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Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Docket No. 01P-4595 (Citizen Petition Submitted by Apotex Corp.)

These comments are submitted by R.W. Johnson Pharmaceutical Research Institute (RWJPRI) and Ortho-McNeil Pharmaceutical, Inc. (OMP) (hereafter referred to jointly as "Ortho-McNeil") in response to a citizen petition, dated October 24, 2001, submitted by Apotex Corp. The petition requests the Food and Drug Administration (FDA) to make certain determinations regarding changes that were previously made in the labeling of Ultram® (tramadol hydrochloride) and regarding the safety and effectiveness of proposed labeling for generic tramadol products. RWJPRI is the sponsor of the NDA for Ultram, and OMP markets the product. As explained in these comments, the Apotex petition lacks merit and should be denied.

I. History of Ultram Labeling Changes

Ultram is indicated for the management of moderate to moderately severe pain. The drug has side effects that may cause patients to terminate therapy. The events most commonly associated with discontinuance of treatment are dizziness/vertigo, nausea, and vomiting.

Ultram was originally approved with a recommended dosing of 50 to 100 mg every 4 to 6 hours, not to exceed 400 mg/day. Ortho-McNeil undertook post-approval clinical studies to investigate whether other dosing regimens would reduce the adverse events associated with use of Ultram and thereby reduce the incidence of treatment discontinuance. In a study that was the basis of FDA's approval of revised labeling in August 1998, Ortho-McNeil showed that a slow titration of the drug beginning with 50 mg/day and increasing over ten days to 200 mg/day could reduce discontinuance due to adverse events, particularly dizziness and vertigo, in comparison to no titration or a four day titration. The study did not demonstrate a statistically significant reduction in nausea and vomiting.

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Another study was subsequently undertaken to determine whether an even slower titration schedule would result in reduction of nausea and vomiting leading to termination of therapy. The study was a multicenter, randomized, double-blind study of patients with chronic pain. The study demonstrated that starting with an initial dose of 25 mg/day with gradual dosing increases to 200 mg/day through a 16-day titration schedule reduced the incidence of discontinuance due to nausea and vomiting in subjects who previously had difficulty tolerating tramadol because of nausea and/or vomiting. The percentage of subjects who discontinued treatment due to nausea -- the primary cause of treatment discontinuance -- and vomiting was significantly lower in the 16-day titration group (about 22%) than in the 10-day titration group (46.3%).

Based on this study, FDA on January 3, 2000, approved a change in the Dosage and Administration section of the Ultram labeling. For patients "not requiring rapid onset of analgesic effect," the 16-day titration regimen is recommended. For "the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risks of discontinuation due to adverse events associated with initial higher doses," a nontitrated regimen of up to 400 mg/day is recommended.

II. The Apotex Petition

Apotex states in its petition that it has submitted an abbreviated new drug application ("ANDA") for 50 mg tramadol tablets. The Apotex petition requests that FDA make three determinations: (1) that the titration regimen was not added to the Ultram labeling due to safety or effectiveness reasons; (2) that omission of the titration regimen from the labeling of its proposed tramadol product would not render its product less safe or effective than Ultram; and (3) that the Apotex tramadol product may use the discontinued Ultram labeling that was previously approved by FDA.

III. The Process in 21 C.F.R. § 314.161 Is Inapplicable to Ultram

The threshold basis for Apotex's petition is its contention that the process set forth in 21 C.F.R. § 314.161 applies to generic tramadol products. Nothing in that regulation, or in the statutory provision that it implements, supports Apotex's position.

Under section 505(j)(2)(A)(i) of the Federal Food, Drug, and Cosmetic Act ("the Act" or "FFDCA"), an ANDA may be submitted only for a "listed drug" that is identified in the Orange Book pursuant to section 505(j)(7). All drugs approved for safety and effectiveness must generally be listed. Section 505(j)(7)(C) provides, however, that if the approval of a drug was withdrawn or suspended, or "if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons," the drug "may not be published in the [Orange Book] list" or "if the withdrawal or suspension occurred after its publication in such list, it shall be immediately removed from such list."

The regulations in 21 C.F.R. § 314.161 implement these provisions. The regulations include a procedure that allows a drug that has been withdrawn from the market and is no longer listed in

the Orange Book to be “relisted if the agency has evidence . . . that the withdrawal is not for safety or effectiveness reasons.” 21 C.F.R. § 314.161(e). This determination can be made “at any time after [the drug’s] removal from the list . . .” *Id.*

These provisions do not apply to changes in labeling and therefore do not apply to Ultram. Under the terms of the statute, it applies only when “a drug” is withdrawn. The drug Ultram has not been withdrawn from the market. Nothing in section 505(j)(7) or 21 C.F.R. § 314.161 make them applicable to a labeling revision.

Moreover, FDA is not authorized to provide the remedy that Apotex is seeking. The only actions that FDA is authorized to take under section 505(j)(7) and 21 C.F.R. § 314.161 are (1) removing the listing of a drug from the Orange Book if the drug was withdrawn for reasons of safety or effectiveness, and (2) relisting the drug in the Orange Book if it has been removed from the list and FDA determines that the drug was not withdrawn for reasons of safety or effectiveness. Since Apotex is not seeking to have Ultram removed from the Orange Book, it must be attempting to come within the second, relisting provision.

To even arguably come within this relisting provision, Apotex would need to contend that the listing of Ultram has been removed from the Orange Book and that FDA should relist it because the original labeling was not revised for reasons of safety or effectiveness. Ultram’s inclusion in the Orange Book, however, has been uninterrupted since it was originally approved. Since there has been no “removal from the list” of Ultram and it therefore cannot be “relisted,” the regulations simply do not authorize the remedy that Apotex is seeking. Moreover, since Ultram is already in the Orange Book, “relisting” based on different labeling is not feasible. Orange Book listings do not refer to a drug’s labeling, and the Orange Book could therefore not establish two forms of Ultram as reference drugs, each differing only in terms of labeling.

In short, since the statute and regulations on which Apotex rely do not authorize the FDA action it seeks, the petition lacks legal support.

IV. The Titration Regimen Was Added to the Ultram Labeling for Reasons of Safety and Effectiveness

Apotex argues that the titration regimens were added to the Ultram labeling not because of “concerns for safety or effectiveness of the dosing schedule” but rather “to reduce the incidence of discontinued drug usage.” (Pet. at 4) This attempted distinction between issues of safety and effectiveness, on the one hand, and discontinued treatment due to adverse reactions, on the other hand, is wholly specious.

As indicated above, the titration regimens were shown in clinical trials to reduce the incidence of dizziness, vertigo, nausea, and vomiting. There is no doubt that those conditions are adverse reactions, and they are listed as such in the Ultram labeling. Indeed, Table 2 in the labeling identifies dizziness/vertigo and nausea as the two most common adverse reactions observed in the clinical trials supporting the Ultram new drug application.

FDA has published a list of the drugs that were withdrawn from the market for reasons of safety or effectiveness. 63 Fed. Reg. 54082 (Oct. 8, 1998). Most of those products were withdrawn because of adverse reactions. While Ultram's adverse reactions are obviously less severe than those of the products that were withdrawn, it is clear that withdrawal based on adverse reactions is considered to be for reasons of safety.

Similarly, use of a dosing regimen that reduces the incidence of adverse reactions is without doubt an improvement in the safety of a product. A labeling revision to introduce a safer dosing regimen is clearly a change for reasons related to safety. Moreover, in the case of Ultram, for which the safety improvement allows a greater percentage of patients to remain on the effective tramadol therapy, the reduction in the number of patients discontinuing therapy results in the product being more effective in practice.

V. A Generic Product That Omitted the Titration Regimen Would Not Be As Safe and Effective as Ultram

The FDA regulations provide that the labeling of a generic product must generally be identical to the labeling of the reference listed drug but that the generic may omit aspects of the reference drug's labeling that are protected by patent or exclusivity if the resulting differences in the labeling "do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 C.F.R. §§ 314.94(a)(8)(iv); 314.127(a)(7). This standard governs whether a generic tramadol product could be approved with labeling that does not include the 16-day titration regimen.

As outlined above, Ortho-McNeil's clinical studies have demonstrated that the 16-day titration regimen, which starts patients at 25 mg/day, is safer than the nontitrated regimen, which starts patients at doses of up to 400 mg/day. The titration regimen was proven to result in lower incidences of dizziness/vertigo, nausea, and vomiting. The titration regimen is also more effective in practice than high initial doses because the side effects of the higher doses result in a higher rate of treatment discontinuance.

If the titration regimen is deleted from the labeling of a generic tramadol product, the resulting product would be less safe and less effective for the remaining nontitrated dosing regimen. As the approved labeling states, the nontitrated regimen should be used only if the benefits of rapid onset of analgesic effect outweigh the adverse effects on safety and effectiveness associated with that regimen. Unless the comparative benefits of the titration regimen are explained in the labeling, a physician would have no basis for assessing whether the benefits of the nontitrated regimen outweigh its risk of discontinuance due to adverse events. Incomplete labeling could result in the prescription of the nontitrated, up-to-400 mg/day regimen for patients who would be prescribed the titration regimen if complete information were available, and these patients will suffer a higher incidence of adverse effects and a lower rate of effectiveness as a result. Thus, if presented in the labeling by itself, the nontitrated regimen would be less safe and less effective than it is when presented in the context of the full approved labeling. Under the standard in the

FDA regulations, labeling that includes only the nontitrated regimen may therefore not be approved.

The attached letter from Dr. Russell K. Portenoy, a renowned expert in pain management, discusses the possible labeling of generic tramadol products. He concludes that "slower titration, preferably starting from an initial dose of 25 mg per day, leads to a lower rate of adverse events and therapy discontinuation as a result of side effects." On that basis, Dr. Portenoy states that

"the labeling for tramadol should recommend gradual dose titration for patients who are administered the drug for the ongoing treatment of chronic pain. If the labeling says otherwise, and physicians dose according to the label, then the therapy is likely to lead to a relatively higher rate of side effects and treatment discontinuation."

If FDA were to approve generic tramadol products with labeling that omitted the titration regimen, physicians would be misled and many patients would be denied the benefits of the safer and more effective titration regimen that they would receive if the titration regimen were included in the labeling.

VI. FDA Lacks Authority To Allow Apotex To Use Ultram's Discontinued Labeling

Finally, FDA must reject Apotex's request to use labeling that was previously approved for Ultram but that is no longer the approved labeling. The agency lacks the legal authority to allow the use of discontinued labeling by a product approved through an ANDA.

The Act requires that an ANDA contain:

"information to show that the labeling proposed for the [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because . . . the [generic] drug and the listed drug are produced or distributed by different manufacturers."

FFDCA § 505(j)(2)(A)(v). Based on this statutory language, FDA has promulgated detailed regulations governing the submission and consideration of ANDAs.

With respect to labeling, the regulations require that the ANDA applicant compare its proposed labeling to "currently approved" labeling for the listed drug. 21 C.F.R. § 314.94 (a)(8). The ANDA applicant must state that the labels are the same except for an enumerated list of allowable differences, the most relevant for the issues raised by the Apotex request being "*omission* of an indication or other aspect of labeling protected by patent or accorded exclusivity under [the Act]." 21 C.F.R. § 314.94 (a)(8)(iv) (emphasis added). Thus, while it is established that generic labeling can omit a protected element of innovator drug labeling, see Bristol-Myers Squibb v. Shalala, 91 F.3d 1493 (D.C. Cir. 1996), there is no regulatory basis for substituting unprotected, but obsolete, terms into the generic label, particularly when the substituted labeling would result in a less safe and less effective product.

Moreover, the finding requested by Apotex conflicts with the statutory ANDA provisions. Apotex seeks a determination that its proposed labeling is as safe and effective as the currently approved labeling of the listed drug. FDA, however, is not permitted to assess the safety and effectiveness of proposed labeling in the context of an ANDA. The Act allows the agency to consider the safety of inactive ingredients in the ANDA process, § 505(j)(4)(H), but there is no such statutory authorization with regard to labeling, where the only touchstone is sameness to the listed drug's labeling, § 505(j)(4)(G). If such a comparative safety and efficacy assessment is necessary for approval, then the drug in question cannot be reviewed via the ANDA process. Apotex is requesting approval of what amounts to a hybrid ANDA -- a route to approval found nowhere in the statute.

Although we believe that FDA lacks the statutory authority to reach the result that Apotex requests, even if FDA had such authority it could implement it only through notice-and-comment rulemaking. As noted above, the FDA regulations require a generic drug to copy the "currently approved" labeling of the reference drug, except for permitted *omissions* of protected material, if the omissions do not result in the product being less safe or effective. The result requested by Apotex conflicts with that regulation, since it seeks to use discontinued labeling, and therefore FDA could grant Apotex's request only if it first amends the regulation.

It is a settled matter of administrative law that "[i]f a second rule . . . is irreconcilable with [a prior legislative rule], the second rule must be an amendment of the first; and, of course, an amendment to a legislative rule must itself be legislative." National Family Planning v. Sullivan, 979 F. 2d 227, 235 (D.C. Cir. 1992). Legislative rules may be issued or amended only through notice-and-comment rulemaking, subject to certain exceptions that are not applicable here. 5 U.S.C. § 553. Thus, even if FDA had the authority to grant Apotex's request, it could do so only after amending the regulations through the required procedure.

VII. Conclusion

FDA should deny Apotex's petition for several reasons:

- The statute and regulations cited by Apotex do not authorize FDA to permit a generic drug to use a reference drug's discontinued labeling upon a finding that the labeling was revised for reasons other than safety and effectiveness.
- In any event, the titration regimen was included in the Ultram labeling to reduce the incidence of therapy discontinuance due to adverse effects, and this constitutes a revision for reasons of safety and effectiveness.
- Failure to include the titration regimen in the labeling of a generic tramadol product would make the product less safe and effective than Ultram.

Dockets Management Branch
January 22, 2002
Page 7

- FDA lacks the authority to permit a generic product to use the discontinued labeling of its reference drug.

Respectfully submitted,

A handwritten signature in cursive script that reads "Helen Torelli".

Helen Torelli

cc: Daniel Troy, OGC
Elizabeth Dickinson, OGC
Gary Buehler, OGD