DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 3 2014

William S. Craig, Ph.D.
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Re: Docket No. FDA-2013-P-1508

Dear Dr. Craig:

This letter responds to your citizen petition that we received on November 4, 2013 (Petition), submitted on behalf of Cadence Pharmaceuticals, Inc. The Petition asks FDA to refrain from approving any abbreviated new drug application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)) or new drug application (NDA) submitted under section 505(b)(2) of the FD&C Act for an acetaminophen solution for intravenous injection that does not contain the same inactive ingredient composition as Ofirmev (acetaminophen injection), unless the ANDA or 505(b)(2) application includes evidence from nonclinical studies and adequate and well-controlled clinical trials demonstrating that the product is as safe and effective as Ofirmev. For the reasons discussed below, your petition is denied.

I. BACKGROUND

A. Ofirmev

Ofirmev is a parenteral formulation of acetaminophen intended for intravenous injection to treat pain and fever in adults and children. It is used in situations where the administration of oral or rectal dosage forms of acetaminophen is impractical or contraindicated. Each 100 milliliter (mL) contains 1,000 milligrams (mg) acetaminophen USP; 3,850 mg mannitol USP; 25 mg cysteine hydrochloride, monohydrate USP; and 10.4 mg dibasic sodium phosphate USP. The drug product's pH is adjusted with hydrochloric acid and/or sodium hydroxide.

B. Summary of Legal and Regulatory Framework for ANDAs and 505(b)(2) Applications

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created the statutory provisions governing ANDAs and 505(b)(2) applications. The Hatch-Waxman Amendments reflect Congress's attempt to balance the need to encourage innovation with the desire to speed the availability of lower-cost alternatives to approved drugs. With passage of the Hatch-Waxman Amendments, the

FD&C Act describes different routes for obtaining approval of two broad categories of drug applications: (1) an NDA, for which the requirements are set out in section 505(b) and (c) of the FD&C Act and (2) an ANDA, for which the requirements are set out in section 505(j) of the FD&C Act. One type of NDA, referred to as a 505(b)(2) application may rely, in part, on FDA's finding that the listed drug it references is safe and effective as evidence in support of the proposed product's own safety and effectiveness. Because your petition addresses both ANDAs and 505(b)(2) applications, this background section will first summarize, in relevant part, the legal framework for these two types of applications.

1. Section 505(j) Applications (ANDAs)

To obtain approval of an ANDA, an applicant does not submit clinical studies to demonstrate safety and effectiveness but, instead, relies on the Agency's finding that the reference listed drug (RLD) is safe and effective.[1] An ANDA must identify a listed drug on which it seeks to rely and, generally, an ANDA must have the same active ingredient, strength, dosage form, route of administration, conditions of use, and, with limited exceptions, labeling as the listed drug it references (sections 505(j)(2)(A) and (j)(4)).[2]

In addition, an ANDA applicant must establish that its drug is bioequivalent to the listed drug it references (505(j)(2)(A)(iv) and 505(j)(4)(F)). A drug described in an ANDA is bioequivalent to the listed drug if:

> the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . .[3]

FDA regulations at 21 CFR 314.94(a)(7) describe in further detail the bioequivalence requirements for an ANDA. Procedures for determining bioequivalence are set forth in 21 CFR part 320. The regulations explicitly permit submission of "[i]nformation to show that the drug product is bioequivalent to the reference listed drug which would permit FDA to waive the submission of evidence demonstrating in vivo bioequivalence . . . ."[4]

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[1] A reference listed drug or RLD is "the listed [i.e. approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 C.F.R. 314.3).

[2] FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations. FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

[3] 21 U.S.C. 355(j)(8)(B)(i)); see also 21 CFR 320.1(e) and 320.23(b).

[4] 21 CFR 320.21(b)(2); see also 21 CFR 320.22(b).

2. *ANDAs for Parenteral Drug Products*

Section 505(j)(4)(H) of the FD&C Act provides that FDA will approve an ANDA for a drug unless, among other things:

> information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.

Consistent with the statute, FDA has issued implementing regulations on inactive ingredients in products proposed in ANDAs. In general, an ANDA may have different inactive ingredients from the reference listed drug (RLD) as long as the ANDA demonstrates that the different inactive ingredients do not affect the safety or efficacy of the proposed drug product (21 CFR 314.94(a)(9)(ii)). However, for ANDAs for parenteral drug products, the only differences in inactive ingredients that are routinely permitted are changes in a preservative, a buffer, or an antioxidant. FDA's regulation at § 314.94(a)(9)(iii) concerning the content and format of an ANDA states the following:

> Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant . . . . However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

The corresponding provision that addresses the refusal to approve an ANDA, 21 CFR 314.127(a)(8)(ii)(B), provides the following:

> FDA will consider an active ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the [ANDA] unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and, if it differs from the listed drug in a preservative, buffer, or antioxidant, the application contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product.

These provisions require ANDAs for parenteral products to contain the same inactive ingredients, in the same concentrations, as the reference listed drug with the exception of preservatives, buffers, and antioxidants (so-called *exception excipients*). They also require applicants to demonstrate that any differences in the stated exception excipients do not affect the safety or efficacy of the drug product.

3. *NDAs Under 505(b)(2)*

A 505(b)(2) application shares characteristics of both an ANDA and a stand-alone NDA. Like a stand-alone NDA, a 505(b)(2) application is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c). As such, it must satisfy the same statutory requirements for safety and effectiveness information as a stand-alone NDA. A 505(b)(2) application is similar to an ANDA as well because it may rely, in part, on FDA's finding that the listed drug it references is safe and effective as evidence in support of the proposed product's own safety and effectiveness. However, although a drug product approved under an ANDA is generally required to duplicate an innovator product (with a few limited exceptions) — and an ANDA therefore generally may not include new clinical studies to demonstrate safety or effectiveness to support approval — a 505(b)(2) application often describes a drug with substantial differences from the listed drug it references.[5] These differences may include, for example, a different active ingredient or a new indication, dosage form, strength, formulation, or route of administration.[6] To the extent that the listed drug and the drug proposed in the 505(b)(2) application differ, the 505(b)(2) application must include sufficient data to demonstrate that the proposed drug meets the statutory approval standard for safety and effectiveness.

FDA's long-standing interpretation of section 505(b)(2) of the FD&C Act is intended to permit the pharmaceutical industry to rely, to the greatest extent possible under the law, on what is already known about a drug. Our approach is to use the 505(b)(2) drug approval pathway to require that drug applicants conduct and submit only those studies that are scientifically necessary.

II. DISCUSSION

In your petition you state that although acetaminophen is stable in its dry state, it will undergo hydrolysis in aqueous solutions (Petition at 3). You state that if hydrolysis is not properly controlled, *p*-aminophenol will undergo oxidation to produce free radicals. These free radicals will, in turn, react with the acetaminophen in the solution to develop colored polymer compounds, which, if they rise above a certain threshold, could undermine the safety and effectiveness of the drug product. You assert that any formulation of acetaminophen solution must contain a buffering agent and an antioxidant to prevent hydrolysis and oxidation-catalyzed polymerization, and the manufacturing process must control the amount of residual oxygen in the solution to minimize the level of *p*-aminophenol that could contribute to these processes.

You assert that the components of the Ofirmev formulation were carefully chosen to maximize the stability of the product and that it is highly likely that a formulation that differs from the approved Ofirmev formulation in any way would not protect against these degradation processes to the same extent as the approved Ofirmev formulation (Petition at

[5] Under 21 CFR 314.101(d)(9), we may refuse to file a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the FD&C Act.

[6] See draft guidance for industry *Applications Covered by Section 505(b)(2)* (October, 1999), available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079345.pdf

4). You therefore request that FDA refrain from approving any ANDA or 505(b)(2) NDA for an acetaminophen solution for intravenous injection that does not contain the same inactive ingredient composition as Ofirmev unless the application includes evidence from nonclinical studies and adequate and well-controlled clinical trials demonstrating that the product is as safe and effective as Ofirmev. Effectively, you ask the Agency to predetermine what type of data is necessary to support any future application for acetaminophen injection referencing Ofirmev that differs in inactive ingredient composition.

Your request is denied. Although FDA agrees that the possibility of the hydrolysis of acetaminophen may raise a safety concern for potential formulations of parenteral acetaminophen products, the Agency does not believe it is appropriate to impose a blanket rule that any application for an alternative formulation of acetaminophen solution referencing Ofirmev must contain data from nonclinical studies and adequate, well-controlled clinical trials demonstrating the safety and effectiveness of the product. Such a blanket rule would be inappropriate because FDA's regulations and the application review processes for ANDAs and 505(b)(2) NDAs are adequate to evaluate these potential issues.

A. ANDAs Referencing Ofirmev

As explained above, FDA regulations generally require that a generic formulation of a parenteral drug product be identical to the RLD in both active and inactive ingredients; in an ANDA for a parenteral drug product, the only differences in inactive ingredients that are routinely permitted are in preservatives, buffers, or antioxidants (so-called *exception excipients*), provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed generic drug product. Generally, if FDA concludes that the differences affect the proposed generic drug product's safety or efficacy, FDA will refuse to approve the ANDA.[7]

If the review of an ANDA referencing Ofirmev demonstrated that the proposed formulation created excess hydrolysis of acetaminophen or otherwise raised safety or efficacy concerns, FDA could request additional data, or find the product not to be approvable. The specific types of data necessary to evaluate the stability of the product would be determined on a case-by-case basis as part of the review. If the information submitted is sufficient to characterize the proposed differences from the RLD and demonstrate that they do not affect the safety or efficacy of the drug product, FDA may determine that no additional study data is necessary. Therefore, we will not, as the Petition requests, require that every ANDA for an injectable acetaminophen product referencing Ofirmev must include evidence from nonclinical studies or adequate, well-controlled clinical trials.[8] The need for such data will be determined, case-by-case, as part of our

[7] See 21 CFR 314.127(a)(8)(ii)(A)-(B).

[8] If the proposed change in inactive ingredients required data from clinical studies to demonstrate safety and efficacy, we would likely require that the product be reviewed under section 505(b)(2), rather than as an ANDA. See draft guidance for industry *Applications Covered by Section 505(b)(2)* (October, 1999), available at

review of such ANDAs.

In sum, although it is possible that a proposed ANDA whose formulation differs from Ofirmev in some allowable respect could raise questions of safety and efficacy as you suggest, it is not appropriate to prejudge the need for specific studies. Instead, we will make such a determination on a case-by-case basis.

B. 505(b)(2) Applications Referencing Ofirmev

If a proposed formulation of acetaminophen solution referencing Ofirmev differs from Ofirmev in non-exception excipients (i.e., inactive ingredients other than preservative, buffer, or antioxidant), or we otherwise conclude that the proposed formulation changes would require data from studies not typically included in an ANDA, such as human clinical safety or efficacy trials, the proposed drug product would likely have to be submitted in a 505(b)(2) NDA.[9]

As explained above, a 505(b)(2) applicant may rely on FDA's finding of safety and effectiveness for a listed drug to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, route of administration, strength, indication, conditions of use) in common with the listed drug. To the extent that the listed drug and the drug proposed in the 505(b)(2) application differ, the 505(b)(2) application must include sufficient data to demonstrate that the proposed drug meets the statutory approval standard for safety and effectiveness. In some instances, approval of a 505(b)(2) application may require evidence from nonclinical studies or clinical safety and efficacy studies.

The adequacy of data submitted to demonstrate that the proposed changes in inactive ingredients do not affect the safety or effectiveness of the drug product are evaluated as part of the review process and depend on the nature of the inactive ingredients, the nature of the drug product, and the conditions for use under which the product is seeking approval. FDA considers whether the information contained in the application to support the safety of the proposed inactive ingredients is adequate. Among other things, the review division considers the type and quantity of inactive ingredients and the manner in which they are to be used in the drug. The need for additional data would be determined, case-by-case, as part of our review of the applications.

More specifically, changes in inactive ingredients in a 505(b)(2) application generally are evaluated for their effect on the stability and purity of the drug product. For an injectable acetaminophen product, FDA's review analyzes the proposed formulation for quality and stability. This review evaluates whether, as you suggest, the different formulation could result in excessive hydrolysis and oxidation-catalyzed polymerization and whether to

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http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079345.pdf (stating that an application is appropriate for filing under 505(b)(2) if it is for a proposed drug product that contains a different quality or quantity of an excipient(s) than the listed drug where the studies required for approval are beyond those considered limited confirmatory studies appropriate to a 505(j) application).

[9] *Id.*

require clinical safety or efficacy trials to address any such hydrolysis and polymer formation issues as are raised in the petition. We therefore disagree with the Petition that we must — in all cases — require data from clinical trials to approve a 505(b)(2) application relying on FDA's finding that Ofirmev is safe and effective.[10]

Before submission of an NDA, sponsors may meet with FDA staff to discuss specific information that is needed to support the proposed NDA. If necessary, FDA can request additional information after the filing of the NDA.

In sum, although nonclinical or clinical data on efficacy or safety may at times be required for a 505(b)(2) application to support proposed changes, including changes to the product formulation, the need for such data is determined on a case-by-case basis and requires review of the formulation and an evaluation of the specific differences between the proposed product and listed drug.

III. CONCLUSION

For the foregoing reasons, your petition is denied.

Sincerely,

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

[10] We note that if a proposed injectable acetaminophen product is shown to undergo significant hydrolysis and oxygen-catalyzed polymerization, to the extent that human clinical trials would be necessary to assure the safety and efficacy of the product, performing such trials may be ethically questionable, particularly if the changes to the formulation offer no clinical benefit. Such issues would likely result in further discussion with the applicant.