GRAYCARY

1625 Massachusetts Avenue NW, Suite 300
Washington, DC 20036-2247
drosen@graycary.com
www.graycary.com
O] 202-238-7749
F] 202-238-7701

July 25, 2003

VIA FACSIMILE & 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 Citizen Petition dated July 16, 2003, Submitted by Hogan & Hartson, L.L.P. on behalf of ICN Pharmaceuticals, Inc. and Ribapharm, Inc. Requesting that Commissioner of Food and Drugs Refrain from Approving ANDAs for Ribavirin Capsules, 200mg that Carve Out Information in the Labeling on the Use of Ribavirin in Combination with PEG-Intron (peginterferon alfa-2b)

The Petition is Without Merit and Should be Denied

Dear Sir/Madam:

I am writing to you on behalf of Three Rivers Pharmaceuticals, LLC and their marketing partner, Par Pharmaceutical, Inc. regarding the above referenced Citizen Petition requesting that the Commissioner of Food and Drugs refrain from approving abbreviated new drug applications ("ANDAs") for Ribavirin Capsules 200mg that carve out information in the labeling pursuant to Section 505(j)(2)(A)(viii) of the Federal Food, Drug and Cosmetic Act (the "FD&C Act") and Section 314.94(a)(8)(iv) of FDA's implementing regulations on the use of Ribavirin in combination with PEG-Intron (peginterferon alfa-2b).

This Citizen Petition is merely another tactical maneuver by a brand name pharmaceutical company after losing a summary judgment ruling, in a last minute, desperate effort to delay generic competition for Ribavirin Capsules. The Citizen Petition is without merit and should be denied. Moreover, the Citizen Petition should in no way delay the immediate approval of ANDAs for Ribavirin Capsules. The American public who suffer with Hepatitis C

should have access to high quality, therapeutically equivalent, lower cost versions of Ribavirin Capsules. The bases on which this Citizen Petition should be denied are set forth below.

I. The Action Requested by the Petitioner is Contrary to the Law

The Petitioner is requesting that Commissioner of Food and Drugs refrain from approving ANDAs for Ribavirin Capsules 200mg that omit information in the labeling on the use of Ribavirin in combination with PEG-Intron (peginterferon alfa-2b). The Petitioner asserts that "...such a labeling "carve-out" is subject to competing statutory requirements that prohibit the marketing of misbranded and unapproved products."

The Petitioner's assertion that carving out certain information in the labeling of the reference listed drug that may be protected by patent(s) and/or periods of market exclusivity somehow causes a product to be misbranded and unapproved is without any support whatsoever.

The Petitioner acknowledges that the Federal Food, Drug and Cosmetic Act (the "FD&C Act") and FDA's regulations permit differences between the labeling of the reference listed drug and that of the generic product, and specifically permits the omission of an indication or any other aspect of the labeling that may be protected by patent or accorded a period of market exclusivity, provided that the proposed ANDA drug product is not less safe and effective for all remaining non-protected conditions of use. The courts have recognized that the FDA can legally approve ANDA's that include labeling that differs from the reference listed drug. See for example, Bristol-Myers Squibb Co., v. Shalala, 91 F.3d 1493 (D.C. Cir 1996); Zeneca, Inc. v. Shalala, 1999 WL 728104 (D.Md.), *aff'd*, 213 F.3d 161 (4th Cir. 2000); and Sigma Tau Pharmaceuticals, Inc. v. Schwetz, 288 F.3d 1419 (4th Cir. 2002).

With respect to the current situation, carving out labeling information pertaining to the use of the proposed ANDA Ribavirin Capsules in combination with PEG-INTRON™, does not make the proposed ANDA Ribavirin product any less safe or effective than the reference listed drug, Rebetol® for all remaining non-protected conditions of use. In fact, Petitioner quotes the correct "affect safety or effectiveness" standard (Petition at 7-8), yet offers no data or information purporting to show that a carve-out of PEG-INTRON™ labeling statements will adversely affect the safety or effectiveness of the proposed ANDA Ribavirin Capsules with INTRON®-A. The Petitioner simply asserts that because labeling for PEG-INTRON™ includes references to combination therapy with Rebetol®, a generic version of Ribavirin Capsules that carves-out such information is nonetheless still intended for use with PEG-INTRON™ and as such, is misbranded and an unapproved product. The Petitioner's assertion is contrary to law and should be summarily dismissed. The bases for denying the Petitioner's request are further discussed below.

Rebetol® (ribavirin) Capsules are currently FDA approved and sold in a stand alone package for use only in combination with *either* INTRON®-A (Interferon alpha-2a, recombinant) or PEG-INTRON™ (peginterferon alpha-2b) all of which are manufactured and sold by Schering Corporation. Carving out labeling information relative to the use of Ribavirin

Capsules with PEG-INTRON™ that may be protected by patents and afforded a period of market exclusivity does not render the proposed ANDA Ribavirin Capsules less safe or effective than the reference listed drug, Rebetol® (Ribavirin) Capsules for all remaining non-protected conditions of use, *i.e.*, use in combination with INTRON®-A. The information in the labeling concerning the use of Rebetol® (ribavirin) Capsules in combination with PEG-INTRON™ is separate and distinct from the information in the labeling concerning the use of Rebetol® Capsules in combination with INTRON®-A. This information in the labeling concerning the use of Rebetol® (Ribavirin) Capsules in combination with PEG-INTRON™ can be readily carved out of the product labeling. That carve-out includes the dosing information for ribavirin in combination with PEG-INTRON™, which appears in one sentence in the Rebetol® package insert and three sentences in the Rebetol® medication guide. This dosing information can easily be removed without disturbing the clear, truthful and non-misleading dosing information for ribavirin taken with INTRON®-A. The remaining product labeling concerning the use of Rebetol® (or the proposed ANDA Ribavirin Capsules) in combination with INTRON®-A is complete and will provide health care practitioners and patients with adequate and appropriate information on the safe and effective use of Ribavirin with INTRON®-A.

The proposed ANDA product, Ribasphere™ (Ribavirin Capsules, USP) will include all labeling information included in the approved labeling for the reference listed drug, Rebetol® (ribavirin) Capsules, including information in a medication guide for combination therapy with INTRON®-A. Proposed labeling carving out such information on PEG-INTRON™ while maintaining adequate and appropriate labeling for use of the drug in combination with INTRON®-A is currently submitted in Three Rivers ANDA for Ribasphere™ (Ribavirin Capsules, USP). Since Rebetol® (Ribavirin) Capsules was and currently is marketed for use with INTRON®-A, so can the proposed ANDA product, Ribasphere™ (Ribavirin Capsules, USP).

The proposed ANDA product, Ribasphere™ (Ribavirin Capsules, USP) is intended for and labeled *only* for use in combination with INTRON®-A. Merely because Rebetol® (ribavirin) Capsules can also be used in combination with PEG-INTRON™ and includes dosing information and references to respective labeling for combination therapy with PEG-INTRON™ does not make a generic version of Ribavirin Capsules less safe or less effective than the reference listed drug Rebetol® if such information relative to combination therapy with PEG-INTRON™ is carved out of the ANDA labeling. Such a carve out of the labeling protected by patent or accorded a period of market exclusivity is consistent with the provisions of the FD&C Act and FDA regulations.

II. The Petitioner Misstates the Law; ANDA Applicants Can Carve-Out Combination Therapy with PEG-INTRON™ From Ribavirin Labeling

The proposed ANDA product, Ribasphere™ (Ribavirin Capsules, USP) is *not* intended to be *nor* is it proposed to be labeled for use in combination with PEG-INTRON™. The Petitioner argues that since Rebetrol and PEG-INTRON™ are used in combination therapy, a generic ribavirin product must include all information associated with the combination therapy with

PEG-INTRON™. The Petitioner asserts that combination therapy cannot be carved out of the labeling because it is only changing one half of the combination therapy. There is no basis for the Petitioner to conclude that even though the proposed ANDA product is not labeled, promoted or advertised for use in combination with PEG-INTRON™ it is nonetheless still intended for use with PEG-INTRON and without labeling information on combination therapy with PEG-INTRON™, the proposed ANDA Ribavirin product is misbranded and unapproved. The Petitioner's logic is faulty and their position is without any merit.

First, Petitioner's focus on the labeling for peg-interferon alpha 2b is clearly misplaced. Three Rivers, the ANDA applicant is seeking approval for Ribavirin, not for peginterferon alpha 2b. Thus, the reference listed drug labeling for purposes of ANDA filing and ultimately approval is that of Rebetol® and not PEG-INTRON™. Three Rivers has used the most recently FDA approved labeling for Rebetol® as the basis for preparing labeling that has been submitted in its ANDA. Second, as noted above, the proposed ANDA product, Ribasphere™ (Ribavirin Capsules, USP) is *not* intended to be *nor* is it proposed to be labeled for use in combination with PEG-INTRON™. Without such claims in the labeling, the Petitioner's assertion, that nonetheless, the generic Ribavirin Capsules are intended for use with PEG-INTRON™ and without inclusion of such information the product is misbranded and unapproved is without any support. The FD&C Act, FDA regulations and the courts all support the position that an ANDA applicant can carve-out information that is protected by patent and/or market exclusivity. There is no basis nor any merit to the Petitioner's attempt to ascribe intended uses to the proposed ANDA product if such uses are not included in the labeling or promotional material of the proposed ANDA product.

Rebetol® Capsules are approved by FDA for use in combination with *either* INTRON®-A or PEG-INTRON™. While Rebetol® is labeled only for use in combination with *either* INTRON®-A or PEG-INTRON™, all three products are available as stand alone packages. ANDA applicants can readily carve out information in the Rebetol® labeling associated with combination therapy with PEG-INTRON™, information that may be protected by patent and market exclusivity. Since the proposed ANDA product is not intended for nor is it labeled for use in combination with PEG-INTRON™, the Petitioner is clearly wrong in asserting that a generic version that doesn't include such uses in its labeling is adulterated and or misbranded. The carving out of information that is protected by patent or market exclusivity is expressly permitted in the FD&C Act. Moreover, since Rebetol® was and still is marketed for use in combination with INTRON®-A (this treatment combination was and still is safe and effective for use in treating patients with Hepatitis C); generic Ribavirin products should be permitted to do the same. The Petitioner has not identified any issue that would make a generic version of Ribavirin Capsules less safe or less effective than the reference listed drug Rebetol® if such information relative to combination therapy with PEG-INTRON™ is carved out of the ANDA labeling.

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

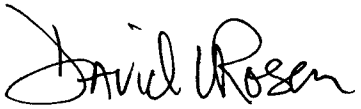
The Petitioner is asserting that in providing input into the labeling for generic ribavirin capsule products, the Agency must follow good guidance practices, issue a public guidance document and seek public comment on such labeling recommendations. The Petitioner is only suggesting that the Agency use a public process to develop labeling guidance for Ribavirin Capsules in the attempt to delay ANDA approval. 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 such as corticosteroids or oral contraceptives; rather the Agency is providing specific comments in response to proposed labeling submitted during the course of ANDA review. Three Rivers has referred to the most recently approved version of the labeling for the reference listed drug (*i.e.*, Rebetol®, for which there have been numerous recent updates) and has prepared and submitted labeling for their ANDA based on the reference listed drug labeling. It is the same process that has been utilized in the review and approval process for ANDAs for many years. The Petitioner is suggesting a dramatic procedural change that is unwarranted and is clearly directed as an attempt to delay the approval of Ribavirin Capsules.

* * * * * * * * * * * * * * * * * * * *

In conclusion, the Petitioner's assertion that an ANDA applicant for a generic version of Ribavirin Capsules can not carve-out information in the current approved labeling for Rebetol® concerning combination therapy with PEG-INTRON™, a use that is protected by patents and market exclusivity is without merit. There are no issues that would make a generic version of Ribavirin Capsules less safe or less effective than the reference listed drug Rebetol® if such information relative to combination therapy with PEG-INTRON™ is carved-out of the ANDA labeling. Furthermore, a public process is not needed to provide specific input and comments on the proposed labeling for an individual drug product.

The Petitioner, after having summary judgment granted against them, is merely raising issues, in a last, desperate attempt to delay competition for Ribavirin Capsules. The Citizen Petition is without merit and should be denied.

Sincerely yours,



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

cc: Three Rivers Pharmaceuticals, LLC
Mr. Donald Kerrish

Par Pharmaceutical, Inc.
Mr. Paul Campanelli