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February 17, 2004

Dockets Management Branch  
U.S. Food and Drug Administration  
Room 1061  
5630 Fishers Lane  
Rockville, Maryland, 20852

RE: Docket 2003P-0321

**Comments Of Teva Pharmaceuticals USA, Inc.  
In Opposition To ICN/Ribapharm's Petition For Stay  
Of Approval Of ANDAs For Generic Ribavirin Drug Products**

On behalf of Teva Pharmaceuticals USA, Inc. ("Teva"), the undersigned respectfully submits these comments in opposition to the Petition filed July 16, 2003 on behalf of ICN Pharmaceuticals and Ribapharm Inc. (collectively referred to herein as ICN) which requests that FDA "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)." Reference is also made to comments filed in opposition to the Petition on behalf of Three Rivers Pharmaceuticals (Three Rivers) dated July 25, August 21, and October 24, 2003, and on behalf of Geneva Pharmaceuticals (Geneva) dated July 30 and August 26, 2003, as well as supplemental submissions in support of the Petition filed on behalf of ICN on July 29, August 4, and October 3, 2003.

**I. SUMMARY OF AGREED PRINCIPLES AND THE ISSUE IN CONTENTION**

The numerous submissions in this proceeding have described in detail the background of ribavirin capsules, and the two biologic drugs with which it is commonly used, Intron-A® (interferon alfa-2b, recombinant) and PEG-Intron® (peginterferon alfa-2b), and that background will not be repeated herein. However, before turning to the core issues in dispute, it will be useful to summarize the key points on which there is no disagreement among the interested parties. In particular, it is undisputed that:

- Generic drug products may be approved with labeling that differs from the approved labeling of the reference listed drug (RLD) where such difference is due to the generic labeling "carving out" conditions of use that are protected by patents or regulatory exclusivities, so long as such carve-out does not "render the proposed [generic] drug

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product less safe or effective than the listed drug for all remaining, non-protected conditions of use.” 21 C.F.R. § 314.127(a)(7) (emphasis added). See Petition at 1, 7-8 (FDA “regulations allow for a generic product to differ from the RLD if ‘an indication or other aspect of labeling’ is protected by patent or exclusivity.”); Three Rivers/July 25 at 2-3; Geneva/July 30 at 2-3.

- The relevant ribavirin capsule RLD<sup>1</sup>, Rebetol®, is approved for two different and independent uses: (1) combination therapy with Intron-A; and (2) combination therapy with PEG-Intron. Rebetol is not approved for monotherapy. Petition at 3; Three-Rivers/July 25 at 2; Geneva/July 30 at 2.
- U.S. Patent No. 6,177,074 (the '074 patent) is listed in the Orange Book for Rebetol, with “Use Code” U-454 (“Method of tx a pt suspected of having hepatitis C by admin, in combination, a conjugate comprising peg 12000 & interferon alfa-2b in an amt of from 0.5mcg/kg to 2mcg/kg, once weekly, and ribavirin.”) (abbreviations as in original). The '074 patent purports to claim the use of ribavirin with pegylated interferon alfa-2b (i.e., PEG-Intron). Therefore, generic ribavirin capsule products may not currently be approved with labeling for one of Rebetol’s two independent approved uses – i.e., use with PEG-Intron.<sup>2</sup>
- Thus, generic ribavirin products meet the threshold requirements for obtaining approval with “carved out” labeling, because one of multiple approved conditions of use -- combination therapy with PEG-Intron – is protected by a listed patent. The other approved condition of use – combination therapy with Intron-A – is the subject of several patents, which have been challenged by the generic applicants, and which have been found by a United States District Court not to be infringed by the generic products. Although an appeal of that decision is pending, there is no longer any 30-month stay blocking the approval of the relevant ANDAs. Thus, under normal circumstances FDA’s only task would be to determine whether such a carve out would render generic ribavirin capsule products less safe than Rebetol for the use in combination therapy with Intron-A.

The agreement among the companies ends there, however, as ICN takes the position that these are not normal circumstances because a carved out generic ribavirin label is otherwise prohibited under *other* provisions of law, namely the FDCA’s misbranding provisions and the “intended use” doctrine. The “core argument” of ICN’s Petition, ICN/July 29 at 3, is that the labeling of *PEG-Intron* causes generic ribavirin products, labeled without reference to use with PEG-Intron, to be “intended for use” with PEG-Intron, and that such generic ribavirin products

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<sup>1</sup> ICN’s Petition refers generally to “ribavirin products,” but the products specifically at stake in this matter are generic ribavirin capsule products for which Teva and the other generic companies have filed ANDAs.

<sup>2</sup> Such labeling could be approved if an ANDA applicant files a Paragraph IV Certification with respect to the '074 patent, and either has not been sued for infringement, or if it has been sued, either the 30-month stay has elapsed or the court has ruled that the patent is invalid or not infringed.

would therefore be misbranded and non-approvable because their labeling would not include adequate directions for use with PEG-Intron. Petition at 8, 10-12; ICN/July 29 at 1-3.

As shown herein, ICN's position would require FDA to adopt radical new interpretations of *both* the "intended use" doctrine, and the misbranding provisions of the FDCA. Adoption of ICN's position would also be contrary to longstanding Agency practice that has allowed approval of drugs without labeling regarding a combination use that is described in the approved labeling of the other drug in the combination regimen. Accordingly, the Petition should be denied.

## II. ICN MISINTERPRETS THE INTENDED USE DOCTRINE

The first prong of ICN's argument is that generic ribavirin products are implicitly "intended" for use with PEG-Intron because the *PEG-Intron* labeling refers to combination use with ribavirin. As ICN argues,

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. . . . On this basis alone, the labeling of *PEG-Intron* is central to, and defines, the intended use of Rebetol. . . . In short, the ANDA applicants. . . 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.

Petition at 11 (emphasis added).

ICN's argument misinterprets the intended use doctrine in this context, because the branded ribavirin drug, Rebetol, has two separate and independent "intended uses" – use with PEG-Intron, *or* use with Intron-A. By omitting labeling references to use with PEG-Intron, generic ribavirin applicants clearly and appropriately limit the intended use of their products solely to use with Intron-A. The legal authority for generic applicants to unilaterally limit the intended uses of their products through labeling carve outs is well established and beyond challenge. As the D.C. Circuit held in *Bristol-Myers Squibb v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996), the fact that a branded drug is labeled for more uses than a competing generic version does not preclude approval of the generic even where the generic is known and expected to be substituted by pharmacists for the branded drug for the very uses that are omitted from the generic drug's labeling. If ICN's intended use argument were correct, *Bristol-Myers* would have been decided very differently than it was.

Moreover, as discussed in Geneva's comments, "intended use" of a product under the FDCA is defined and limited by the labeling of the drug itself, and not by extrinsic evidence of actual or potential use by others outside the bounds of the drug's actual

labeling. See Geneva/July 30 at 5-6, (citing *Brown & Williamson Tobacco Corp. v. FDA*, 153 F.3d 155, 163 (4<sup>th</sup> Cir. 1998) (“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.”), *aff’d*, 529 U.S. 120 (2000)).

**III. GENERIC RIBAVIRIN PRODUCTS WILL NOT BE MISBRANDED;  
RATHER, ICN HAS DEMONSTRATED THAT THE PEG-INTRON  
LABELING IS UNLAWFUL**

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The second prong of ICN’s argument is that generic ribavirin products which limit their labeling to the intended use with Intron-A are misbranded because they fail to provide “adequate directions for use” with PEG-Intron. As ICN states its argument, “[a]pproval of labeling for one component of a combination product that is not reciprocal or mutually reinforcing of the labeling for the other component would...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.” Petition at 12-13. See also ICN/October 3 at 7 (“where two products are specifically approved for use in combination...unless [a generic] 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.”). ICN’s argument is fallacious, not only because it would require FDA to accept the phantom intended use of generic ribavirin products with PEG-Intron, but also because it is contrary to the approach used by FDA in approving numerous drugs for use in combination regimens but for which there is no “reciprocal or mutually reinforcing” labeling for both components of the combination. ICN argues that under the scenario at issue here – where one component of a combination regimen omits reference to the regimen and the other drug of the regimen – “at least one of the products [is] misbranded.” *Id.* Even if ICN is correct, its proposition that it is the generic ribavirin capsule products that would be misbranded is incorrect. To the extent there is any misbranding at all, it is the PEG-Intron labeling that is misbranded and unlawful, and which should be changed, if any labeling change is necessary to permit approval of ribavirin ANDAs.

Perhaps the best illustration of how FDA has in the past dealt with circumstances such as those posed with ribavirin and PEG-Intron, is the approach used with Searle’s Cytotec® (misoprostol). Misoprostol is intended, approved, and labeled only for use in combination with non-steroidal anti-inflammatory drugs (NSAIDs) to reduce the gastrointestinal side-effects of NSAIDs. No approved NSAIDs have labeling that refers to use with misoprostol. Moreover, another drug, Mifeprex® (mifepristone) (also known as RU-486) is intended, approved, and labeled for use in combination with misoprostol, for medical abortion in early pregnancy. The labeling for Mifeprex includes numerous references to the required use of misoprostol as part of the approved combination abortion regimen, but the approved labeling of misoprostol makes no reference, and provides no directions whatsoever, to use with mifepristone to terminate pregnancy. Moreover, the approved dosing of misoprostol for *its* sole intended use – reducing GI side effects of NSAIDs – is 200 mcg four times daily with food, a very different dosing regimen than the misoprostol dosing recommended in the mifepristone labeling (400 mcg at one time, two days after administration of mifepristone). Under ICN’s flawed reasoning, all NSAIDs are misbranded and unlawfully approved because their labels do not provide adequate directions for

use with misoprostol, and in turn, misoprostol is misbranded and unlawfully approved because its labeling does not include directions for use with mifepristone. Obviously, this is not the case with NSAIDs or misoprostol, nor is it the case that generic ribavirin products would be misbranded for lack of reference to use with PEG-Intron.

There are numerous other examples of drugs that would have to be deemed misbranded, and approval of which would have to be revoked by FDA, if the Agency were to accept ICN's arguments. For example, Fuzeon (enfuvirtide for injection), is labeled only for combination use with other drugs, including protease inhibitors (lopinavir, atazanavir), and nucleoside analogues (*including ribavirin*, zidovudine, lamivudine, abacavir, emtricitabine), but the labeling of these other drugs make no mention whatsoever to use with Fuzeon. Similarly, Emtriva (emtricitabine capsules) is approved only for use with other anti-HIV medicines, including protease inhibitors such as lopinavir, atazanavir, and nucleoside analogues *including ribavirin*, zidovudine, lamivudine, and abacavir. Again, none of these other drugs are labeled for use with Emtriva. And, Emend (aprepitant capsules) is approved only for use with other antiemetics, but the other anti-emetics (i.e. dexamethasone and ondansetron) do not have labeling that refers to their use with Emend. The following table illustrates how for both ribavirin/PEG-Intron, and numerous other combination regimens, reciprocal labeling should not be, and has not been, required.

<b>Drug</b>	<b>Labeled for Use With</b>	<b>Reciprocal Labeling?</b>
PEG-Intron® (peginterferon alfa-2b)	ribavirin	PEG-Intron® (peginterferon alfa-2b) not mentioned in labeling of generic ribavirin.
Cytotec® (misoprostol)	NSAIDs	Cytotec® (misoprostol) not mentioned in labeling of NSAIDs.
Mifeprex® (mifepristone)	misoprostol	Mifeprex® (mifepristone) not mentioned in labeling of Cytotec® (misoprostol).
Fuzeon® (enfuvirtide)	zidovudine	Fuzeon® (enfuvirtide) not mentioned in labeling of Retrovir® (zidovudine) Capsules.
Fuzeon® (enfuvirtide)	lamivudine	Fuzeon® (enfuvirtide) not mentioned in labeling of Epivir® (lamivudine) Oral Solution or Epivir® HBV (lamivudine) Oral Solution.
Fuzeon® (enfuvirtide)	abacavir	Fuzeon® (enfuvirtide) not mentioned in labeling of Ziagen® (abacavir) Oral Solution or Trizivir® (abacavir sulfate, lamivudine, and zidovudine) Tablets.

<b>Drug</b>	<b>Labeled for Use With</b>	<b>Reciprocal Labeling?</b>
Fuzeon <sup>®</sup> (enfuvirtide)	emtricitabine	Fuzeon <sup>®</sup> (enfuvirtide) not mentioned in labeling of Emtriva <sup>®</sup> (emtricitabine) Capsules.
Emtriva <sup>®</sup> (emtricitabine)	lopinavir	Emtriva <sup>®</sup> (emtricitabine) not mentioned in labeling of lopinavir (Kaletra <sup>®</sup> , a combination of lopinavir/ritonavir).
Emtriva <sup>®</sup> (emtricitabine)	atazanavir	Emtriva <sup>®</sup> (emtricitabine) not mentioned in labeling of Reyataz <sup>®</sup> (atazanavir) Capsules.
Emtriva <sup>®</sup> (emtricitabine)	ribavirin	Emtriva <sup>®</sup> (emtricitabine) not mentioned in labeling of Rebetol <sup>®</sup> (ribavirin) Capsules or Copegus <sup>®</sup> (ribavirin) Tablets.
Emtriva <sup>®</sup> (emtricitabine)	zidovudine	Emtriva <sup>®</sup> (emtricitabine) not mentioned in labeling of Retrovir <sup>®</sup> (zidovudine) Capsules.
Emtriva <sup>®</sup> (emtricitabine)	lamivudine	Emtriva <sup>®</sup> (emtricitabine) not mentioned in labeling of Epivir <sup>®</sup> (lamivudine) Oral Solution or Epivir <sup>®</sup> HBV (lamivudine) Oral Solution.
Emtriva <sup>®</sup> (emtricitabine)	abacavir	Emtriva <sup>®</sup> (emtricitabine) not mentioned in labeling of Ziagen <sup>®</sup> (abacavir) Oral Solution or Trizivir <sup>®</sup> (abacavir sulfate, lamivudine, and zidovudine) Tablets.
Emend <sup>®</sup> (aprepitant)	dexamethasone	Emend <sup>®</sup> (aprepitant) not mentioned in the labeling of Decadron <sup>®</sup> (dexamethasone).
Emend <sup>®</sup> (aprepitant)	ondansetron	Emend <sup>®</sup> (aprepitant) not mentioned in the labeling of Zofran (ondansetron) Tablets, ODT, Oral Solution, or Injection.

As these examples demonstrate, ICN is not only categorically wrong to argue that the absence of reciprocal labeling of generic ribavirin for use with PEG-Intron renders generic ribavirin capsule products misbranded, ICN's position would require a broad scale effort by FDA to revoke approvals, or force the relabeling, of a vast range of approved drugs which are used in one or more combination regimens.

ICN also argues in its supplemental submissions that “even if the sponsor of a generic Rebetol product were to ‘disclaim’ any use with PEG-Intron, *the labeling of PEG-Intron would still render the generic product unlawful.*” ICN/July 29 at 2 (emphasis added); *see also* ICN October 3 at 3 (“It is the repeated references to Rebetol *in the labeling of PEG-Intron* that is the focus of ICN/Ribapharm’s Petition.” (emphasis in original)). These are very significant, and fatal, admissions by ICN because under the FDCA, it is unlawful for a person to “cause” the misbranding of another drug product. 21 U.S.C. § 331(b) (“The following acts *and the causing thereof* are prohibited: . . . The adulteration or *misbranding* of any food, drug, device, or cosmetic in interstate commerce.”). If, as ICN argues, the PEG-Intron labeling “renders” generic ribavirin products misbranded, *it is the PEG-Intron labeling*, and not the proposed generic drug labeling, *that is in violation of the FDCA* because it has caused the alleged misbranding of generic ribavirin products.<sup>3</sup>

The appropriate remedy for any misbranding caused by the PEG-Intron labeling would be to require amendments to the PEG-Intron labeling to eliminate or modify any aspects of that labeling, as necessary to allow approval of generic ribavirin products labeled for their sole intended use with Intron-A. Indeed, this is the approach FDA took with respect to Cytotec (misoprostol), after mifepristone was approved for combination use with misoprostol in medical abortions. Before mifepristone was approved, misoprostol’s labeling included a categorical black-box contraindication against use by pregnant women. Once mifepristone was approved with instructions to use misoprostol as part of the medical abortion regimen (obviously in pregnant women), FDA worked with G.D. Searle to approve amendments to the Cytotec labeling to state that “Cytotec should not be taken by pregnant women *to reduce the risk of ulcers induced by non-steroidal anti-inflammatory drugs.*” (Emphasis added). In this way, the Cytotec labeling avoided being misbranded with respect to mifepristone (by eliminating the *categorical* prohibition against use by all pregnant women), but at the same time, this labeling change did not establish a new intended use for Cytotec and did not require full reciprocal misoprostol labeling with respect to use with mifepristone for medical abortions.

#### **IV. GENERIC RIBAVIRIN LABELING WILL NOT INCREASE THE RISK OF MEDICATION ERRORS**

Finally, ICN argues that the different dosing recommendations for ribavirin as between use with Intron-A and PEG-Intron, as described in the PEG-Intron and Rebetol patient Medication Guides, raises concerns about possible medication errors because the ribavirin dosing listed in the PEG-Intron Med Guide differs depending on whether the patient is taking PEG-Intron or Intron-A. ICN/October 3 at 8-9. ICN’s concerns are both overstated and easily addressed.

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<sup>3</sup> Teva does not agree with ICN’s argument that the proposed generic products would in fact be misbranded in any way, but to the extent FDA were to give credence to ICN’s misbranding argument, it is necessary to correctly identify the source of any such misbranding, and take corrective action with respect to the source of the misbranding. Here, as ICN explicitly concedes, the source of any misbranding is the PEG-Intron labeling, and not the proposed generic labeling.

First, there are numerous other dosing variations for which PEG-Intron and PEG-Intron combination therapy are approved, but which do not appear in the PEG-Intron Med Guide. Specifically, reduced dosage requirements, some of which are generally stated and some of which are specific to certain at risk patient populations, are approved for PEG-Intron. For example, the approved PEG-Intron insert states “If a serious adverse reaction develops during the course of treatment...discontinue or modify the dosage of PEG-Intron and/or REBETOL until the adverse event abates or decreases in severity.” Additionally, the PEG-Intron labeling instructs that patients may require discontinuation or dose modification as a result of platelet decreases. Lastly, for patients with a history of stable cardiac disease, the PEG-Intron dose should be reduced by half and the ribavirin dose by 200 mg/day if a  $>2$  g/dL decrease in hemoglobin is observed during any 4 week period. Significantly, *all of these special dosing considerations are absent from the PEG-Intron Med Guide*. Thus, ICN’s focus on the Med Guide’s abbreviated discussion of dosing differences as a source of potential medication errors proves too much, and to the extent FDA considers these differences to create a “misbranding” situation or a safety concern, as noted above, such issues can and should be rectified through changes to the PEG-Intron Med Guide and/or labeling.

It is apparent that ICN has gone to great pains to enshroud the adequacy of generic ribavirin labeling, perhaps even to the extent of designing the PEG-Intron Med Guide language more toward this purpose than toward clarity. Generic drug applicants have experienced such delay tactics often enough to recognize them immediately. The bottom line is that physicians determine the proper dosage for each patient based on the approved package insert, and their knowledge and experience, and not on the information provided in a Med Guide. Even if one were to assume that the Med Guide is a primary source of dosing instruction, which of course it is not, ICN’s Med Guide would have to be viewed as incomplete and therefore misbranded.

**V. ICN’S “KITCHEN SINK” ARGUMENTS DESERVE SUMMARY REJECTION**

Much ink has been spilled by ICN and the other commenters with respect to ICN’s request that FDA’s generic ribavirin approval decision be made in a public proceeding under FDA’s Good Guidance Practices. Likewise with respect to ICN’s argument that the generic applicants’ settlement agreements with Schering establish an intended use of generic ribavirin products with PEG-Intron. These arguments are red herrings designed to delay a decision on this petition and deflect attention from the real issues to be decided. For the reasons set forth in Geneva’s and Three-Rivers’ comments, ICN is wrong on both points, and its arguments must be summarily rejected.

**VI. CONCLUSION**

FDA’s decision on this petition is now overdue, and generic ribavirin applicants are entitled to immediate approval of their ANDAs. Teva is dismayed that, once again, a branded sponsor has successfully delayed the approval of safe, effective, and more affordable generic versions of a branded product through the last-minute filing of a clever but meritless petition. The Agency’s inability to promptly resolve petitions of this sort is a serious and embarrassing

public policy issue. We urge the agency to immediately devote whatever resources are necessary to promptly approve the pending ribavirin capsule ANDAs,<sup>4</sup> to respond to and deny the ICN petition, and to establish a more effective administrative process for dealing with future petition-based efforts to delay and prevent lawful generic competition.

Respectfully submitted,



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<sup>4</sup> Although styled as a “Citizen Petition,” the Petition is more accurately described as a Petition for Stay of Agency Action, because ICN requests that FDA stay the effective date (now past) of eligibility for final approval of pending ribavirin ANDAs. As such, the Petition should be governed by 21 C.F.R. § 10.35, which prohibits FDA from withholding regulatory action otherwise required (in this case approval of the ANDAs) unless the Agency *first* grants the petition to stay such actions. 21 C.F.R. § 10.35(d). Because nothing, other than the petition, currently stands in the way of approval of ribavirin ANDAs, FDA’s refusal to grant such approvals based on the pending decision on ICN’s petition is contrary to law, arbitrary, and capricious.