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October 17, 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 response to the additional comments submitted by ICN Pharmaceuticals, Inc. and Ribapharm Inc. (collectively "ICN") on October 3, 2003, in connection with the above-referenced Citizen Petition.

In its latest submission, ICN responds to Geneva's comments, including those which were filed with the FDA more than two months earlier. ICN's Citizen Petition itself was filed only after a court declared that Geneva's generic ribavirin product does not infringe ICN's patents. ICN did not express any concern to the FDA for the two years prior to ICN's Citizen Petition during which Geneva's ANDA was under consideration by the FDA. Only after the court decision of noninfringement did ICN belatedly invite the FDA to rewrite its well-established regulations concerning patent carve-outs, "intended use" and combination products in order to preserve ICN's monopoly with its licensee, Schering-Plough.

It is indisputable that a generic manufacturer can carve out from its labeling information protected by patent and that Geneva has properly done so here. In its eleventh-hour objection, ICN argues that by carving out the protected indication of ribavirin in combination with PEG-Intron, Geneva's labeling is somehow misbranded. As discussed in Geneva's comments submitted on July 30, 2003, that is simply not the case.

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ICN's attempt to establish an intended use for generic ribavirin by focusing on the labeling of PEG-Intron is misguided. ICN gives short shrift to the fundamental principle that the "intended use" of a drug is determined, first and foremost, by the labeling of that drug. 21 C.F.R. § 201.128; Sigma-Tau Pharm., Inc. v. Schwetz, 288 F.3d 141, 146-47 (4th Cir. 2002). 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)).

ICN cannot dispute that the labeling of Geneva's generic ribavirin product contains instructions for administration only with standard interferon; it does not instruct physicians to administer Geneva's product in combination with PEG-Intron. Nor does ICN point to any other statements made by Geneva that its product is intended to be used with PEG-Intron.¹ A physician following the labeling of Geneva's product will administer 1,000 to 1,200 mg/day ribavirin in combination with Intron A, an indication that the FDA has determined is safe and effective. This is also not contested by ICN. Instead, ICN shifts the focus to the labeling of a different product, PEG-Intron, and assumes that physicians will ignore the clear labeling of Geneva's generic ribavirin product and administer it in combination with PEG-Intron.

ICN further argues that generic ribavirin and PEG-Intron are a combination product. They are not. The FDA rules clearly state that a combination product is one in which a new drug product "according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product" 21 C.F.R. § 3.2(e) (emphasis added). Geneva's product is intended for use only with standard interferon, Intron-A. Geneva's product is a combination product with Intron-A, not with PEG-Intron. Thus, Geneva's product and PEG-Intron are not a combination product.

ICN has advanced a new argument, that the labeling for Geneva's ribavirin product presents a risk of medication error. (ICN Comments (October 3, 2003) at 8) This argument is based on the assumption that doctors will prescribe Geneva's generic ribavirin product in combination with PEG-Intron, an indication for which Geneva does not seek approval. This

¹ As discussed in Geneva's comments dated August 26, 2003, the license agreement between Schering and Geneva was made before any ruling in the litigation concerning the validity and infringement of ICN's patents. The agreement, therefore, addresses the *possibility* that Geneva's ribavirin might be approved for use in combination with PEG-Intron, depending on the outcome of the litigation, but it does not evidence an *intent* by Geneva to market ribavirin for use with PEG-Intron (and, in fact, Geneva will not market its product for use with PEG-Intron). For that reason, ICN's citation to *FDA Warning Letter to Global Pharm. Corp.* (July 20, 1998) is inapposite.

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argument is further based on the fallacious assumption that physicians will ignore the labeling of PEG-Intron, which clearly instructs the proper dosage administration of PEG-Intron in combination with Rebetol. A physician or patient following the labeling of PEG-Intron will administer 800 mg/day Rebetol in combination with PEG-Intron, a use that the FDA has determined is safe and effective. ICN misleadingly focuses on the PEG-Intron Medication Guide which omits some dosing information for Rebetol®, but neglects to mention that the dosing information for Rebetol® in combination with PEG-Intron is clearly set forth in the labeling of PEG-Intron. Geneva respectfully submits that if the FDA sees the absence of dosing information for Rebetol in the PEG-Intron Medication Guide as a concern, the PEG-Intron Medication Guide should be amended to clarify the proper dosing regimen. As discussed in Geneva's July 30 submission, the Medication Guide for Geneva's product provides an additional opportunity to address any concerns regarding the required dosing regimen of Geneva's product.

Moreover, ICN suggests that in certain states pharmacists will be required by law to substitute generic ribavirin when a physician prescribes Rebetol® in combination with PEG-Intron. (ICN Comments (October 3, 2003) at 9, n.5) Again, ICN is dealing in half-truths. In states with generic drug substitution laws, pharmacists are required to dispense a generic drug only if a generic is available and approved for the use for which the brand drug was prescribed. Geneva's ribavirin product will not be approved and, therefore, will not be available (without specific physician authorization) for use with PEG-Intron. Thus, the state generic drug substitution laws will not apply.

Lastly, ICN reiterates its call for a guidance document but does not even attempt to address how the FDA's determination that generic manufacturers can carve out a protected indication communicates "new or different regulatory expectations to a broad public audience for the first time" or "regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public audience" that would necessitate a guidance document. See 21 C.F.R. § 10.115(e). The mere fact that the FDA's determination regarding generic ribavirin labeling is applicable to more than one generic applicant does not mean that the determination is of sufficient magnitude to warrant a guidance document. The FDA is merely applying well-established rules to this generic drug. This request, too, should be denied.

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Geneva respectfully submits that the FDA should promptly approve Geneva's ribavirin ANDA as submitted.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'J. J. Oelke', written in a cursive style.

Jeffrey J. Oelke

JJO:cg