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February 12, 2002

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

Re: Docket No. 01P-0495 Apotex Corp. Citizen Petition Regarding Ultram®
(Tramadol)

Dear Food and Drug Administration:

These comments are submitted by Apotex Corp. (Apotex) in support of its October 24, 2001 citizen petition, which asked FDA to determine that a generic version of Ultram® tablets (tramadol) could be approved after omission of exclusivity-protected titration dosing labeling information. Specifically, these comments respond to a January 22, 2002 comment submitted by R. W. Johnson Pharmaceutical Research Institute (R. W. Johnson), the sponsor of the NDA for Ultram. For the reasons discussed below, R. W. Johnson's comments are without merit. Therefore, FDA should promptly grant Apotex's requested relief.

As a threshold matter, Apotex notes that its citizen petition addressed two exclusivity-protected labeling statements, currently identified in the Orange Book as D-44 (titration dosing in increments of 50mg per day every three days) and D-63 (titration dosing using a 25mg dose). While Apotex continues to believe that the relief requested in its citizen petition is appropriate with respect to both the D-44 and D-63 exclusivities, this comment will focus on the D-63 exclusivity, because the D-44 exclusivity will expire in the very near future.

Most importantly, R. W. Johnson's statement that Ultram's D-63 titration dosing labeling results in safer and more effective use of Ultram is belied by the firm's own statements. In the firm's February 23, 1999 and April 16, 1999 letters to FDA, R. W. Johnson characterized the supplemental NDA that led to the D-63 exclusivity as providing for, in relevant part, proposed labeling changes to "further enhance compliance and tolerability of the product." (Copies of these letters were attached to Apotex's citizen petition.) If R. W. Johnson truly believed that the proposed labeling revision embodied in the D-63 exclusivity would have improved the product's safety or effectiveness, we assume that the firm would have prominently stated that view in its correspondence with FDA. Therefore, there is no support for R. W. Johnson's assertion that a generic tramadol product without the exclusivity-protected labeling information would be less safe and less effective than Ultram.

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R. W. Johnson contends that FDA lacks the legal authority to allow an ANDA sponsor to rely on discontinued labeling. Apotex disagrees. In Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1500 (D.C. Cir. 1996), the U.S. Court of Appeals for the District of Columbia Circuit upheld FDA's regulation that permits an ANDA sponsor to omit an exclusivity-protected indication. FDA's rationale in that case – with which the D.C. Circuit agreed – is that the omission of an exclusivity-protected indication is sanctioned by the Hatch-Waxman provision that permits deviations from the innovator product's labeling "because the [generic drug and the innovator] drug are produced or distributed by different manufacturers," 21 U.S.C. § 355(j)(2)(A)(v). That rationale extends with equal force to the use of discontinued labeling. (We note that FDA has tentatively reached the same conclusion, as set forth in the agency's October 2000 draft guidance on the use of discontinued labeling.)

Finally, R. W. Johnson contends that, even if FDA does have statutory authority, the relief Apotex seeks could only be implemented through notice-and-comment rulemaking. That contention is without merit. FDA has repeatedly stated that it can regulate directly from the statute in the area of generic drug approvals. The courts have accepted FDA's authority to do so. See Teva Pharmaceuticals, USA, Inc. v. United States Food and Drug Administration, 182 F.3d 1003, 1011 (D.C. Cir. 1999). Moreover, the relief that Apotex seeks is not inconsistent with any existing FDA regulations. This further supports the conclusion that rulemaking is not required. (Again, Apotex notes that FDA has tentatively reached the same conclusion, as the agency's October 2001 draft guidance does not envision rulemaking. Legally, of course, a guidance is very different from a regulation adopted through notice-and-comment rulemaking. See 21 U.S.C. § 371(h).)

For the reasons discussed in Apotex's citizen petition and in this comment, FDA should promptly grant Apotex's requested relief. R. W. Johnson's comments are nothing more than an effort to prolong its monopoly and deny consumers the benefit of lower cost, generic versions of Ultram, an important drug product. Apotex thanks the agency for its consideration of the petition and these additional views.

Respectfully submitted,



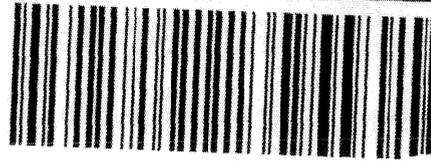
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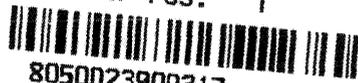
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