DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
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Re: Docket Nos. 01P-0495/CP1, 02P-0191/CP1, & 02P-0252/CP1

Dear Ms. Macdonald, Ms. Jaskot, and Mr. Hurst:

This letter responds to three petitions concerning approval of abbreviated new drug applications (ANDAs) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for generic tramadol hydrochloride (tramadol) 50 milligram (mg) tablets. Ultram is the reference listed drug for the subject ANDAs. The petitions, dated October 24, 2001, April 30, 2002, and May 30, 2002, respectively, were submitted by Apotex Corp. (Apotex petition), Teva Pharmaceutical USA (Teva petition), and Caraco Pharmaceuticals Laboratories, Ltd. (Caraco petition).[1] The petitions ask the Food and Drug Administration (FDA) to immediately approve generic products that are labeled with dosage instructions to administer 50 to 100 mg of tramadol hydrochloride every 4 to 6 hours as needed for pain relief, not to exceed 400 mg per day.[2]

[1] Apotex submitted comments dated February 12, 2002, April 11, 2002, May 2, 2002, May 8, 2002, and June 6, 2002. Teva submitted comments dated April 30, 2002, May 23, 2002, and June 5, 2002. Johnson submitted comments dated January 22, 2002, May 17, 2002, and May 31, 2002. Eon Labs submitted a comment dated March 7, 2002. The Caraco petition was also submitted as a comment to the Apotex and Teva petitions.

[2] The October 24, 2001, Apotex petition asked FDA to determine that the non-titrated dosing regimen originally approved for Ultram tablets was not withdrawn from the labeling for reasons of safety or effectiveness, that a generic tramadol labeled with the discontinued dosing regimen will not be less safe or effective than Ultram with its current labeling, and that an ANDA for a generic tramadol may use the discontinued dosing regimen. In response to Teva's petition, Apotex submitted a supplement to its petition dated May 8, 2002, asking FDA to immediately approve its ANDA for a generic tramadol. This

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The petitions are granted in part and denied in part. Teva's petition is denied insofar as it proposes that generic tramadol be labeled only for use for acute pain and contain only the second paragraph of Ultram's "Dosage and Administration" section. Teva's petition is granted insofar as the Agency will approve Teva's ANDA if it is labeled as described below and all other conditions of approval are met. The labeling described below omits an aspect of labeling protected by patent or exclusivity while not rendering the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use. *See* 21 CFR 314.127(a)(7).

Apotex's petition is granted in part. Apotex's petition is granted insofar as the Agency will approve Apotex's ANDA if it is labeled as described below and all other conditions of approval are met. Because adequate information to label a generic tramadol remains in the unprotected portion of Ultram's existing labeling, FDA does not reach the question raised in the Apotex petition of whether an ANDA can rely on information that has been discontinued from Ultram's labeling.

Caraco's petition is granted in part and denied in part. Caraco's petition is granted insofar as it "respectfully asks that the FDA describe precisely what label it would find acceptable." Because the Agency has identified the appropriate labeling for a generic tramadol, FDA does not reach the question of whether Caraco's ANDA can be approved using the alternative labeling Caraco suggests.

I. Background

When Ultram was originally approved on March 3, 1995, for management of moderate to moderately severe pain, the approved dosing regimen was 50 to 100 mg administered every 4 to 6 hours as needed for pain relief, not to exceed 400 mg per day.

On August 21, 1998, R.W. Johnson Pharmaceutical Research Institute (Johnson), the NDA holder for Ultram, received approval for a dosing schedule that provided for titration in increments of 50 mg per day every 3 days until an effective dose (not exceeding 400 mg per day) was reached.[3] The labeling approved to reflect the results of the 50 mg, 10-day titration trial included the original non-titration dosing information followed by the statement, "In a clinical trial, fewer discontinuations due to adverse events, especially dizziness and vertigo, were observed when titrating the dose in increments of 50 mg/day every 3 days until an effective dose (not exceeding 400 mg/day) was reached." Although this titration schedule did not specify a starting dose, a 50 mg/day starting dose can be inferred from the titration schedule specified. Clinical trials supporting this change demonstrated that titration from 50 mg over 10 days to reach an

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supplement also asks the Agency to decide what labeling is appropriate for a generic tramadol product and to give Apotex the opportunity to propose such labeling.

[3] This schedule contemplates dosing as follows: Days 1-3, 50 mg; Days 4-6, 100 mg (50 mg 2 times per day); Days 7-9, 150 mg (50 mg 3 times per day); Day 10, 200 mg (50 mg 4 times per day); thereafter, 50-100 mg every 4-6 hours as needed up to 400 mg/day).

effective dose increases the tolerability of Ultram and results in statistically significant reductions in discontinuations due to dizziness and vertigo. This 50 mg, 10-day titrated dosing schedule was granted 3 years of marketing exclusivity (that expired on August 21, 2001) and then received a pediatric exclusivity extension that expired February 21, 2002.

On December 23, 1999, Johnson received approval for an even slower, 16-day titration schedule that uses a 25 mg/day starting dose. This schedule recommends titration in 25 mg increments every 3 days until a 100 mg dose is reached, followed by a dose increase in 50 mg increments, as tolerated, every 3 days to reach 200 mg/day.[4] Clinical trials supporting this titration schedule were conducted in a population of patients who, during an open label run-in phase, had previously discontinued use of tramadol due to nausea and vomiting. The trials demonstrated that, for patients who have previously shown intolerance to a higher dose of tramadol, the 25 mg, 16-day titration resulted in a statistically significant reduction in discontinuations due to nausea and vomiting and fewer discontinuations due to any cause than did a 10-day or 4-day titration schedule. The labeling approved to reflect the results of the 25 mg, 16-day titration trial added the slower titration schedule, and it also indicated that the original, non-titrated dosing instructions were for patients who require "rapid onset of analgesic relief." Johnson was granted 3 years of marketing exclusivity (to expire on December 23, 2002) for this dosing schedule, and then received a pediatric exclusivity extension that will expire on June 23, 2003. Johnson also has listed a use patent in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) for a titration dosing regimen for the treatment of pain using an initial dose of about 25 mg.[5]

Teva and Apotex contend that despite the exclusivity and patent protection for the 25 mg, 16-day titration schedule, generic tramadol products nevertheless may be approved with appropriate labeling describing the safe and effective use of the drug.

II. Ultram's Current Labeling

Ultram (tramadol hydrochloride tablets) is a synthetic compound with opioid activity. The "Indications and Usage" section of Ultram's labeling states: "ULTRAM is indicated for the management of moderate to moderately severe pain. "

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[4] This schedule contemplates dosing as follows: Days 1-3, 25 mg; Days 4-6, 50 mg (25 mg 2 times per day); Days 7-9, 75 mg (25 mg 3 times per day); Days 10-12, 100 mg (25 mg 4 times per day), Days 13-15, 150 mg (50 mg 3 times per day); Day 16, 200 mg (50 mg 4 times per day); thereafter, 50-100 mg every 4-6 hours as needed up to 400 mg/day).

[5] When a drug product is granted three years of exclusivity under sections 505(c)(3)(D)(iv) and 505(j)(5)(D)(iv) of the Act for new clinical investigations essential to the approval of an NDA supplement, FDA may not approve an NDA described in section 505(b)(2) or an ANDA for the change described in the supplement for 3 years. When a method of using a drug is claimed in a listed patent, an ANDA applicant may either seek approval for labeling that omits the protected use, section 505(j)(2)(A)(viii), or challenge the method of use patent by filing a "paragraph IV certification" under section 505(j)(2)(A)(vii)(IV). This petition response addresses the former case, when an ANDA applicant seeks to omit protected labeling.

The "Dosage and Administration" section of Ultram's labeling currently states:

> Adults (17 years of age and over)
>
> For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of ULTRAM can be improved by initiating therapy with the following titration regimen: ULTRAM should be started at 25 mg/day qAM and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg q.i.d.). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After titration, ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours **not to exceed 400 mg/day.**
>
> For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, ULTRAM 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, **not to exceed 400 mg per day.**

Ultram's current labeling contains a section entitled "Titration Trials" that describes the clinical studies that were performed for approval of the current 16-day titration dosing regimen and the 10-day titration dosing regimen approved in the 1998 supplement. That section states:

> In a randomized, blinded clinical study with 129 to 132 patients per group, a 10-day titration to a daily ULTRAM dose of 200 mg (50 mg q.i.d.), attained in 50 mg increments every 3 days, was found to result in fewer discontinuations due to dizziness or vertigo than titration over only 4 days or no titration. In a second study with 54 to 59 patients per group, patients who had nausea or vomiting when titrated over 4 days were randomized to re-initiate ULTRAM therapy using slower titration rates. A 16-day titration schedule, starting with 25 mg qAM and using additional doses in 25 mg increments every third day to 100 mg/day (25 mg q.i.d.), followed by 50 mg increments in the total daily dose every third day to 200 mg/day (50 mg q.i.d.), resulted in fewer discontinuations due to nausea or vomiting and fewer discontinuations due to any cause than did a 10-day titration schedule.

III. FDA's Authority to Approve an ANDA That Omits Labeling Protected by Exclusivity or Patent

FDA has authority to approve ANDAs that omit protected labeling carried by the listed drug. The Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." 21 U.S.C. 355(j)(2)(A)(i). The Act also requires that an ANDA contain "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug . . . ." 21 U.S.C. 355(j)(2)(A)(v). The Act specifies two exceptions to this requirement. ANDA labeling may differ from that of the listed drug because changes from the listed drug were approved pursuant to an ANDA suitability petition, or because the drugs are produced or distributed by different manufacturers. 21 U.S.C. 355(j)(2)(A)(v). This requirement that the ANDA labeling be the same as that of the reference listed drug (except for differences approved under a petition or because the drugs are produced and distributed by different manufacturers) is repeated in the section of the Act that provides the grounds for not approving an ANDA. 21 U.S.C. 355(j)(4)(G).

FDA regulations flesh out the statutory exceptions to the "same labeling" requirement. 21 CFR 314.94, "Content and format of an abbreviated application," provides:

> Labeling (including the container label and package insert) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, *or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.*"

21 CFR 314.94(a)(8)(iv)(emphasis added).

The regulations further provide that to approve an ANDA that omits an aspect of labeling protected by patent or exclusivity, the Agency must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 CFR 314.127(a)(7).

The courts have upheld FDA's authority to approve generic drugs with necessary labeling differences from the listed drugs they reference. In *Bristol-Myers v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996), the court rejected a challenge to FDA's regulations at 21 CFR 314.94(a)(8)(iv) and 21 CFR 314.127(a)(7). In so doing, the court upheld FDA's authority to approve a generic captopril that omitted from its labeling an indication in the listed drug's labeling that was protected by exclusivity, as well as protected indication-specific dosing instructions. The court held that omission of an indication protected by exclusivity was a difference in labeling "required . . . because the drug and the listed drug are produced or distributed by different manufacturers" within the meaning of the statute.

Finally, the Act contemplates that an innovator company may submit to FDA's Orange Book patents claiming a method of using a drug product and that ANDA applicants may omit from proposed labeling methods of use covered by those patents. Sections 505(b)(1) and (c)(2) of the Act state that innovators may submit patents to FDA that claim the approved drug "or method of using such drug." If a method-of-use patent listed by the innovator does not claim a use for which an ANDA applicant is seeking approval (because it is omitted from the proposed ANDA labeling), the ANDA applicant may submit a statement to FDA that it is not seeking approval for a use claimed by a listed patent. 21 U.S.C. 355(j)(2)(A)(viii). These two statutory provisions, which use the same "method of use" term, mirror each other; a method of use claimed by a patent is also a method of use that an ANDA applicant may propose to carve out of the labeling.[6]

Whether the proposed ANDA may be approved is a separate question. That issue depends on whether the generic product, when labeled to exclude protected information, will be rendered less safe or effective than the listed drug "for all remaining, non-protected conditions of use." 21 CFR 314.127(a)(7).

Thus, FDA has the authority to approve ANDAs with labeling that is not identical to that of the listed drug. The specific question at issue is not whether a generic drug may omit protected information from its labeling. It is whether generic tramadol products, when labeled to exclude protected information currently in the Ultram labeling, will be rendered less safe or effective than Ultram "for all remaining, non-protected conditions of use." 21 CFR 314.127(a)(7).

IV. Safety and Effectiveness of a Tramadol Product with Protected Labeling Omitted

A. The Positions of the Parties

[6] FDA's regulation implementing this statutory provision uses the term "indications" to refer to what the ANDA applicant omits from its labeling in the context of submitting a statement that a protected use of a drug is not claimed in a listed patent. 21 CFR 314.94(a)(12)(iii). However, the preambles for the proposed and final rule express no intent to distinguish between method of use and indication, and use the terms interchangeably. See, for example, 59 Fed. Reg. 50338, 50347 (October 3, 1994).

In determining whether the protected portions of Johnson's Ultram labeling can be carved out to allow the approval of a generic, the parties have devoted considerable attention to the question of whether Ultram has been approved for both acute and chronic pain. Teva states that Ultram's labeling "provides for two separate and distinct therapeutic uses of tramadol, each of which requires a separate and distinct dosing regimen." Teva Petition at 3. Teva asserts that these two uses are: (1) "treatment of 'moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect" and (2) "[t]reatment of acute pain, i.e., pain for which 'rapid onset of analgesic effect is required." Teva Petition at 3. In support of its position that Ultram was approved for two different uses, Teva points to a 1996 FDA talk paper stating that Ultram was approved for the management of acute and chronic pain, Talk Paper T-96-23 (April 3, 1996), as well to excerpts from the review history that suggest that approval for both chronic and acute pain was intended. Medical Team Leader Review, Anti-Inflammatory, Analgesic and Ophthalmic Drug Products Division, NDA #20-281, Feb. 23, 1999, p. 4 (available at http://www.fda.gov/ohrms/dockets/dailys/01/Oct01/102501/cp00001.pdf at 77).

Johnson argues, on the other hand, that Ultram was and is approved for only a single indication – the treatment of moderate to moderately severe pain. Johnson points to the "Indications and Usage" section of Ultram's labeling, which states simply: "Ultram is indicated for the management of moderate to moderately severe pain," and contains no reference to chronic pain or to acute pain. Johnson notes that acute pain relief has only accounted for a small proportion of Ultram's prescriptions. It contends that Teva's labeling, which proposes to limit dosing instructions to those for "acute pain," would be impermissibly silent as to the appropriate dosing regimen for the majority of patients for whom it is indicated. Both Teva and Johnson marshal evidence from the labeling, the review history, and the postmarketing history to support their respective views.

The question of whether Ultram is separately indicated for chronic and acute pain does not need to be resolved at this juncture for FDA to approve generic tramadol during Johnson's exclusivity period for the 25 mg, 16-day titration regimen. ANDAs for tramadol may be approved without deleting all of the labeling regarding dosage and administration for what Teva characterizes as "chronic" pain. Portions of Ultram's current labeling related to the 50 mg, 10-day titration schedule are not protected by patent or exclusivity and they may – and should – be included in the labeling. In fact, the labeling proposed in the citizen petitions, because it would omit non-protected information from the innovator's labeling, fails to comply with the statutory and regulatory "sameness" requirement. Inclusion of this labeling would result in generic products that are not "less safe and effective than the listed drug for all remaining non-protected conditions of use." 21 CFR 314.127(a)(7).

B. Ultram's Protected Labeling and the Safety and Effectiveness of Generic Tramadol Products

Teva's proposed labeling (which seeks to include dosage and administration information only for pain requiring rapid onset of analgesic relief and proposes to carve out all

references to titration) poses difficult questions that would require resolution before a product with the labeling proposed could be approved. The scope of Johnson's exclusivity does not, however, require such a dramatic deletion from the approved labeling. Johnson's remaining protection covers only the information about the 25 mg, 16-day titration that was new and essential to the approval of the 1999 labeling supplement – it does not protect information included in the labeling related to the 50 mg, 10-day titration trial or in the original pivotal clinical trials (for which all exclusivity has now expired).

Generic tramadol applications can be approved without including the 25 mg, 16-day titration schedule. Although the 25 mg, 16-day trial provided information related to the narrow question of the tolerability of the drug in patients who have previously been shown to be tramadol-intolerant, and although the reduction of nausea and vomiting in this tramadol-intolerant population was statistically significant, labeling derived from information learned in that trial can be carved out of Ultram's labeling without rendering a generic tramadol less safe and effective than Ultram for the remaining non-protected conditions of use. The study supporting the supplemental new drug application for the 25 mg titration schedule did not test the hypothesis that a 16-day titration schedule will result in better tolerance (or fewer discontinuations due to nausea and vomiting) than a 10-day titration schedule in patients who have not previously reacted adversely to tramadol. Because the trial supporting the 1999 labeling supplement to add the 25 mg, 16-day titration information was conducted in patients previously shown to be intolerant of tramadol, it does not necessarily reflect the response of the general population to the drug. It cannot be assumed that a 25 mg, 16-day titration schedule will result in a statistically significant reduction in discontinuations due to nausea and vomiting compared to a 10 day titration in the general population. Therefore, the utility of the information granted exclusivity for doctors prescribing tramadol to patients who have not previously shown tramadol intolerance is limited.

Johnson argues that the slower titration schedule increases efficacy by increasing the number of patients who can tolerate it long enough to reach an effective dose. It is not obvious, however, that the slower titration increases tolerability for patients who have not been shown to be intolerant of tramadol previously. Moreover, as considered by FDA's physicians, it may be that the protected schedule results in decreased efficacy by delivering a subtherapeutic dose for up to 16 days.

In contrast to the 25 mg, 16-day trial, the 10-day, 50 mg trial provided essential safety information that can and should remain in the labeling. It was the 10-day, 50 mg titration trial that convinced FDA that titration improves the tolerability of Ultram for the general population of patients who do not require rapid relief. Information derived from that trial allows physicians to weigh the benefits of titration against those of rapid onset of relief. Because exclusivity relating to this dosing information has expired, general information about the benefits of titration (learned from this trial) can remain in the "Dosage and Administration" section. Only information relating to the specific 25 mg, 16-day titration schedule remains protected. Similarly, in the "Titration Trials" section of the labeling,

references to the 10-day, 50 mg titration can remain in the labeling while references to the 25 mg, 16-day titration must be carved out. Information about side effects of tramadol in the adverse events section of the labeling was obtained from the initial clinical trials and thus will also appear in a generic product's labeling. From this information, a physician evaluating patient treatment options can assess the risks and benefits to the general population related to the use of tramadol in a titration regimen.

In Johnson's May 31, 2002, submission to the docket, the company asserts that a certain portion of the Ultram labeling regarding rapid onset of analgesic effect is also protected by exclusivity, and thus may not be included in labeling for generic tramadol. Specifically, Johnson claims that the underlined portion of the labeling below must be omitted from generic tramadol:

> For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, ULTRAM 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, **not to exceed 400 mg per day.**

Johnson argues that because this language was part of the supplement to add information regarding the 25 mg, 16-day titration schedule to the Ultram labeling, it is protected by exclusivity.

Although certain labeling regarding the 25 mg, 16-day titration schedule is protected by exclusivity, it is not necessarily the case that all labeling added at the same time is also protected.[7] The labeling identified by Johnson is not protected by the exclusivity granted to the 25 mg, 16-day titration schedule. The underlined portion of the labeling relies upon information related to risk of discontinuation due to adverse events associated with the higher doses (50 mg and greater on a non-titrated schedule), which was available to the division in data from the 50 mg, 10-day titration trial, and the original approval trials. The 25 mg, 16-day titration trial information was not essential for approval of this portion of the labeling. Accordingly, it is not protected by Johnson's exclusivity. The 3 years of exclusivity does apply to aspects of the current labeling for which the 25 mg, 16-day titration trial provided information essential to approval. That protected labeling must be omitted from the labeling proposed in any ANDA.

[7] A sponsor may not obtain exclusivity for changes that do not require clinical trial data for approval by including them in an application or supplement that also includes changes for which exclusivity is appropriate. The regulation governing 3-year exclusivity for supplements states in relevant part that if a supplement contained reports of new clinical investigations that were essential to approval, the Agency will not make effective for a period of 3 years the approval of an abbreviated new drug application for a change "that relies on the information supporting a change approved in the supplemental new drug application." 21 CFR 314.108(b)(5).

C. Proposed Tramadol Labeling

FDA has reviewed the approved ULTRAM labeling to determine what may be included in labeling for generic tramadol, and whether such labeling may be approved under 21 CFR 314.127(a)(7). When protected information is deleted from the approved ULTRAM labeling to generate labeling for generic tramadol, the "Dosage and Administration" section would read:

> For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of tramadol can be improved by initiating therapy with a titration regimen. The total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After titration, tramadol 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours **not to exceed 400 mg/day.**
>
> For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, tramadol 50 mg to 100 mg can be administered as needed for pain relief every 4 to 6 hours, **not to exceed 400 mg per day.**

Thus the "Dosage and Administration" section will include a titrated and a non-titrated 50 mg dosing schedule. The 50 mg titration schedule that remains in the "Dosage and Administration" section (and that is further described in the "Titration Trials" section) is the same titration schedule that was previously approved for Ultram. Including the statement from the first paragraph of the "Dosage and Administration" section that "the tolerability of tramadol can be improved by initiating therapy with a titration regimen," and including the table of adverse events from the pivotal trials that appears in Ultram's labeling gives the physician a context to understand the statement regarding the risk-benefit calculation that the second paragraph requires.

The "Titration Trials" section would not contain the discussion of the 16-day, 25 mg titration trial and would not include the 16-day titration component in the graph that follows that discussion. However, that section would include the first sentence from Ultram's labeling that states:

> "In a randomized, blinded clinical study with 129 to 132 patients per group, a 10-day titration to a daily tramadol dose of 200 mg (50 mg q.i.d.), attained in 50 mg increments every 3 days, was found to result in fewer discontinuations due to dizziness or vertigo than titration over only 4 days or no titration."

This sentence would help the physician understand that titration reduces discontinuations due to adverse reactions. It would also provide the practitioner seeking to titrate a patient on the 10-day, 50 mg schedule with information about how to do so safely. Although this paragraph does not state an explicit starting dose for titration, a physician can infer a 50 mg/day starting dose from the dosing schedule as it is described. Ultram's labeling (before the 25 mg, 16-day titration schedule was added) also did not include a specific starting dose in the context of the 10-day, 50 mg titration regimen.

The "Adverse Reactions" section of a generic tramadol product's labeling would be exactly the same as in Ultram's labeling because these adverse reactions were reported in the original clinical trials for the drug. The first and second most frequent adverse reactions listed in the table of adverse reactions are dizziness/vertigo and nausea. Vomiting is listed as the sixth most common side effect. Thus, inclusion of the "Adverse Reactions" section would also acquaint physicians with the adverse reactions to tramadol.

In sum, FDA believes that a generic tramadol product labeled as described above would be as safe and effective as Ultram for the remaining non-protected conditions of use.

V. Tablet Scoring

There are two issues pertaining to the scoring of generic tramadol tablets. The first is whether FDA may approve ANDAs for 50 mg tablets that are not scored. The second is whether FDA may approve ANDAs for 50 mg tablets that are scored.

FDA may approve ANDAs for generic tramadol tablets that are not scored. Drug products approved under Section 505(j) of the Act are required to be the same as the listed drug in certain enumerated ways. Section 505(j)(2)(A). FDA's regulations implementing these provisions provide additional detail on the application of these requirements. 21 CFR 314.94 Neither the statute nor the regulations address ANDA approval requirements when the listed drug is scored to permit it to be administered in doses smaller than the labeled strength of the drug product. However, because drug products (generally tablets) are scored to permit dosing of the drug in accordance with the Dosage and Administration section of the approved labeling,[8] it is appropriate to use the approved labeling of the innovator product as the reference point for considering whether the generic product must also be scored.

The current Ultram labeling describes a titration regimen using a 25 mg dose. Ultram 50 mg tablets are scored so that tablets may be divided into two 25 mg doses that may be used for this 25 mg titration dosing regimen. When generic tramadol products do not include the 25 mg titration schedule in the labeling, it is reasonable to conclude that the 50 mg tablets need not be scored. The 50 mg minimum dose in the labeling for the generic products may be achieved by administering the entire 50 mg tablet. Because the

[8] An alternative to scoring a tablet to achieve the lower dose is to obtain approval for the drug product in the same dosage form, but for the lower strength.

unscored 50 mg tablet will permit the patient to use the product in accordance with the approved labeling, the lack of scoring is not a bar to approval of the ANDA.[9]

The next issue is whether FDA may approve ANDAs for generic tramadol tablets that are scored to permit 25 mg doses. The Agency concludes that, because of Johnson's exclusivity, scored generic tramadol tablets may not be approved.

The 25 mg dosing regimen is protected by 3-year exclusivity. Johnson asserts that therefore FDA may not approve a scored generic tramadol product without violating Ultram's exclusivity. May 17, 2002 Johnson letter at 8-9. FDA agrees with Johnson that the score was added to the Ultram tablet to allow users of the product to split the tablet to reach a 25 mg starting dose. Because that starting dose is part of the 16-day titration regimen and has no other basis in the approved labeling, and because that regimen remains protected by exclusivity and patent, the Agency currently will not approve an ANDA for a scored generic tramadol product.

FDA has described its general approach to scoring issues in MAPP 5223.2 "Scoring Configuration of Generic Drug Products." The approach taken to generic tramadol is consistent with that described in the MAPP.

VI. AB Rating

Johnson argues that Teva's tramadol product, using the labeling Teva proposes, cannot be AB-rated as therapeutically equivalent to Ultram because the safety profile of Teva's product would be "far different" from the safety profile of Ultram. May 17, 2002 Johnson letter at 7. Johnson supports its position with a number of statements from FDA's Orange Book (21st ed.):

> Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Orange Book at viii.
>
> Products evaluated as therapeutically equivalent can be expected, in the judgment of FDA, to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling. Orange Book at xii.

[9] FDA's Orange Book acknowledges that certain permissible differences among therapeutically equivalent products may require attention on the part of the health professional. It states that in such cases, "[t]he Agency will use notes in this publication to point out special situations such as potential differences between two drug products that have been evaluated as bioequivalent and therefore therapeutically equivalent, when they should be brought to the attention of health professionals. . . . For example, in rare instances, there may be variations among therapeutically equivalent products in their use or in conditions of administration. Such differences may be due to patent or exclusivity rights associated with such use. When such variations may, in the Agency's opinion, affect prescribing or substitution decisions by health professionals, a note will be added to section 1.8." Orange Book at xv.

Johnson also refers to the statement in the Orange Book that drugs considered to be therapeutically equivalent may differ only in "minor aspects of labeling (e.g., the presence of specific pharmacokinetic information)." Orange Book at viii. Johnson argues that the "reference to pharmacokinetic information is telling because such information would rarely if ever be used by a physician in prescribing a product. By contrast, an entirely different dosing regimen for a product would be pivotal to how it is used and could hardly be characterized as a difference in a minor aspect of its labeling." May 17, 2002, Johnson letter at 8.

FDA disagrees with Johnson that a generic tramadol product cannot be AB-rated to Ultram. As noted above, FDA routinely approves ANDAs that omit a condition of use, such as an indication, found in the innovator's labeling. Although the labeling that FDA would approve in this instance does not omit an indication, it does omit a portion of the labeling that is protected by exclusivity and patent. In assessing whether two drugs may be rated as therapeutically equivalent to each other, FDA assesses whether they "can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." In this case, dosing the generic product in conformance with the proposed labeling set forth in section IV above permits a generic tramadol to be as safe and effective as Ultram when used in conformance with its labeling.[10] This assessment involves the same considerations as the determination under 21 CFR 314.127(a)(7) that an omission of protected labeling information from a generic will not render the proposed product less safe or effective for the remaining, non-protected conditions of use.

FDA has consistently maintained that the omission of information protected by exclusivity will not be a basis for altering a therapeutic equivalence rating. 59 Fed. Reg. 50338, 50357 (October 3, 1994). In the present case, FDA has determined there is no reason to believe that a tramadol product approved under an ANDA would not be therapeutically equivalent to Ultram, when administered to patients under the conditions specified in the labeling.

VII. Conclusion

Teva's petition is denied in part and granted in part. Teva's petition is denied insofar as it proposes that generic tramadol be labeled only for use for acute pain and contain only the

[10] The question of AB ratings when one product is scored and the other is not also bears mentioning. The Orange Book discussion of therapeutic equivalence notes that drug products are considered by FDA to be therapeutically equivalent if they meet the criteria described in the Orange Book "even though they may differ in certain other characteristics such as ... scoring configuration.... When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity." (Orange Book at viii). As noted above, the Orange Book permits notation of additional information when differences in A-rated products require attention on the part of prescribers and dispensers of drugs. Orange Book at xv. Because the generic product will not be scored and the 25 mg starting dose for the titration schedule suggested in Ultram's labeling cannot be obtained using an unscored tablet, FDA anticipates that this difference may be brought to the attention of health care professionals through an Orange Book notation.

second paragraph of Ultram's "Dosage and Administration" section. Teva's petition is granted insofar as the Agency will approve Teva's ANDA if it is labeled as described in section IV above and all other conditions of approval are met.

Apotex's petition is granted in part. Apotex's petition is granted insofar as the Agency will approve Apotex's ANDA if it is labeled as described in section IV above and all other conditions of approval are met. Because adequate information to label a generic tramadol remains in the unprotected portion of Ultram's existing labeling, FDA does not reach the question of whether Apotex can rely on sections that have been discontinued from Ultram's labeling.

Caraco's petition is granted in part. Caraco's petition is granted insofar as it "respectfully asks that the FDA describe precisely what label it would find acceptable." Because the Agency has identified the appropriate labeling for a generic tramadol, FDA does not reach the question of whether Caraco's ANDA can be approved using the alternative labeling Caraco suggests.

Sincerely yours,

FOR Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research