, the proposed carve out includes the removal of "three sentences" from the Rebetol Medication Guide on the dosing of ribavirin for use with PEG-Intron. Three Rivers/Par Comments (July 25, 2003) at 3. With this carve out, if only one patient who is prescribed the PEG-Intron/Rebetol combination receives generic Rebetol in place of the brand-name product, that patient will have been placed at risk for a serious medication error. The patient will be directed by the PEG-Intron Medication Guide to follow the instructions in the Rebetol or ribavirin Medication Guide.

4/ Ribavirin is a toxic substance; it is the subject of both a black box warning section and a patient-directed Medication Guide. *See ICN/Ribapharm Petition*, Tab 1 (Rebetol labeling) and Tab 7 (Rebetol MedGuide). It should always be used at the lowest effective dose.

The patient will, in turn, be directed by the generic's Medication Guide to use a higher dose of ribavirin than is necessary. Even more, the patient may not even realize that the Medication Guide omits the correct dosing information. The purpose of giving patients user-friendly labeling, for products that present serious health risks, will be completely undermined if the generics are allowed to proceed as they suggest.5/

"Patient safety" is one of five initiatives that make up the agency's recently announced Strategic Plan. *See* FDA's Strategic Action Plan Protecting and Advancing America's Health: Responding to New Challenges and Opportunities (Aug. 2003). Reducing preventable medication errors, by providing patients with accurate and comprehensive information about their medications, is a cornerstone of the agency's Strategic Plan. In the face of these important goals, it defies logic that the generics would continue to seek permission to market generic Rebetol *by removing dosing information from mandatory patient labeling* on a use that now represents the standard of care for Hepatitis C patients.6/

5/ Nor can the generics claim that the substitution of generic Rebetol, for patients who are prescribed PEG-Intron/Rebetol combination therapy, is merely speculative. At least 12 states have now enacted laws mandating the substitution of generic products in place of equivalent innovator products. *See* Tab 1, attached, National Assoc. of Boards of Pharmacy, *2002-2003 Survey of Pharmacy Law*, at 52-53. Pennsylvania (the home state of Three Rivers Pharmaceuticals) specifically mandates the substitution of A-rated generics as listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("*Orange Book*"). *See* 35 Pa. Cons. Stat. Ann. 960.2 and 960.3(a) (2003) (pharmacists "shall substitute" less expensive "generically equivalent drugs," defined as A-rated drugs listed in FDA's *Orange Book,* unless the purchaser or prescriber requests otherwise); *see also* 105 Code Mass. Regs. 720.050 (2003) (automatically listing FDA A-rated drugs on the Massachusetts List of Interchangeable Drug Products). For purposes of assessing the safety of the proposed generic products, particularly where the generic products intentionally omit information for well known uses of the drug from patient-directed labeling, these laws are clearly relevant.

6/ The National Institutes of Health (NIH) has issued a "consensus statement" finding, among other things, that there is evidence from at least three large clinical trials that treating Hepatitis C with pegylated interferon and ribavirin produces a considerably better sustained viral response than monotherapy or standard interferon-ribavirin combination therapy. *See* Tab 2, attached hereto, NIH Consensus Statement on Management of Hepatits C: 2002 (June 12, 2002), at 17-20 and 25-26. According to Schering, "PEG-Intron and Rebetol combination therapy is now the most-prescribed treatment for chronic hepatitis C worldwide." *See* Tab 3, attached hereto, *Schering-Plough to Initiate First Head-to-Head Study of Leading Hepatitis C Therapies*, PRNewsire-FirstCall (Sept. 23, 2003).

IV. The Need for Public Process

Geneva and Three Rivers/Par assert that guidance on carving out appropriate labeling for generic ribavirin is not required because the agency's advice and counsel on the topic falls within the scope of providing "comments" on proposed labeling "submitted during the course of ANDA review" and was "directed to individual persons or firms." Three Rivers/Par Comments (July 25, 2003) at 5; Geneva Comments (July 30, 2003) at 7.

Based on public information, it appears that the key meetings involving the carve out for ribavirin were conducted by the Office of Chief Counsel, not the review division. The available information indicates that the decision applies to all "generic drug *applicants*." *See ICN Pharmaceuticals, Inc. v. Geneva Pharmaceuticals Technology, Inc.*, 272 F. Supp.2d 1028, at 1048, n. 18 (C.D. Calif. July 14, 2003) (emphasis added). Thus, the letter establishes agency policy concerning a class of products, not routine ANDA review. Therefore, the agency must follow its good guidance practices.

V. Conclusion

The generic sponsors cannot "label around" the fact that Rebetol is a combination product whose intended use is defined as much by its own labeling as by the labeling of PEG-Intron. With or without the labeling carve out, the labeling of PEG-Intron describes and defines key intended uses for the proposed generic Rebetol products. The failure by the generics to seek approval for these uses, and to include these uses in their labeling, renders them unapprovable as a matter of law and unsafe as a matter of sound medical practice.

For these reasons, we respectfully request that the agency grant the Petition in full.

Sincerely,

David M. Fox

Enclosures