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October 24, 2003

VIA FEDERAL EXPRESS

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 – Docket Number 2003P-0321**

Comments Regarding the Letter dated October 3, 2003, Submitted by Hogan & Hartson, LLP on behalf of ICN Pharmaceuticals, Inc. and Ribapharm, Inc.

The Petition is Without Merit and Should Immediately Be Denied

Dear Sir/Madam:

On behalf of Three Rivers Pharmaceuticals, LLC and their marketing partner, Par Pharmaceutical, Inc., this letter responds to the additional comments filed on October 3, 2003 by ICN Pharmaceuticals, Inc. and Ribapharm Inc. (collectively "Ribapharm"). Ribapharm's latest comments simply rehash arguments described initially in its Citizen Petition and supplemented in a letter dated July 29, 2003. These comments do nothing more than continue the further delay of generic competition for Ribavirin Capsules currently pending approval before the Agency, since Ribapharm has already lost its patent case before the courts.

As stated in our previous response, the Citizen Petition is without merit and should be denied, with the immediate approval of Three Rivers' ANDA for Ribavirin Capsules. Americans who suffer with Hepatitis C should have immediate access to a high quality, therapeutically equivalent, lower cost version of Ribavirin Capsules.

I. Intended Use Must Focus on the Labeling of the Manufacturer's Product

Ribapharm begins by restating its insistence that "the labeling of PEG-Intron® establishes that Rebetol® is intended for use with PEG-Intron® " and that Rebetol® is "one-half of an approved combination product." [Ribapharm Letter at 2]. Based on these facts, Ribapharm insists that generic ribavirin must be labeled with an intended use for use with PEG-Intron® and that without such labeling the product will be misbranded. Ribapharm is simply incorrect. This argument ignores the key principle that an analysis of intended use must focus on the labeling of the reference listed drug

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product; that it is the manufacturer of the reference listed drug who controls the intended use, not other products that may also reference the drug. See 21 CFR § 201.128. In this case, the reference listed drug is Rebetol®. Likewise, Ribapharm asserts that "equal weight must be given to the labeling of PEG-Intron® " [Ribapharm Letter at 4], yet provides no support whatsoever for such a standard. This is not surprising since the meaning of "intended use" has been definitively settled by the courts, who have noted that the regulations are clear when they state "intended use is defined as the objective intent of the persons legally responsible for the labeling of drugs" ... and that furthermore "no court has ever found that a product is intended for use ... within the meaning of the [FDCA] absent manufacturer claims as to that product's use." Sigma-Tau Pharmaceuticals, Inc. v. Schwetz, 288 F.3d 141, 146-147 (4th Cir. 2002) (quoting Brown & Williamson Tobacco Corp. v. FDA, 153 F.3d 155, 163 (4th Cir. 1998), (internal quotes omitted), aff'd 529 U.S. 120 (2000).

Here the facts are clear. Ribapharm cannot, and in fact does not dispute that Three Rivers' proposed ANDA product, Ribasphere™ (Ribavirin Capsules, USP) is labeled for use *only* with INTRON®-A (Interferon alpha-2a, recombinant). Nor can Ribapharm point to any other claims made by Three Rivers that Ribasphere™ is intended for use with PEG-Intron®.[1] Absent any labeling or claims from Three Rivers, the law is clear that Ribapharm cannot impute intended use to Three Rivers' Ribasphere™ product.

The fact that Ribasphere™ is not indicated for use with PEG-Intron® also precludes Ribasphere™ from being considered a combination product. Despite Ribapharm's contrary argument, a product cannot be a combination product if it is not labeled as such, since the regulations require the product to be "intended for use" with the combination product, and intended use is determined by the manufacturer's labeling, as explained above. See 21 CFR § 3.2(e) ("*Combination product includes:* a drug ... packaged separately that according to its ... proposed labeling is intended for use only with an approved individually specified drug...." (emphasis added)).

II. Ribapharm's Concerns of Medication Errors are Misplaced

Ribapharm's comments do raise one new proposition, that the labeling of the proposed generic ribavirin products present a high risk of medication error. [Ribapharm Letter at 8]. However, Ribapharm's concerns of medication errors are misplaced. To begin, Ribapharm assumes that generic ribavirin will be prescribed for use in combination with PEG-Intron®, whereas as described above, this presumes an intended use for which no generic ribavirin manufacturer is seeking approval. As proof of this risk to patient safety however, Ribapharm points to a deficiency not in the generic ribavirin package insert, but to a potential deficiency in the Medication Guide that is included with PEG-Intron® . Ribapharm asserts that the Medication Guide for PEG-Intron® omits dosing information for use with Rebetol®. Yet Ribapharm conveniently omits the fact that the

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[1] As noted in our comments dated August 21, 2003, Ribapharm's attempt to demonstrate intent based on the licensing agreement between Three Rivers/Par and Schering is without merit. The licensing agreement was entered prior to disposition of the patent case and bears no relevancy to the intended use of the proposed product.

package insert labeling of PEG-Intron® clearly includes dosing information for use with the brand product Rebetol®, not generic ribavirin.[2] It is puzzling that Ribapharm would argue that the absence of specific dosing information for Rebetol® in the Medication Guide for PEG-Intron® should require FDA to withhold approval for generic ribavirin, rather than amending the PEG-Intron® MedGuide to clarify any confusion. Nevertheless, since the package insert labeling for PEG-Intron® clearly includes dosing information for use in combination with Rebetol®, such concerns are overstated and should not affect the immediate approval of Three River's Ribasphere™ product.

III. A Public Process is Not Needed For FDA to Provide Input on Ribavirin Labeling

Finally, Ribapharm reiterates its final desperate plea to delay generic competition, the amorphous need for "public process". [Ribapharm Letter at 10]. Ribapharm fails to even suggest what further good or purpose could come from such "public process" aside from continued delay, but it is clear that FDA's Good Guidance Practices do not require any further public process. As described in our previous comments, FDA provides comments to ANDA applicants on proposed labeling for each and every ANDA submitted. The Agency is not providing guidance on a class of drug products but merely providing specific comments in response to proposed labeling submitted during the course of ANDA review.

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In conclusion, Ribapharm has raised no issues which should further delay the approval of Three Rivers' ANDA for Ribasphere™ (Ribavirin Capsules, USP). Three Rivers' product is properly labeled and safe and effective for its intended use with INTRON®-A (Interferon alpha-2a, recombinant). The petition should be denied and Three Rivers' ANDA should be immediately approved.

Sincerely yours,

David L. Rosen, R.Ph., J.D.

Cc: Three Rivers Pharmaceuticals, LLC
Mr. Donald Kerrish

Par Pharmaceutical, Inc.
Mr. Paul Campanelli

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[2] It states, "The recommended dose of REBETOL is 800 mg/day in 2 divided doses, two capsules (400mg) with breakfast and two capsules (400mg) with dinner."