



ROPE & GRAY LLP  
 ONE METRO CENTER 700 12TH STREET, NW SUITE 900 WASHINGTON, DC 20005-3948 202-508-4600 F 202-508-4650  
 BOSTON NEW YORK PALO ALTO SAN FRANCISCO WASHINGTON, DC www.ropesgray.com

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Terry S. Coleman  
 202-508-4646  
 Terry.Coleman@ropesgray.com

Division of Dockets Management  
 Food and Drug Administration  
 Department of Health and Human Services  
 5630 Fishers Lane, Room 1061  
 Rockville, MD 20852

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**CITIZEN PETITION**

The undersigned submits this petition on behalf of Ortho-McNeil, Inc. under Section 505 of the Federal Food, Drug, and Cosmetic Act (“Act”) and 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs determine that any version of tramadol for once-daily dosing, including any version that is the subject of an application submitted by CIPHER Pharmaceuticals, Inc. (“CIPHER”), cannot be approved until the three-year exclusivity period for Ultram® ER (tramadol HCl) Extended-Release Tablets expires on September 8, 2008.

**ACTION REQUESTED**

As detailed in this petition, the Act grants three-year periods of exclusivity for innovative changes in a drug product. In the case of NDA 21-692 for Ultram® ER, the innovative change was the once-daily dosing regimen for tramadol. FDA based its approval on this dosing regimen, and it relied on clinical investigations showing that the once-daily dosing regimen was safe and effective. FDA did not base its approval of NDA 21-692 on any particular formulation of tramadol. Petitioner therefore requests that the Commissioner determine that any versions of tramadol for once-daily dosing will not be approved prior to the expiration of the three-year period of exclusivity for Ultram® ER.

**STATEMENT OF GROUNDS**

Ortho-McNeil, Inc. has learned that CIPHER might be seeking to circumvent the three-year exclusivity period awarded to Ultram® ER. This petition is being filed to set forth Ortho-McNeil, Inc.’s interpretation of the scope of this three-year exclusivity period and to obtain FDA’s concurrence in that interpretation.

2007P-0127

CPI

### Background

NDA 21-692 for Ultram® ER was originally filed under Section 505(b)(2) of the Act by Biovail Laboratories, Inc. NDA 21-692 covers three dosages of tramadol hydrochloride extended-release tablets: 100 mg, 200 mg, and 300 mg. Ortho-McNeil has licensed NDA 21-692, and the drug has been given a new tradename – Ultram® ER.

Prior to the approval of NDA 21-692, the dosing instructions for the immediate release form of Ultram® specified a titration period, after which “ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours **not to exceed 400 mg/day**” [emphasis in original]. By contrast to that dosing schedule, the instructions approved in NDA 21-692 specified once-daily administration:

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 in original]

### Legal Standard

Section 505(c)(3)(E) of the Act sets forth the scope of the three-year exclusivity. Section 505(c)(3)(E)(iii) prohibits FDA from approving subsequent 505(b)(2) applications for the “*conditions of approval*” of the drug awarded exclusivity. Similarly, Section 505(c)(3)(E)(iv) provides a three-year exclusivity period for “a *change approved* in [a] supplement[al]” new drug application.<sup>1</sup> The implementing regulations essentially repeat the statute without elaboration. 21 C.F.R. §§ 314.108(b)(4)(iv) and (5)(ii).

In implementing the statute, FDA has interpreted the scope of the three-year exclusivity as protecting the “innovative change” involved. Specifically, FDA stated: “Thus exclusivity would protect . . . the *innovative change* in a non-new chemical entity from generic competition even after FDA had approved subsequent full new drug applications for subsequent versions of the drug.” Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28872, 28897 (proposed rule July 10, 1989) (Attach. 1) (emphasis added).<sup>2</sup> FDA emphasized that “exclusivity attaches . . . to an innovative change” and that ANDAs and 505(b)(2) applications

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<sup>1</sup> Analogous provisions protecting innovations against ANDAs appear in Section 505(j)(5)(F) of the Act.

<sup>2</sup> FDA provided a telling example of the broad scope of the three-year exclusivity in its Notice of Proposed Rulemaking by explaining that when two 505(b)(2) applications are co-pending and one is approved, the other’s approval will be delayed until after the exclusivity period expires. 54 Fed. Reg. at 28901. FDA further explained that its broad interpretation of three-year exclusivity is consistent with Congressional intent. *Id.*

“with that . . . innovative change will be delayed until the innovator’s exclusivity has expired.”  
*Id.*<sup>3</sup>

Moreover, FDA has specifically stated that new dosing regimens are entitled to the three-year exclusivity period. For example, the preamble to the final rules stated that “changes in dosing regimen have resulted in grants of 3-year exclusivity.” Abbreviated New Drug Application Regulations, 59 Fed. Reg. 50338, 50357 (final rule Oct. 3, 1994) (Attach. 4). The FDA Orange Book lists over a hundred dosing regimens for which exclusivity has been granted.

When FDA has determined that approval of a subsequent product was not barred by the three-year exclusivity for a previous similar product, the basis for the decision was the nature of the clinical trials supporting the exclusivity. In a decision reviewed in *Zeneca, Inc. v. Shalala*, No. 99-307, 1999 U.S. Dist. LEXIS 12327, at \*38-39 (D. Md. Aug. 11, 1999) (Attach. 5), FDA had ruled that Zeneca’s exclusivity over a propofol product containing the preservative EDTA barred only other propofol products containing EDTA, not propofol products containing other preservatives. The basis for FDA’s decision was that the clinical investigations supporting Zeneca’s product related to EDTA specifically and not to preservatives generally. As the court said,

The clinical investigations it submitted to the FDA with that supplement were necessitated by specific concerns related to EDTA, not to propofol products with other preservatives in general. Thus, the exclusivity applies to propofol products including EDTA, not to propofol products with other preservatives.

*Id.* at \*38.

Three-year exclusivity cannot be circumvented by a product that includes a change from the protected product that is not relevant to the basis for the exclusivity. For example, the provisions on abbreviated new animal drug applications, including the exclusivity provisions in section 512(c)(2)(F) of the Act, are essentially the same as the provisions for human drugs. In a case where an animal drug manufacturer had three-year exclusivity based on the route of administration, FDA approved a suitability petition for a generic product of a different strength, but even with the different strength, the generic product was still subject to the

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<sup>3</sup> The legislative history demonstrates that Congress intended to reward with three years of exclusivity only those investigations that require a considerable investment of time and money, *see* Cong. Rec. S10505 (daily ed. Aug. 10, 1984) (statement of Sen. Hatch) (Attach. 2), and that are necessary for approval of important innovations requiring substantial study, such as significant new therapeutic uses, *see* Cong. Rec. H9114 (daily ed. Sept. 6, 1984) (statements of Rep. Waxman) (Attach. 3).

innovator's exclusivity over the route of administration.<sup>4</sup> In other words, the "conditions of approval" of the innovator product that are protected by exclusivity refer to the reasons for the exclusivity.

### Approval History

A review of the approval history of Ultram® ER demonstrates that FDA's focus was always on the once-daily dosing regimen, not on the particular mechanism, formulation, or dosage form by which Ultram® ER achieved that objective.

The sponsor, Biovail, proved effectiveness through four clinical studies.<sup>5</sup> In approving Ultram® ER based on these four clinical studies, nowhere did the medical officer's review state that approval of the drug was based on anything other than its safety and effectiveness for once-daily dosing, *i.e.*, over a 24-hour period. The approval of Ultram® ER was not based on specific concentration profiles of tramadol in patients' plasma over a 24-hour period, nor was it based on a specific formulation or dosage form of tramadol.

The chemistry reviewer did not find that the physical characteristics of the drug were significant to its approval. The reviewer noted that the tablets consisted of a tablet core surrounded by a semipermeable membrane, but the reviewer attributed no significance to that product design. In addition, he found that "the particle size of the tramadol HCl drug substance is not considered an important attribute." Chemistry Review for NDA 21-692, at 7 (Aug. 30, 2005). He similarly found no other physical aspect of the product to be significant, *see id.*, thus confirming that the once-daily dosing regimen, not the particular mechanism, formulation, or dosage form, was the basis for FDA's approval.

### Application of the Legal Standards

The "innovative change" for which Ultram® ER is entitled to a three-year exclusivity period is its once-daily dosing. As the record shows, FDA did not base its approval on the specific formulation or dosage form of Ultram® ER. In fact, as noted above, the chemistry review officer stated that the specific characteristic of the formulation was not an

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<sup>4</sup> Letter from Steven D. Vaughn, DVM to Bioniche Animal Health, Inc., Docket No. SP 04P-0376/CP1 (Nov. 3, 2004) (Attach. 6).

<sup>5</sup> The four clinical trials Biovail used to prove efficacy included Study Nos. B00.CT3.014 (Study "14"), B00.CT3.015 (Study "15"), B02.CT3.021 (Study "21"), and B02.CT3.023 (Study "23"). Study 14 was a double-blind, randomized, placebo-controlled, 12-week trial of Ultram® ER in chronic back pain. Study 15 was a double-blind, randomized, placebo-controlled, 12-week trial of Ultram® ER in osteoarthritis of the knee. Study 21 was a randomized, double-blind, placebo- and active-controlled, dose ranging, 12 week trial in patients with osteoarthritis of the knee and/or hip. Study 23 was a randomized, double-blind, placebo-controlled, 12 week trial in patients with osteoarthritis of the knee or hip. Medical Review of NDA 21-692, Division Director Review, at 2-3 (Sept. 8, 2005). Biovail proved the safety of Ultram® ER by submitting "a complete reanalysis of the safety data," which was reviewed and approved by Lourdes Villalba, M.D. *Id.* at 3-4.

important attribute. If the formulation of Ultram® ER had been important to the approval process, the record would have reflected such importance. The “innovative change” was the new dosing regimen.<sup>6</sup> Patients will benefit from the innovative once-daily dosing regimen regardless of what formulation or dosage form is used, and the exclusivity therefore covers the dosing regimen.

Moreover, the clinical studies supporting the approval of Ultram® ER were not designed to investigate the specific formulation or dosage form of the product but were designed to show the safety and effectiveness of once-daily dosing. Thus, this case is not analogous to the *Zeneca* case, in which the clinical studies were designed to investigate an aspect of the specific formulation at issue.

From publicly available information, it appears that Cipher may be seeking approval of a capsule formulation of extended-release tramadol, in contrast to the tablet version approved in NDA 21-692. The difference between capsules and tablets is not material to the scope of the exclusivity awarded to Ultram® ER. Several years ago, FDA considered whether tablets and capsules should be considered to be the same dosage form but concluded that they should not because of distinctions related to “ease of swallowing and scorbability” and the reliance of the elderly on “the appearance of their medications.”<sup>7</sup> These factors have no relevance to the innovation that was approved in NDA 21-692 and awarded exclusivity. Exclusivity cannot be evaded by changing a product aspect that has no bearing on the basis for the exclusivity.

Finally, any failure to give full effect to the exclusivity over the once-daily dosing regimen of Ultram® ER would imperil all future awards of exclusivity based on new dosing regimens. As noted above, FDA has expressly stated that new dosing regimens qualify for three years of exclusivity. If that exclusivity could be evaded by a subsequent applicant duplicating the dosing regimen but making a product change, exclusivity for new dosing regimens would be meaningless. Any refusal to recognize the exclusivity covering the dosing regimen would be incompatible with the law.

### **Conclusion**

The original sponsor of Ultram® ER invested considerable time and money to develop the drug product, conduct the clinical studies, and apply for FDA approval. FDA based its approval on this innovation and not on any specific formulation or dosage form of tramadol.

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<sup>6</sup> Since Ultram® ER was approved as a wholly new product, its exclusivity is designated in the Orange Book as “NP” – new product exclusivity. Since the basis of the exclusivity was the dosing regimen, the fact it was also a new product does not somehow diminish the protection afforded to the innovative dosing regimen.

<sup>7</sup> Letter from Janet Woodcock, M.D., to Alan H. Kaplan, et al., in Docket Nos. 95P-0262/CP1 and 96-0317/CP1, at 5 (Dec. 1, 2000) (Attach. 7).

Therefore, FDA may not approve Cipher's application nor any other ANDA or 505(b)(2) application for a once-daily dosing version of tramadol.

### **ENVIRONMENTAL IMPACT**

Petitioner claims a categorical exclusion from preparation of an Environmental Assessment or an Environmental Impact Statement under 21 C.F.R. § 25.31.

### **ECONOMIC IMPACT**

This information will be submitted if requested by the Commissioner.

### **CERTIFICATION**

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Sincerely,



Terry S. Coleman

TSC:pjz  
Attachments

**ATTACHMENTS**

1.	PROPOSED RULE, ABBREVIATED NEW DRUG APPLICATIONS, 54 Fed. Reg. 28872 (July 10, 1989).
2.	CONG. REC. S10505 (daily ed. Aug. 10, 1984) (statement of Sen. Hatch).
3.	CONG. REC. H9114 (daily ed. Sept. 6, 1984) (statements of Rep. Waxman).
4.	FINAL RULE, ABBREVIATED NEW DRUG APPLICATIONS, 59 Fed. Reg. 50338 (October 3, 1994).
5.	<i>Zeneca, Inc. v. Shalala</i> , No. 99-307, 1999 U.S. Dist. LEXIS 12327 (D. Md. Aug. 11, 1999).
6.	Letter from Steven D. Vaughn, DVM to Bioniche Animal Health, Inc., Docket No. SP 04P-0376/CP1 (Nov. 3, 2004).
7.	Letter from Janet Woodcock, M.D., to Alan H. Kaplan, et al., in Docket Nos. 95P-0262/CP1 and 96-0317/CP1 (Dec. 1, 2000)