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*BY 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

**Re: FDA Docket Number 2003P-0321/CP1  
Reply to Opposing Comments by Teva**

Dear Sir or Madam:

On July 16, 2003, we submitted the above-referenced petition on behalf of Valeant Pharmaceuticals International ("Valeant") (formerly known as ICN Pharmaceuticals Inc. and Ribapharm, Inc.) challenging the proposed marketing of generic versions of Rebetol® (ribavirin, USP) that lack approval or labeling for use with PEG-Intron® (peginterferon alfa-2b) (the "Petition").

After more than seven months, Teva Pharmaceuticals USA, Inc. ("Teva") has now submitted comments in opposition to the Petition. The comments, dated February 17, 2004, consist primarily of a random collection of off-point approval decisions. In fact, what is striking about Teva's comments is this: Each time Teva begins to confront one of the basic statutory arguments on which the Petition rests, Teva ducks the statute and grabs for "an illustration." As shown below, no amount of discussion of products such as Mifeprex®, Fuzeon®, Emtriva®, and Emend® (see Teva Comments at 4-7) can overcome Teva's abject failure to come to terms with the law and the facts at issue in this matter.

2003P-0321

RC 2

Dockets Management Branch (HFA-305)

March 16, 2004

Page 2

**I. TEVA FAILS TO ADDRESS THE STATUTORY LABELING ARGUMENT**

After providing a self-serving “summary of agreed principles” (Teva Comments at 1-2), Teva’s substantive argument begins with “the doctrine of intended use.” Teva Comments at 3. That is Teva’s first of many errors.

The starting point for addressing the Petition is not the legal principle of intended use; the starting point is the term “labeling” as defined in section 201(m) of the Federal Food, Drug, and Cosmetic Act (“FDCA”). *See* 21 USC 321(m). The intended use of a product is generally determined by reference to “labeling” and all other relevant evidence. *See generally Action on Smoking and Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980) (noting that “it is well established that the ‘intended use’ of a product, within the meaning of the [FDCA] is determined from its label, accompanying labeling, promotional claims, advertising and any other relevant source”). Moreover, while labeling is not the exclusive source of evidence of intended use (*see* Valeant Petition, Tab 7 at n.1), if a use can be established through reference to labeling, it is decisive. Thus, the focus of Valeant’s Petition has been on labeling, within the meaning of the FDCA, and on defining the universe of written materials that represent “labeling” of the proposed generic products. *See* Valeant Petition at 8, 10-11; Valeant Supplemental Petition at 1-4 (July 29, 2003); Valeant Reply to Opposing Comments at 1-6 (Oct. 3, 2003).

As we have maintained throughout this proceeding, the term “labeling” has been interpreted broadly by FDA to ensure that sponsors do not seek to evade their regulatory obligations by separating a product from the words that describe the product. As FDA explained in a recent draft guidance:

The act defines “label” to mean “a display of written, printed, or graphic matter upon the immediate container of any article . . . .” (21 U.S.C. 321(k).) “Labeling” means “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.” (21 U.S.C. 321(m).) According to *Kordel v. United States*, 335 U.S. 345 (1948), the language “accompanying such article” in the “labeling” definition includes what supplements or explains an article, “in the manner that a committee report of the Congress accompanies a bill. No physical attachment one to the other is

Dockets Management Branch (HFA-305)  
March 16, 2004  
Page 3

necessary. It is the textual relationship that is significant . . . .”  
FDA regulations thus define as “labeling” a wide variety of  
written, printed, or graphic matter that bears a textual  
relationship with a drug or device. (See 21 CFR 202.1(l)(2)).

Draft Guidance for Industry, “Help-Seeking” and Other Disease Awareness  
Communications by or on Behalf of Drug and Device Firms, at 2 (Jan. 2004).

Here, Teva and the other generic applicants are referencing a drug  
that is approved only as part of a combination product. See 21 USC 353(g), 360bbb-  
2, 21 CFR 3.2(e). That is a critical point in determining the universe of labeling  
that bears on or can be said to accompany the proposed generic products. Not  
surprisingly, it is a point that Teva (and Geneva Pharmaceuticals, Inc. and Three  
Rivers Pharmaceuticals, LLC in their comments) completely avoids.

The reference product – Rebetol – cannot lawfully be marketed with  
stand-alone labeling. See Valeant Petition at 9-12; Valeant Supplement at 1-4;  
Valeant Reply at 1-7. It is approved only as part of a combination product and,  
therefore, is governed by laws and policies that are unique to combination products.  
Among other things, it is absolutely the case that the universe of labeling that  
governs the proposed generic products *includes* the labeling of the companion  
products that have been approved specifically for use with Rebetol.

Teva, we know, would insist that it alone can dictate the uses for  
which its seeks approval, and that Teva can choose not to market generic Rebetol  
for use with PEG-Intron. That is, Teva believes that all can be cured with a  
labeling “carve out” and a brisk reference to the *Bristol-Myers* case. See *Bristol-  
Myers Squibb v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996). That is Teva’s second error.

Teva, like Geneva and Three Rivers before it, fails to confront the  
overwhelming degree to which PEG-Intron (as well as Intron-A) is cross-labeled for  
use with ribavirin. See Valeant Petition at 3-6, 11; Valeant Supplement at 1-2;  
Valeant Reply at 3. As we have shown repeatedly in this proceeding, removing  
language from the package insert and Medication Guide (“MedGuide”) for the  
proposed generics – or even adding disclaimers to the inserts or MedGuide – cannot  
cure the problem. See Valeant Petition at 11-12; Valeant Supplement at 1-2;  
Valeant Reply at 8-9. No matter how well crafted the generic labeling may be, the

Dockets Management Branch (HFA-305)  
March 16, 2004  
Page 4

package insert and MedGuide for PEG-Intron clearly states that PEG-Intron and ribavirin are to be used in combination.

Teva's only other response to this fundamental problem is to suggest that the problem lies with the labeling of PEG-Intron. *See* Teva Comments at 4, 7. Teva makes the perfect lawyers argument that it is the labeling of PEG-Intron that would render the generic products misbranded and, therefore, if any product is misbranded, it is PEG-Intron. *Id.* at 7. Once again, in the case of a combination product, it is not an "either/or" issue. If the generic products lack labeling for use with peginterferon, it is the Ribavirin/Peginterferon combination product as a whole that is misbranded. And, as we showed in the Petition, FDA cannot approve generic ribavirin in a manner that causes it, or any other approved combination product, to be rendered misbranded. *See* Valeant Petition at 10; Valeant Reply at 2, 6.

## **II. THE CONTRACT BETWEEN TEVA AND SCHERING IS DIRECTLY RELEVANT TO THE LABELING ISSUE**

Teva urges "summary rejection" of the argument that the contracts between the generic sponsors and Schering-Plough Corporation ("Schering") bear on the intended use of the generics. *See* Teva Comments at 8. Teva, again, is missing the issue.

The contracts bear directly on the issue of *labeling* and, only by extension, on intended use. If Schering's PEG-Intron labeling also constitutes labeling of the generic products, then the question of intended use is all but decided.

The issue, again, is the legal standard for determining whether a given set of written materials constitutes "labeling" within the meaning of the FDCA. As we have shown, two factors that may be used to determine whether written materials constitute labeling are: textual relationship to the product and evidence of a shared economic relationship. *See Kordel v. United States*, 335 U.S. 345 (1948); *United States v. Urbuteit*, 335 U.S. 355 (1948). The financial relationship between two seemingly unrelated parties is a relevant factor in determining whether material distributed by one person constitutes labeling of another person's product. *United States v. LeBeau*, 985 F.2d 563 (7th Cir. 1993) (unpub. opinion) (holding that the "core relationship" between a booklet and drug product is "slightly more attenuated" but still intact for purposes of labeling, where the drug manufacturer does not technically sell the booklet but informs purchasers of its products where it

Dockets Management Branch (HFA-305)  
March 16, 2004  
Page 5

can be obtained); *United States v. Ballistrea*, 101 F.3d 827 (2d Cir. 1996) (upholding a conviction under 21 USC 331(a) for selling devices and drugs that were labeled without therapeutic claims contained in literature and audiotapes separately distributed to consumers and to downstream distributors for eventual delivery to consumers); *see also* Valeant Petition at 10, n.12; Valeant Supplement at 2-3; Valeant Reply at 4-6.

Under the licensing agreements between the generics and Schering, the generics will pay Schering a royalty based on the sale of the generic ribavirin. This promise of payment – *with no apparent limitation on whether the generic products are sold for use with interferon or peginterferon* – bears directly on the labeling issue. It is neither a “red herring” nor a “delay” tactic; it is unrebutted evidence in the administrative record that sits directly within the legal standard on labeling. *See Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 885 (D.C. Cir. 2004) (FDA must base its decisions on the entire administrative record).

Finally, the contract with Schering is also relevant to Teva’s argument that Teva is entitled to a labeling carve out based on Schering’s U.S. Patent No. 6,177,074 (the ‘074 patent). *See* Teva Comments at 2. It is our understanding that Teva received a license to the ‘074 patent under the contract with Schering. *See* Valeant Supplement, at 2-3; Valeant Reply, at 4-5. There is no basis in law for a labeling carve out based on a patent where the generic applicant has obtained contractual rights to the patent from the manufacturer of the listed drug.<sup>1/</sup> *Cf.* 21 USC 355(j)(2)(A)(v) (requiring that the labeling for the proposed generic be the same

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<sup>1/</sup> We also note that FDA has already determined that at least two other listed method-of-use patents for ribavirin – Nos. 5,797,097 and 6,063,772 – are not eligible for submission of a section viii statement and, therefore, cannot be carved out of the labeling. *See* Tab 1 hereto, Letter from G. Buehler, FDA, dated April 8, 2002 (stating that “[t]he agency has reviewed the record in this matter, and determined it would not be appropriate for any ANDA applicant referencing Schering’s Rebetol® to submit a section viii statement for the ‘097 and ‘772 patent”); *see also* Tab 2 hereto, The Pink Sheet, *FDA Developing Brand/Generic Labeling “Carve Out” Notification Process*, at 13 (Oct. 27, 2003) (quoting an FDA official as explaining that: “If you submit a [Paragraph IV] to a certain patent that also has a method of use attached to it . . . then that language should be in your [proposed generic label],” and the only time “you can carve that out is if you submit a section viii statement, then you may remove that corresponding language as defined in the Orange Book with the use code”). By disallowing the section viii statement, the agency effectively disallowed a labeling carve out for the ‘097 and ‘772 patents, which expire in 2016.

Dockets Management Branch (HFA-305)  
March 16, 2004  
Page 6

as the labeling for the listed drug “except for changes required because . . . the new drug and the listed drug are produced or distributed by different manufacturers”).

### III. TEVA’S RELIANCE ON THE *BRISTOL-MYERS* CASE IS MISPLACED

According to Teva, “[t]he legal authority for generic applicants to unilaterally limit the intended uses of their products through labeling carve outs is well established and beyond challenge.” Teva Comments at 3 (citing *Bristol-Myers Squibb v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996)). We agree, but only to a point. As we acknowledged in our Petition and Reply to Opposing Comments, the statute and the implementing regulations permit carve outs in appropriate, limited circumstances. See Valeant Petition at 1, 9-12; Valeant Reply at 6-7. It should be clear by now that such circumstances do not exist here.

Foremost, a labeling carve out that causes the proposed product to stand in violation of other provisions of the FDCA cannot stand. See, e.g., Valeant Petition, Tab 7 at 3 (stating that the FDCA prohibits “introducing or causing the introduction into interstate commerce of a drug or device intended for a use that has not been approved or cleared by FDA, even if that same product is approved or cleared for a different use” (footnotes omitted)). Here, as we have shown throughout this proceeding, the fact that ribavirin is approved only as part of a combination product introduces issues of law and fact that were not present in *Bristol-Myers*. The *Bristol-Myers* case centered on products such as Estrace® (in the district court) and Capoten® (in the court of appeals), neither of which is approved with combination or companion labeling. The court in *Bristol-Myers*, therefore, simply did not have to consider the legal impact of a labeling carve out in the context of a cross-labeled combination product.

Our case, in contrast, involves a companion set of labeling (for PEG-Intron) that contains dozens of references to the very use for which the generics seek a carve out. Valeant Petition at 4-7; Valeant Reply at 3. Even more, our case involves cross-referenced and interlocking MedGuides, where the removal of information from the generic MedGuide renders the labeling for the generic misleading under section 201(n) of the FDCA. Valeant Petition at 4-7; Valeant Reply at 3. As shown in Valeant’s Petition and Reply to Opposing Comments, the patient-directed MedGuide that accompanies PEG-Intron specifically refers to the companion MedGuide that accompanies ribavirin. *Id.* The omission of PEG-Intron

Dockets Management Branch (HFA-305)

March 16, 2004

Page 7

dosing information from the generic MedGuide serves only to render the proposed generic product, and the combination, misbranded. *See* 21 USC 321(n) (in determining whether the labeling of the drug is misleading, the agency “shall take into account” the extent to which the labeling fails to reveal material facts with respect to the use of the product “under such conditions of use as are customary or usual”). The *Bristol-Myers* court did not have to address such issues.

Teva’s comments demonstrate this point perfectly, with reference to at least three specific examples of drugs that are approved with stand-alone labeling. According to Teva:

- Fuzeon® (enfuvirtide for injection) is labeled for use with protease inhibitors, “*but the labeling of these other drugs makes no mention whatsoever to use with Fuzeon.*”
- Emtriva® (emtricitabine capsules) is approved for use with anti-HIV products, but “*none of these other drugs are [sic] labeled for use with Emtriva.*”
- Emend® (aprepitant capsules) is approved for use with anti-emetics, but they “*do not have labeling that refers to their use with Emend.*”

Teva Comment at 5 (emphasis added). Ribavirin, in contrast, is approved for use with PEG-Intron and, importantly, PEG-Intron *does* have labeling that specifically refers to use with ribavirin. Valeant Reply at 3 (“The package insert for PEG-Intron contains *more than one hundred references* to the use of PEG-Intron with ‘ribavirin’ and ‘Rebetol.’” (Emphasis added)). 2/

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2/ Fuzeon, Emtriva, and Emend are generally approved for use with other categories of products, and not an “*individually specified* drug, device, or biological product.” 21 CFR 3.2(e) (emphasis added); *see* Fuzeon Labeling (approved for use with “other antiretroviral agents”), Emend Labeling (approved for use with “other antiemetic agents”), Emtriva Labeling (approved for use with “other antiemetic agents”). The other example raised by Teva, Mifeprex® (mifepristone), is the subject of a currently pending citizen petition. *See* American Ass’n of Pro Life Obstetricians and Gynecologists Citizen Petition and Request for Administrative Stay, Docket No. 02P-0377 (Aug. 20, 2002).

Dockets Management Branch (HFA-305)  
March 16, 2004  
Page 8

Simply put, FDA approves drug products that include general references to uses with other drug products as a matter of course. Nothing in Valeant's Petition would require the agency to change its general approach to the labeling of such products. The Ribavirin/Peginterferon combination falls into an entirely different category; it is a drug-biologic combination product in which FDA specifically approved interlocking labeling. As such, and in contrast to the *Bristol-Myers* case, one cannot simply remove information from one component of the combination without raising a fundamental question as to whether the combination as a whole has been rendered unapproved and misbranded.

**IV. TEVA'S COMMENTS SUPPORT THE NEED FOR A GUIDANCE PROCESS**

Teva is now the third company to submit comments on Valeant's Petition. In addition, more than 90 individuals and interest groups have submitted comments to the docket. This matter has reached the point where it should be self-evident that a guidance process – as requested in the opening Petition – is required as a matter of law. *See* 21 CFR 10.115(e) (“These [good guidance practices] *must be followed* whenever regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public audience.” (Emphasis added)).

**V. CONCLUSION**

Teva's comments serve only to reinforce the legal and factual arguments in support of the Petition: (1) Teva offered no response to the central issue of “labeling;” (2) Teva failed to show why its promise of payment of royalties to Schering is irrelevant; and (3) Teva demonstrated why the *Bristol-Myers* case does not determine the outcome of this matter.

Respectfully submitted,



David M. Fox

Enclosures