MEMORANDUM

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DATE: May 7, 2010

SUBJECT: Scope of Three-year Exclusivity Granted to Ryzolt (tramadol hydrochloride) extended-release tablets

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Labopharm's NDA 21-745 for Ryzolt (tramadol hydrochloride) extended-release tablets, 100 mg, 200 mg, and 300 mg, was approved on December 30, 2008, for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.[1] Ryzolt was approved through the 505(b)(2) pathway and relied, in part, upon FDA's finding of safety and/or effectiveness for NDA 20-281 for Ultram (tramadol hydrochloride) tablets, an immediate-release formulation. The 505(b)(2) application for Ryzolt contained reports of a new clinical investigation (other than a bioavailability study) that was essential to the approval of the application and conducted or sponsored by the applicant. Accordingly, Ryzolt was granted three years of exclusivity ending on December 30, 2011 (see section 505(c)(3)(E)(iii) of the Federal Food, Drug, and Cosmetic Act (FFD&C Act)). This memorandum addresses the scope of Ryzolt's three-year exclusivity with reference to the tentatively-approved 505(b)(2) application (NDA 22-370) for tramadol hydrochloride extended-release capsules, 100 mg, 200 mg, and 300 mg, submitted by Cipher Pharmaceuticals (Cipher).

Background

Ryzolt is the second extended-release formulation of tramadol hydrochloride approved by FDA. FDA approved Biovail Technologies, Ltd.'s NDA 21-692 for Ultram ER (tramadol hydrochloride) extended-release tablets on September 8, 2005. Ultram ER was approved through the 505(b)(2) pathway and relied, in part, upon FDA's finding of safety and/or effectiveness for NDA 20-281 for Ultram (tramadol hydrochloride) tablets. Ultram ER was granted three years of exclusivity upon its approval.

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[1] The Ryzolt NDA is now held by Purdue Pharma.

Subsequent to approval of Ultram ER, Labopharm requested a meeting with FDA to discuss the regulatory pathway for Labopharm's submission of an NDA for extended-release tramadol hydrochloride tablets in light of the recent approval of Ultram ER. At the October 25, 2005 meeting, several regulatory approaches were discussed, including (b) (4) (b) (4) (b) (4) submission as a 505(b)(2) application under various scenarios.

On November 25, 2005, Labopharm submitted a 505(b)(2) application for Ryzolt that identified Ultram [immediate-release] tablets as the listed drug relied upon. FDA determined that Ryzolt had sufficiently different biopharmaceutical features from Ultram ER, another extended-release tramadol hydrochloride product, to allow filing and review as a 505(b)(2) application.[2] However, although Ryzolt is described as being "composed of a dual-matrix delivery system with both immediate-release and extended-release characteristics," these biopharmaceutical characteristics are not reflected in the indication or conditions of use for this product, as they were not determined to be clinically relevant. On May 3, 2005, FDA met with Labopharm to discuss Labopharm's request for (b) (4) As described in the meeting minutes from this meeting (b) (4) (b) (4)

FDA issued an approvable letter on September 28, 2006, because Labopharm had not provided substantial evidence that Ryzolt is effective for the proposed indication of the management of moderate to moderately severe pain. Labopharm's conclusion that efficacy had been demonstrated was based on a statistical methodology that FDA considered inappropriate for the imputation of missing data for patients who had dropped out of the studies. A complete response was submitted on December 18, 2006, and FDA issued a second approvable letter on May 30, 2007. This action was formally appealed by Labopharm through the dispute resolution process to the Director of ODE II, the Director of the OND, and the Deputy Director for CDER. A complete response to the approvable letter was submitted on July 2, 2008, and the application was approved on December 30, 2008.

Analysis

The 505(b)(2) application for Ryzolt contained reports of a new clinical investigation (other than a bioavailability study) that was essential to the approval of the application and conducted or sponsored by the applicant. Accordingly, Ryzolt was granted three years of exclusivity (see section 505(c)(3)(E)(iii) of the FFD&C Act). FDA's Approved Drug Products With Therapeutic Equivalence Evaluations (the Orange Book) describes this exclusivity as "NP" ("New Product") exclusivity expiring on December 30, 2011. This memo addresses whether such exclusivity will delay approval of Cipher's 505(b)(2) application for a tramadol hydrochloride extended-release

[2] See Division Director Review and Basis for Approvable Action Memorandum dated September 28, 2006.

capsule product (Cipher extended-release tramadol product) that did not rely upon Ryzolt as a listed drug, and which proposes a different titration schedule than that approved for Ryzolt.

Section 505(c)(3)(E)(iii) of the FFD&C Act provides that if an NDA contains reports of new clinical investigations (other than bioavailability studies) that are essential to approval and were conducted or sponsored by the applicant, FDA may not approve a 505(b)(2) application "for the conditions of approval of such drug in the approved [NDA] … before the expiration of three years from the date of the approval of the application."[3] The implementing regulations at 21 CFR 314.108(b)(4)(iv) provide that if an NDA has received three years of exclusivity

> the agency will not make effective for a period of 3 years after the date of approval of the application the approval of a 505(b)(2) application or an abbreviated new drug application for the conditions of approval of the original application, or an abbreviated new drug application submitted pursuant to an approved petition under section 505(j)(2)(C) of the act that relies on the information supporting the conditions of approval of an original new drug application.

Thus, the three-year exclusivity granted to Ryzolt will delay approval of the Cipher extended-release tramadol product if Cipher is seeking the same conditions of approval as are protected for Ryzolt. The preamble to the proposed rule implementing the statutory exclusivity provision states that "[e]xclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product" (54 Fed. Reg. 28872, 28896 (July 10, 1989)). Therefore, to determine whether Cipher is seeking the same conditions of approval as are protected for Ryzolt, we assess both the "innovation" that was the basis for Ryzolt's exclusivity and the characteristics of the tramadol product for which Cipher seeks approval.

Ryzolt was studied in four 12-week, randomized, double-blind, controlled studies in patients with moderate to severe pain due to osteoarthritis. However, efficacy was demonstrated in only one double-blind, placebo-controlled, randomized withdrawal design study – Study MDT3-005. Accordingly, Study MDT3-005 is the new clinical investigation that was essential to the approval of the application.[4] The conditions of approval for which Ryzolt received 3-year exclusivity reflect the design of the study, and the specific dosing regimen and titration schedule used.

As described above, Ryzolt was not the first extended-release formulation of tramadol hydrochloride approved for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time. Ultram ER was approved for this use in 2005, and received three years of exclusivity. The

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[3] A parallel provision at section 505(j)(5)(F)(iii) delays approval of ANDAs for three years for the same conditions of approval.

[4] In reviewing the Ryzolt record, I have determined that the January 29, 2009 exclusivity summary incorrectly identified the clinical studies essential to the approval of NDA 21-745. The clinical study essential to the approval of Ryzolt was the double-blind, placebo-controlled, randomized withdrawal design study – Study MDT3-005. Studies MDT3-00l/MDT3-001-EI, MDT3-001-EI-AI, MDT3-002, MDT3-003, and MDT3-004 were not the basis for exclusivity.

exclusivity granted to Ryzolt was based on the one study essential to the approval of the Ryzolt drug product, with its specific biopharmaceutical features, and reflects the design of the study with the specific dosing regimen and titration schedule used. The conditions of approval for Ryzolt differ from the previously approved Ultram ER in the Dosage and Administration section of product labeling. For patients not currently on tramadol immediate-release products:

> Treatment with RYZOLT™ should be initiated at a dose of 100 mg/day. Daily doses should be titrated by 100 mg/day increments ***every 2-3 days*** (i.e., start 200 mg/day on day 3 or 4 of therapy) to achieve a balance between adequate pain control and tolerability for the individual patient. For patients requiring the 300 mg daily dose, titration should take ***at least 4 days*** (i.e. 300 mg/day on day 5). The usual daily dose is 200 or 300 mg. The daily dose and titration should be individualized for each patient. Therapy should be continued with the lowest effective dose. RYZOLT™ should not be administered at a dose exceeding 300 mg per day. [emphasis added]

By contrast, the labeling for Ultram ER states:

> ULTRAM ER should be initiated at a dose of 100 mg once daily and titrated up as necessary by 100-mg increments ***every five days*** to relief of pain and depending upon tolerability. ULTRAM ER should not be administered at a dose exceeding 300 mg per day. [emphasis added]

The characteristic of Ryzolt that is protected by exclusivity is thus the difference in the titration schedule between Ryzolt and Ultram. Whether this exclusivity will delay approval of the Cipher extended-release tramadol product depends on whether Cipher is seeking the conditions of approval for which Ryzolt has exclusivity.

Cipher's 505(b)(2) application for tramadol hydrochloride extended-release capsules relies for approval on FDA's finding of safety and effectiveness for Ultram ER and Ultram. Although Cipher's extended-release tramadol product, like Ryzolt, contains both immediate-release and extended-release components, Cipher was determined to have demonstrated bioequivalence to Ultram ER, which does not contain an immediate-release component. Further, the immediate-release/extended-release biopharmaceutical characteristics of the Cipher product, as for Ryzolt, were not determined to be clinically relevant.[5] The conditions for which Cipher's 505(b)(2) application is proposed for approval reflect the conditions of approval of Ultram ER. The proposed labeling for the Cipher product states in the Dosage and Administration section:

> For patients not currently treated with tramadol immediate-release (IR) products, TRADENAME ER should be initiated at a dose of 100 mg once daily and titrated up as necessary by 100 mg increments ***every five days*** to relief of pain and depending upon tolerability. TRADENAME ER should not be administered at a dose exceeding 300 mg per day. [emphasis added].

[5] Indeed, none of the 4 randomized, placebo-controlled clinical trials of Cipher's extended-release tramadol product demonstrated efficacy. However, this may have reflected certain limitations in the design of the studies.

The proposed titration schedule for Cipher's extended-release tramadol product does not represent the same conditions of approval as the titration schedule for which Ryzolt has exclusivity. The Cipher extended-release tramadol product labeling describes a dosing regimen in which the drug "should be initiated at a dose of 100 mg once daily and titrated up as necessary by 100-mg increments ***every five days*** to relief of pain and depending upon tolerability." In contrast, the approved labeling for Ryzolt states that treatment "should be initiated at a dose of 100 mg/day. Daily doses should be titrated by 100 mg/day increments ***every 2-3 days*** (i.e., start 200 mg/day on day 3 or 4 of therapy) to achieve a balance between adequate pain control and tolerability for the individual patient." The faster 2- to 3-day titration schedule for Ryzolt was supported by the data in the Ryzolt application. Cipher is seeking approval only for the 5-day titration schedule.[6] The 5-day and 2- to 3-day titration schedules are not the same conditions of approval. Therefore, the approval of the Cipher extended-release tramadol product will not be delayed by Ryzolt's exclusivity.[7]

The conclusion that the approval of the Cipher extended-release tramadol product should not be delayed by Ryzolt's exclusivity is consistent with the arguments made in the March 13, 2007 Citizen Petition and May 2, 2007 Petition for Stay submitted on behalf of Purdue Pharma L.P. and its affiliates. In the Citizen Petition, Purdue argued that Ultram ER "is clearly most similar to the Cipher extended-release (once a day administration) capsule product and, accordingly, is the relevant reference listed drug" with respect to the Cipher extended-release tramadol product.[8] Although FDA need not decide whether Ultram ER's exclusivity would have required a delay in the approval of Cipher's extended-release tramadol product because that exclusivity has now expired, it is noteworthy that Purdue itself argued that Ultram ER is the relevant reference listed drug with respect to Cipher's product. It would be reasonable to conclude that Cipher is seeking the same conditions of approval as were approved for Ultram ER (including but not limited to

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[6] Notably, the Cipher extended-release tramadol product with the five day titration schedule is not eligible for approval as an ANDA referencing Ryzolt. The five-day titration schedule is not approved for Ryzolt, as would be required for a product seeking approval for that use through section 505(j) (see 505(j)(2)(A)(i) and (v)). The difference in titration schedule is not the type of difference that could be approved in a suitability petition described at 505(j)(2)(C) (i.e., a change in active ingredient in a combination product, dosage form, route of administration, strength).

[7] The analysis of the effect of Ryzolt's exclusivity is complicated somewhat by the fact that the Ryzolt and the Cipher 505(b)(2) applications for extended-release tramadol products apparently were developed in parallel and were pending with FDA at the same time. The Ryzolt NDA was submitted in November 2005, and approved in December 2008; the Cipher NDA was submitted initially in June 2006, and resubmitted in April 2008. The preamble to FDA's proposed rule implementing the three-year exclusivity provision states:

> The exclusivity provisions delay the effective date of approval of any 505(b)(2) application that is for the conditions of use of a previously approved application that contained new clinical investigations essential for approval. Consequently, if two 505(b)(2) applications are under review at the same time and one is approved before the other, the effective date of approval of the second application to be reviewed will be delayed, regardless of the date of submission, if the first contained new clinical investigations essential for approval and thereby qualified for exclusivity

(54 Fed. Reg. at 28901). Although Ryzolt's and Cipher's 505(b)(2) applications for extended-release tramadol products were under review at the same time, the exclusivity granted to Ryzolt upon approval will not delay approval of the Cipher extended-release tramadol product because, as described above, Cipher does not seek the same conditions of approval (or use) as Ryzolt.

[8] See Docket No. FDA-2007-P-0186; see also Docket No. FDA-2007-P-0065.

same indication, dosing and titration schedule).[9] If Cipher's tramadol hydrochloride extended-release capsule product were appropriate for submission in an ANDA referencing the Ultram ER (tramadol hydrochloride) extended-release tablet product and relying on an approved suitability petition for the change in dosage form, under 21 CFR 314.108(b)(4) the relevant exclusivity affecting the timing of approval of the ANDA would be the exclusivity applicable to Ultram ER (i.e., the listed drug relied upon).

Finally, we note that the Cipher 505(b)(2) application does not rely for approval on FDA's finding of safety and effectiveness for Ryzolt. The listed drugs cited by Cipher are Ultram ER and Ultram. Cipher has provided required certifications to patents for the listed drugs relied upon. Cipher was sued for patent infringement as a result of its notice of paragraph IV certification under section 505(b)(2)(A)(iv) of the FFD&C Act. Resolution of that litigation permits approval.

Conclusion

The conditions of approval for which Ryzolt received 3-year exclusivity reflect the design of the study, and the specific dosing regimen and titration schedule used. The data in the Ryzolt NDA supported approval of Ryzolt with a dose titration schedule describing increases of 100 mg/day ***every 2-3 days*** to a dose that should not exceed 300 mg/day. Cipher seeks approval of labeling for its extended-release tramadol product describing titration in 100-mg increments ***every five days*** to a dose that should not exceed 300 mg/day. Cipher is not seeking the same conditions of approval as are protected for Ryzolt. Therefore, Ryzolt's exclusivity will not delay approval of Cipher's extended-release tramadol product.

[9] Cipher's tramadol product differs in dosage form from both Ultram ER and Ryzolt; the Cipher product is an extended-release capsule and the previously approved products are extended-release tablets. A difference in dosage form alone for a proposed product would not necessarily be a basis for concluding that a previous applicant's exclusivity does not delay approval. FDA's regulation at 21 CFR 314.108(b)(4)(iv), for example, states that exclusivity will delay approval of an ANDA submitted pursuant to an approved suitability petition that relies on the information supporting the conditions of approval of an original new drug application. A change in dosage form is one of the changes possible in the suitability petition process.