HOGAN & HARTSON
L.L.P.

1217 '03 JUL 17 AM

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

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

July 16, 2003

ELECTRONIC AND 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

CITIZEN PETITION

The undersigned, on behalf of ICN Pharmaceuticals, Inc., and Ribapharm Inc. (together "ICN/Ribapharm"), submits this petition under 21 CFR 10.30 to request that the Commissioner of Food and Drugs (the Commissioner) refrain from approving abbreviated new drug applications (ANDAs) for ribavirin products with labeling that omits information about the product's use in combination with PEG-Intron® (peginterferon alfa-2b).

As a general matter, a product approved under an ANDA must bear the same labeling, and must be approved for the same conditions of use, as an approved or "reference listed drug" (RLD) product *(see infra)*. The Food and Drug Administration (FDA) by regulation allows labeling for a generic product to differ from the RLD if "an indication or other aspect of labeling" is protected by patent or exclusivity. 21 CFR 314.94(a)(8)(iv). However, in the case of Rebetol® (ribavirin, USP), which is approved *only* for use in combination with certain interferon alfa-2b products (including PEG-Intron), the issue of such a labeling "carve-out" is subject to competing statutory requirements that prohibit the marketing of misbranded and unapproved products.

For this reason, and as explained in detail below, we are compelled to petition the agency to ensure that the labeling for all generic ribavirin products will contain mutually conforming labeling for use with both Intron-A and PEG-Intron.

2003P-0321 CP1

A. ACTIONS REQUESTED

By this petition, the undersigned requests that the Commissioner refrain from approving generic Rebetol products under section 505(j) of the Food, Drug, and Cosmetic Act (the FDCA) with labeling that omits information on the use of ribavirin with PEG-Intron. A generic Rebetol product that omits information on the use of the product with PEG-Intron would be misbranded under section 502 of the FDCA, and would lack the required approval under section 505 of the FDCA. The introduction or delivery for introduction into interstate commerce of a misbranded or unapproved drug is prohibited under section 301 of the FDCA. *See* 21 USC 331, 352, and 355.

Further, any general guidance the agency is providing to the class of sponsors who may be seeking to market generic ribavirin products, on the issue of labeling and cross-labeling, must be provided under the agency's "good guidance practice" regulations, with an opportunity for public participation. *See* 21 USC 371(h) and 21 CFR 10.115. The petitioner, therefore, requests that the Commissioner defer action on the labeling of generic ribavirin products until a public process is initiated and completed on the issues raised in this petition.

B. STATEMENT OF GROUNDS

1. Background

Rebetol (ribavirin, USP) is a component of a drug/biologic combination product, approved exclusively for use with Intron-A (interferon alfa-2b, recombinant) Injection or PEG-Intron (peginterferon alfa-2b) Powder for Injection, for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alpha interferon. 1/ The combination of Rebetol and Intron-A can also be used in patients who have relapsed following alpha interferon therapy.

1/ *See* Rebetol labeling. Tab 1.

Intron-A and PEG-Intron are each approved for use alone or in combination with Rebetol in treating chronic hepatitis C. 2/ Rebetol, however, is not approved for use as a stand-alone "monotherapy." The safety and effectiveness of Rebetol is wholly dependent upon use with Intron-A or PEG-Intron.

For that reason, FDA initially approved Rebetol as a co-packaged product with Intron-A, marketed under the brand name Rebetron®. 3/ Three years later, in July 2001, FDA authorized the marketing of a stand-alone version of Rebetol capsules, to provide patients and healthcare providers with flexibility in adopting individualized ribavirin and interferon-based treatment plans. 4/ Although Rebetol is now available as a separate product, it remains approved solely as a combination product for use with Intron-A and PEG-Intron. It is *not* approved for use as a monotherapy and it has not been found by FDA to be effective against hepatitis C except in combination with Intron-A or PEG-Intron. 5/

The dosing schedule for the combination use of Rebetol differs depending on the type of interferon alfa-2b being used. Rebetol was initially approved for combination use with only Intron-A (Rebetron Combination Therapy), with the recommended dose of Rebetol being 1000 or 1200 mg/day in two divided doses depending on the patient's body weight. 6/ However, when FDA later approved the use of Rebetol with PEG-Intron, the agency approved a lower dosing schedule – only 800 mg/day of Rebetol in two divided doses, regardless of the patient's weight. 7/ This difference in dosing schedules is set forth in the labeling

---

2/ *See* Intron-A labeling; PEG-Intron labeling. Tabs 2; 3.

3/ *See* Approval Letter for Rebetron (June 3, 1998); Rebetol labeling. Tabs 4; 1.

4/ *See* Approval Letter for NDA 20-903/S008 (July 25, 2001). Tab 5.

5/ *See* Rebetol labeling black box warning ("Rebetol monotherapy is not effective for the treatment for chronic hepatitis C virus infection and should not be used alone for this indication"). Tab 1.

6/ *See* Rebetol labeling. Tab 1.

7/ *See* Rebetol labeling; Peg-Intron labeling. Tabs 1, 3.

for Rebetol; the labeling for PEG-Intron contains, as it must, reciprocal dosing information on the combination use with Rebetol. 8/

More specifically, the labeling for Rebetol, Intron-A, and PEG-Intron contains reciprocal information regarding warnings and precautions, clinical studies, indications and usage, and dosage and administration. The labeling for PEG-Intron, as set forth below, includes ribavirin labeling in virtually every section, including numerous instructions to "See Package Insert for Rebetol."

- *Boxed Warning*: Notes potential serious side effects when used with ribavirin (e.g. birth defects, death of the unborn child, hemolytic anemia, and aggravated cardiac disease) and advises users to "see Rebetol package insert for additional information and other warnings."

- *Clinical Studies:* Describes a randomized study that compares two PEG-Intron/Rebetol regimens (800 mg and 1000/1200 mg).

- *Indications and Usages:* PEG-Intron is used as a monotherapy or in combination with Rebetol for the treatment of chronic hepatitis C.

- *Warnings (related to combination use):* Warns of potential bone marrow toxicity, cardiovascular events, pulmonary disorders, anemia, and contains a specific section on "Use with Ribavirin" advising users to "See Rebetol Package Insert".

- *Precautions:* "Patients receiving PEG-Intron ... in combination with Rebetol should be directed in its appropriate use, informed of the benefits and risks associated with treatment, and referred to the *Medication Guides for PEG-Intron and, if applicable, Rebetol."*

- *Carcinogenesis, Mutagenesis, and Impairment of Fertility:* Warns that ribavirin is a potential carcinogen and refers users to the Rebetol package insert for more information "relative to PEG-Intron therapy in combination with ribavirin."

8/ *Id.*

- *Pregnancy Category X: Use with Ribavirin:* Warns that Rebetol therapy is contraindicated in pregnant women and in male partners of pregnant women, and advises users to "See the Rebetol Package Insert".

- *Adverse Reactions:* Contains a table of adverse events in PEG-Intron/Rebetol combination therapy trials.

- *Laboratory Values:* Describes changes in certain laboratory values during PEG-Intron/Rebetol combination treatment.

- *Overdosage:* Describes known maximum overdosage of Rebetol.

- *Dosage and Administration:* Recommends PEG-Intron dosing (1.5ug/kg/wk) and Rebetol dosing (800 mg/day) for combination therapy and guidelines for dose reduction or discontinuation of the combination therapy for patients with depression or hematologic toxicity.

In addition, Rebetol, PEG-Intron, and the co-packaged Rebetron product are among a very limited number of drug products that FDA has determined "pose a serious and significant public health concern" requiring distribution to patients of an FDA-approved Medication Guide (MedGuide). 21 CFR 208.1(a). 9/ FDA concluded that MedGuides are "necessary to patients' safe and effective use" of these drug products, thus requiring that they be distributed to the patient upon the filling of each prescription. 21 CFR 208.1(b), 208.24(b)(1). As with the physician-directed prescribing information, the MedGuide includes product contraindications, warnings, precautions, directions for use, and side effects; however, it is addressed in lay terms and begins with the most important information that the patient should know about the product. A MedGuide is part of the FDA-approved product labeling and a manufacturer must obtain FDA approval of it before distribution. *Id.* at 208.24(a).

9/ *See* Medication Guides for PEG-Intron, Rebetron, and Rebetol. Tab 6. According to the agency, FDA's determination of the necessity of a MedGuide under 208.1(b) "is a high standard that will be met in only a small number of cases." 63 Fed. Reg. 66,378, 66,387 (Dec. 1, 1998). FDA estimated "that on average no more than 5 to 10 products per year would be determined to be of 'serious and significant concern' and would thus require Medication Guides." *Id.* at 66,388.

As with the physician labeling, the MedGuide for PEG-Intron includes numerous cross-references to use with ribavirin. For example, the MedGuide:

- Begins and ends with a bolded instruction for patients taking PEG-Intron/Rebetol combination to also read the MedGuide for Rebetol (ribavirin, USP) Capsules.
- Notes that PEG-Intron and PEG-Intron/Rebetol combination therapy can have serious side effects that may cause death in rare cases.
- Describes the most important information regarding Rebetol (e.g., risk of birth defects and/or death of the unborn child, need to use adequate birth control to avoid pregnancy) and the most important information regarding the PEG-Intron and PEG-Intron/Rebetol therapies (e.g., risk of mental health, heart, blood, and body organ problems).
- Describes how to take PEG-Intron or PEG-Intron/Rebetol, including the instruction to take Rebetol with food, to take it at the same time every day (twice a day with food). In bold, it again advises the patient to read the MedGuide for Rebetol for complete instructions on how to take Rebetol.

In short, the labeling for Rebetol and the labeling for PEG-Intron were approved as a mutually conforming unit. The two products are intended to be used together and, as such, the labeling for each product is designed to ensure complete consistency.

Along these lines, we understand that on February 5, 2003, FDA informed at least one of the proposed generic drug manufacturers, Three Rivers Pharmaceuticals, LLC (Three Rivers), that the agency could not approve an ANDA for a generic ribavirin product that lacks labeling on the combination use of ribavirin with PEG-Intron.

According to the agency's public calendar, representatives of Three Rivers met with senior agency officials on June 24, 2003, to discuss labeling issues associated with generic Rebetol products. On June 27, 2003, we understand that the agency issued a letter that effectively reversed the February 5, 2003, decision. Under the June 27 letter, the agency stated that generic drug applicants, as a class,

may "carve-out" information in the labeling of their products on the use of ribavirin with pegylated interferon. We have no information on the basis for the agency's June 27 letter and whether and how the agency addressed the fact that the other component of the Rebetol combination product, PEG-Intron, continues to bear labeling on the use of ribavirin with pegylated interferon. *See generally* Memorandum of Decision and Order at 30 n.18, *ICN Pharmaceuticals, Inc. et al. v. Geneva Pharmaceuticals Tech. Corp. et al.* (C.D. Cal. July 15, 2003) (Nos. 02-3544-MRP, 02-3543-MRP, 02-8142-MRP, 02-9358-MRP).

2. Statutory and Regulatory Framework

a. Section 505(j)

Under section 505(j) of the FDCA, the agency is authorized to approve drug products without an independent showing of safety and effectiveness, provided the product is shown to be "the same as" a "listed" product previously approved under section 505(b) or 505(j). A product approved under section 505(j) must be approved for the same conditions of use, and must bear the same labeling, as the listed product referenced in the application. 21 USC 355(j)(2)(A)(i) and (v); *id.* at 355(j)(4); 21 CFR 314.92(a)(1).

It is settled that certain specific differences in labeling between the innovator and generic are permitted. *See* 21 USC 355(j)(2)(A)(v). By regulation, FDA has established that to be the "same as" an innovator product, a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted." 21 CFR 314.92(a)(1). More specifically, under the agency's regulations, differences between the labeling of the proposed generic product and the listed drug may include "omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act." 10/ 21 CFR 314.94(a)(8)(iv). However, FDA must refuse to approve an ANDA where labeling differences, because of patent or exclusivity,

---

10/ FDA's regulation authorizing the agency to approve generic drug products that omit a protected indication or other patent- or exclusivity-protected information from the labeling has been upheld in *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996) and in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002).

"render the proposed drug product less safe or effective than the listed drug for all remaining non-protected conditions of use." *Id.* at 314.127(a)(7).

b. Labeling and Intended Use

Under section 502(f) of the FDCA, a drug is misbranded unless its labeling bears adequate directions for the intended use of the product. 21 USC 352(f). The introduction or delivery for introduction into interstate commerce of a misbranded drug is prohibited. *Id. at* 331(a). Moreover, the FDCA prohibits any person from introducing or causing the introduction into commerce of any drug that is intended for a use for which a drug has not been approved by FDA, even if that same drug product is approved for a different use. *Id.* at 355(a) and 331(d). 11/

The label and labeling of a product is the primary basis on which the intended use of a product is determined. *See generally* 21 CFR 201.128. "Labeling is defined in section 201(m) of the FDCA as "all labels and other written, printed, or graphic matter upon any article . . . or accompanying such article." 21 USC 321(m). In *Kordel v. United States*, 335 U.S. 345 (1948), the Supreme Court concluded that the phrase "accompanying such article" included literature that was shipped separately and at different times from the drug products with which they were associated. Under the FDCA, a drug product that does not bear labeling for all of its intended uses is deemed as a matter of law to be misbranded and the introduction of such a drug into commerce is prohibited. 21 USC 331(a) and 331(k); 62 Fed. Reg. 64073, 64075 (Dec. 3, 1997). In addition, the introduction of a new drug into commerce for a use for which it is labeled, but for which it lacks approval, is also prohibited. 21 USC 331(d) and 355(a).

c. Combination Products

As defined in 21 CFR 3.2(e), the term "combination product" includes drug, device, or biological products that are packaged separately but which, according to the labeling of the products, are "intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use . . . ." As FDA recently explained:

11/ *See generally,* Letter from Dept. of Health & Human Services to Washington Legal Found. (Jan. 28, 2002). Tab 7.

> A combination product is also defined to include a product that is intended for use only with an approved product where both are required to achieve the intended use, indication, or effect, and the labeling of the approved product needs to be changed to reflect this use. For example, if a device to aerosolize medication works only with a specific aerosolized drug, the device would be labeled for use with this drug and the two products would be a combination product.

67 Fed. Reg. 65,801 (Oct. 28, 2002).

Mutually conforming labeling or "cross-labeling" ensures that the marketing of one FDA-approved product does not cause another product to enter commerce for an unapproved use or for a use that would render the product misbranded. *See* 21 USC 331 ("The following acts *and the causing thereof* are hereby prohibited: (a) The introduction or delivery for introduction into interstate commerce of any . . . drug . . . that is adulterated or misbranded" (emphasis added)). In addition, mutually conforming labeling helps to decrease medication errors by reducing the possibility of confusion if the labeling of two drug products that are intended to be used together contain inconsistent or alternative information.

3. Argument

Rebetol and PEG-Intron are, respectively, a drug and a biological product. They are approved for use as a drug-biological combination product. *See generally* 21 USC 353(g)(1). While Rebetol and PEG-Intron may be obtained separately, they are intended to be used together and, as such, each is required by law to contain mutually conforming and consistent labeling.

The use of conforming labeling in this instance ensures that the ribavirin component of the combination does not enter commerce for intended uses for which it lacks adequate labeling and for which it lacks approval. It also advances the important policy interest of ensuring that patients and health care providers do not receive inconsistent dosing information when presented with the labeling from both components of the combination.

By "carving-out" from their labeling information regarding use with PEG-Intron, prospective generic manufacturers would, at best, be changing only one-half of the approved combination. They cannot escape the fact that PEG-Intron continues to bear labeling on the use of PEG-Intron with ribavirin. The PEG-Intron labeling establishes an intended use for ribavirin for which the generic ribavirin products must be labeled and approved. The removal of information from one component of an FDA-approved combination regarding use with the other component effectively renders the individual products, as well as the combination, misbranded and unapproved within the meaning of the FDCA.

For these reasons, the agency must not approve a generic version of Rebetol that omits from the required labeling any information on the use of ribavirin with PEG-Intron.

a. Ribavirin is Intended For Use with PEG-Intron

The primary basis on which FDA determines the intended use of a product is by reference to "labeling." *See, e.g.,* 21 CFR 201.128. The term "labeling" is defined broadly to include all written material that accompanies the product and, likewise, is applied broadly to include all material for which there is a "textual relationship" between the materials and the product. *See Kordel v. United States*, 335 U.S. 345 (1948). As the Court stated in *Kordel*, "[n]o physical attachment of one to the other is necessary. It is the textual relationship that is significant." 12/ 335 U.S. at 350; *see also U.S. v. Urbuteit*, 335 U.S. 355 (1948) (analyzing "labeling" based on the extent to which the written materials are part of an "integrated distribution program").

12/ Lower court cases after *Kordel* reinforce a broad reading of the term "accompanying." *See United States v. Diapulse Mfg. Corp. of America*, 389 F.2d 612 (2d Cir. 1968); *V.E. Irons, Inc. v. United States*, 244 F.2d 34 (1st Cir. 1957), *cert. denied*, 354 U.S. 923 (1957). In addition, the courts have considered whether the information and the product are part of an integrated distribution program, where, for example, the information and the product originate from the same source or the information is designed to promote the distribution and sale of the product, even if such sale is not immediate. *See United States v. 47 Bottles, More or Less, Jenasol RJ Formula "60"*, 320 F.2d 564 (3d Cir. 1963); *United States v. Guardian Chemical Corp.*, 410 F.2d 157 (2d Cir. 1969). To the extent that any of the generic manufacturers have entered into co-promotion, marketing, or licensing agreements with the sponsor of PEG-Intron, that would represent clear evidence of an integrated distribution scheme.

As shown above, the textual relationship between the labeling of Rebetol and the labeling of PEG-Intron is manifest. In no less than five instances, the labeling for PEG-Intron specifically refers the reader to the labeling for Rebetol. In at least eleven instances in the physician labeling for PEG-Intron, detailed information is provided on the use of PEG-Intron with Rebetol. The Medication Guide that accompanies PEG-Intron likewise is textually intertwined with the labeling for Rebetol. *See* above. On this basis alone, the labeling of PEG-Intron is central to, and defines, the intended use of Rebetol.

Even more, Rebetol is specifically approved for use with PEG-Intron, and PEG-Intron is specifically licensed for use with Rebetol. They were studied in combination and approved as a combination product. As such, the labeling and intended use of each component of the combination is inextricably linked.

In short, the ANDA applicants seeking approval to market generic Rebetol products cannot change the intended use of their products – to disclaim use with PEG-Intron – simply by changing the labeling of their products. Try as they might, the labeling for PEG-Intron is textually linked to Rebetol and, as such, defines the intended use of Rebetol and any generic versions thereof. By carving PEG-Intron information from the labeling, the generics have not changed the intended use of their products; rather, they have simply rendered their products misbranded and unapproved. *See* 21 USC 352(f) and 355(a).

b. FDA Must Require the Generic Products to Bear Labeling on Use with PEG-Intron

Under section 502(f) of the FDCA, a drug is misbranded unless its labeling bears adequate information on each intended use of the product. 21 USC 352(f). In addition, the labeling of a drug cannot be false or misleading in any particular. 21 USC 352(a). The FDCA prohibits introduction or delivery into interstate commerce any product that is misbranded. 21 USC 331(a). A "new drug" must be approved for each and every use for which it is labeled. 21 USC 355(a). The introduction or causing for introduction into interstate commerce of an unapproved new drug is prohibited. 21 USC 331(d).

Approval of labeling for one component of a combination product that is not reciprocal or mutually reinforcing of the labeling for the other component would, in this instance, render one or both components misbranded as false and misleading, as failing to disclose material facts, and as failing to provide adequate

directions for use. 21 USC 321(n) and 352(f). Among many concerns, the omission of PEG-Intron information from a generic Rebetol product would leave patients and healthcare providers with inconsistent labeling on proper dosing. While the PEG-Intron labeling would instruct on the use of an 800 mg dosing schedule, the ribavirin product would instruct the patient to use a 1000-1200 mg dosing schedule. The potential for erroneous dosing and for confusion is manifest, as is the potential for the ribavirin labeling, in its entirety, to be misleading.

In short, it would be unlawful as a statutory matter, and suspect as a policy matter, to approve generic Rebetol products that omit labeling on use with PEG-Intron. Patients who are prescribed PEG-Intron will continue to be directed to use their products with ribavirin. However, when they endeavor to use the ribavirin component, they will – in the case of one of the proposed generics – be directed by the labeling of the generics to use an incorrect and unapproved dosing schedule.

The agency must solve this issue before it takes any further actions with respect to this class of proposed generic drug products. The agency very clearly cannot approve a misbranded drug, cannot authorize the marketing of a drug that is intended for uses for which it lacks approval, and cannot approve a drug that is labeled in a way that is certain to cause medication errors.

c. FDA Must Initiate a Public Process Before Providing Further Guidance on the Labeling of Ribavirin Products

Finally, in developing labeling for generic ribavirin products, FDA must to adhere to its own good guidance practice (GGP) requirements. 13/ *See* 21 CFR 10.115. The agency is required by law to issue a public "guidance document" to communicate recommendations on the "labeling" for regulated products, except where the communication is directed to individual firms or persons. 21 CFR 10.115(b)(2) and (b)(3). If the issue involves "changes in interpretation or policy that are of more than a minor nature," then the agency must publish a draft of the

---

13/ These regulations, of course, carry the force and effect of law, and FDA, like private parties, is bound to follow them. *Cherokee Nation of Oklahoma v. Babbitt*, 117 F.3d 1489, 1499 (D.C. Cir. 1997) ("An agency is required to follow its own regulations.").

any means – other than a guidance document – to communicate regulatory expectations to a broad public audience. *Id.* at 10.115(e).

Any agency decision on the labeling of generic ribavirin will effect a large class of companies, including those already marketing Rebetol and other approved ribavirin products, as well as at least three (and perhaps more) generic applicants. The agency's decision in this regard is of more than a "minor nature" as it will impact the labeling for an entire class of products. Meetings and correspondence with individual sponsors are insufficient to communicate to the class "such changes in interpretation or policy." As such, FDA is required by regulation to issue guidance and seek public comment.

C. ENVIRONMENTAL IMPACT

The actions requested in this petition are not within any of the categories for which an environmental assessment is required pursuant to 21 CFR 25.22.

D. ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted if requested by the Commissioner.

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

F. CONCLUSION

On behalf of ICN/Ribapharm, we request that the Commissioner refrain from approving ribavirin products under section 505(j) with labeling that carves out information, directions for use, and dosing schedules regarding the combined use with PEG-Intron. We further request that any additional consideration of the generic class labeling issues raised in this petition be done under an appropriate public process, in which all interested persons may participate and comment.

Respectfully submitted,

David M. Fox
Hogan & Hartson LLP
(202) 637-5678

Enclosures