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cadence™
PHARMACEUTICALS

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Division of Dockets Management
Food and Drug Administration
5360 Fishers Lane
Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

Craig Pharma Solutions LLC ("Craig"), on behalf of Cadence Pharmaceuticals, Inc. ("Cadence"), submits this petition pursuant to sections 505(b), 505(j), and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and the Food and Drug Administration's ("FDA's") regulations at 21 C.F.R. § 10.30. In this petition, Craig, on behalf of Cadence, requests that FDA refrain from approving any abbreviated new drug application ("ANDA") or new drug application ("NDA") submitted under Section 505(b)(2) of the FDCA ("505(b)(2) application") 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®.

Ofirmev® is a stable, aqueous formulation of acetaminophen that was developed to meet the United States Pharmacopeia ("USP") specifications and International Conference on Harmonisation ("ICH") Guidelines for an injectable product, as well as the particular specifications applicable to an aqueous acetaminophen solution. While acetaminophen is stable in its dry state, the drug substance is known to undergo hydrolysis in aqueous solutions, meaning that acetaminophen degrades in the presence of water. In addition, research conducted during the Ofirmev® development program showed that aqueous acetaminophen solutions become unstable in the presence of oxygen, which leads to the creation of degradation byproducts that cause the colorless solution to turn yellow or pink and then brown as degradation progresses. Cadence and its licensors, SCR Pharmatop ("Pharmatop") and Bristol-Myers Squibb Company ("BMS"), undertook an extensive research and development program that identified and addressed these complex properties of aqueous acetaminophen solutions in developing Ofirmev®. These efforts resulted in a highly specific formulation and manufacturing process, which together minimize both hydrolysis and oxidation of the acetaminophen and, in turn, ensure the quality, stability, safety, and effectiveness of the approved Ofirmev® drug product.

Ofirmev® is formulated with carefully chosen inactive ingredients that are crucial to maintaining the stability and purity of the drug product. As discussed below, due to the complex properties of aqueous acetaminophen solutions, changes to these highly particularized and extensively researched ingredients could impact the product's safety and effectiveness. Much is unknown about the degradation byproducts that develop in improperly formulated acetaminophen solutions, and the safety

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and performance of such products cannot be assured. For this reason, FDA must require that any ANDA or 505(b)(2) application for an injectable acetaminophen solution be for a product that duplicates the inactive ingredient formulation of Ofirmev®. In the alternative, if FDA accepts an ANDA or 505(b)(2) application for approval of an aqueous acetaminophen solution with changes in the inactive ingredients from those approved in the Ofirmev® formulation, FDA must require applicants to provide evidence from nonclinical studies and adequate and well-controlled clinical trials demonstrating that the changes do not affect the safety or effectiveness of the proposed new product.

I. ACTION REQUESTED

On behalf of Cadence, Craig requests that FDA refrain from approving any ANDA or 505(b)(2) application for an acetaminophen solution injection product that does not contain the same inactive ingredients 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 any change in formulation does not affect the safety or effectiveness of the proposed new product.

II. STATEMENT OF GROUNDS

A. Factual Background

1. Development of Ofirmev®

In 2002, Cadence's licensor, BMS, began marketing aqueous paracetamol—a proprietary intravenous formulation of acetaminophen for the treatment of acute pain and fever—in Europe and other non-U.S. markets under the brand name Perfalgan®. In November 2010, FDA approved this proprietary intravenous formulation of acetaminophen in the United States for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and the reduction of fever in adults and children two years of age and older pursuant to NDA 022450. Cadence has marketed this product in the United States under the trade name Ofirmev® since January 2011.

In its oral form, acetaminophen is the most widely used drug for the treatment of pain and fever in the United States. Acetaminophen was discovered in the late 19th century and was made available for sale in 1955 when it was introduced in the United States under the brand name Tylenol®. Acetaminophen is currently available in more than 600 combination and single-ingredient prescription and over-the-counter medicines, including tablet, caplet, orally-dosed liquid suspension, powder, and suppository forms for use in both adults and children. However, despite the broad usage of acetaminophen, prior to the commercial launch of Ofirmev® in January 2011, no intravenous formulation of acetaminophen was available in the United States.

Injectable formulations of analgesics are typically used when patients are unable to take medications by mouth, when patients would benefit from a faster onset or more potent forms of analgesia, when other administration routes are contraindicated, or when it is more convenient to administer drugs in injectable form. Prior to the approval of Ofirmev®, only two classes of injectable analgesics were available in the United States: opioids and non-steroidal anti-inflammatory drugs ("NSAIDs"). However, both opioids and NSAIDs are associated with a variety of unwanted and potentially life-threatening side effects when used to treat acute pain, particularly in the perioperative setting. The goal in developing an injectable acetaminophen product was to provide a viable alternative for patients requiring analgesia or fever reduction in situations where administration of available oral or rectal dosage forms of acetaminophen are impractical or contraindicated, or where a more rapid onset of action is required.

Injectable formulations of drugs must meet certain USP standards, including requirements for sterility, non-pyrogenicity, particulate matter limits, accuracy of volume in container, and others.[1] In addition to satisfying these requirements, the Ofirmev® development program also addressed issues specific to acetaminophen, including:

- ensuring the acetaminophen concentration remained water soluble at pH values and manufacturing temperatures that avoided natural hydrolysis;
- formulating the acetaminophen solution with a combination of an antioxidant and buffering agent to minimize degradation; and
- designing the finished dosage form to prevent free radical-mediated degradation and its associated formation of colored byproduct compounds.

Research during the Ofirmev® development program showed that acetaminophen hydrolyzes in aqueous solutions in the presence of oxygen, even at optimal pH. As a result, in order to ensure the stability and purity of the acetaminophen solution, it was necessary to: (1) limit hydrolysis leading to the formation of the impurity *p*-aminophenol by optimizing pH; (2) limit free radical degradation and associated production of colored byproducts by adding an antioxidant (i.e., a radical scavenger) to the formulation; and (3) control the amount of dissolved oxygen in the drug product.

Cadence and its licensors conducted extensive research to determine the optimal formulation of ingredients to minimize the chemical processes of hydrolysis and byproduct formation. FDA subsequently approved the specified formulation as ensuring the safety and efficacy of the Ofirmev® drug product in NDA 022450.[2] As a result, any new acetaminophen solution in which any of these essential ingredients are removed or modified will result in a product of unknown stability and purity, and hence, unknown safety and efficacy.

2. Stability of Acetaminophen Solutions

As described above, acetaminophen is stable in its dry state; however, it will undergo hydrolysis in aqueous solutions. This hydrolysis reaction is catalyzed by both acids and bases, and will occur even at a neutral pH to form the hydrolysis byproduct *p*-aminophenol.[3] The occurrence and rate of this hydrolysis is critically dependent on the pH of the solution, making it necessary to control pH in order to prevent hydrolysis of acetaminophen solutions.

Research during the Ofirmev® development program showed 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. The rate and extent of this hydrolysis and subsequent polymerization was found to depend on the oxygen concentration of the solution—the more oxygen, the quicker the reaction—and if the polymeric impurities rise above a certain threshold, the product is no longer administrable to humans, as such degraded formulations have never been tested for safety or efficacy.

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[1] USP <71> Sterility Testing; USP <85> Bacterial Endotoxin Test; USP <151> Pyrogenicity Test; USP <788> Particulate Matter in Injection; USP <1151> Pharmaceutical Dosage Form.

[2] U.S. Patent No. 6,028,222; U.S. Patent No. 6,992,218.

[3] K. Thomas Koshy & John L. Lach, *Stability of Aqueous Solutions of N-Acetyl-p-aminophenol*, 50 J. Pharmaceutical Science 113 (1960) (Attachment 1).

Similar polymerization processes (i.e., development of oxidation products, including both radicals and benzoquinone imines) have been observed in experiments with *p*-aminophenol solutions which were subjected to rapid enzyme-induced or chemical oxidation.[4] Extended oxidation conditions in these experiments caused the solutions to quickly develop colored *p*-aminophenol polymers. These experimental solutions did not have the tightly controlled specification that Ofirmev® does to limit the amount of *p*-aminophenol, demonstrating that alternate acetaminophen solution formulations are likely to undergo polymerization if *p*-aminophenol is not rigorously controlled.

Similarly, during the development of the Ofirmev® formulation, yellow, brown, and pink colored polymers were observed when specific protective anti-hydrolysis and anti-oxidation components were not present in the solution. Colored degradation products have also been observed in Ofirmev® test products when there is either a breach in the integrity of the container closure which causes prolonged oxygen exposure, or where manufacturing conditions failed to attain a sufficiently low oxygen concentration. It is likely that these polymers result from reactions between oxidized molecules of *p*-aminophenol and molecules of acetaminophen, and as such, they may exhibit toxicities similar to *p*-aminophenol polymers. This likelihood underscores the importance of specificity in aqueous acetaminophen solutions, and that changes to the formulation that may provide less protection against polymerization cannot be taken lightly.

It is not known whether the polymer byproducts that develop in improperly formulated acetaminophen solutions are safe for administration to humans, as they have not been tested in appropriate animal models or in a clinical setting. Further, it is difficult to test for the precise levels of these substances by conventional methods, making the inclusion of proper protective ingredients essential. Cadence has found that the *p*-aminophenol that forms in improperly formulated or improperly manufactured acetaminophen solutions undergoing hydrolysis will not accumulate beyond a certain concentration over time and may be consumed due to the oxidation process taking over. Because of this, it can be misleading to depend solely on an assay of *p*-aminophenol concentration or the appearance, without careful analysis, of new degradent peaks in high-performance liquid chromatography ("HPLC") to determine the purity and stability of an acetaminophen solution that does not have adequate buffering and antioxidant components.

It is clear from the science and Cadence's experience that the essential stability and purity of an aqueous acetaminophen solution is dependent on proper formulation and manufacturing—the 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 such processes. Accordingly, the components of the Ofirmev® formulation were experimentally chosen as the best means to accomplish these aims. An acetaminophen solution that differs from the approved Ofirmev® formulation in any way has not been shown to have the same anti-hydrolysis and anti-oxidation properties for protection against potentially toxic degradents. Indeed, based on Cadence's research and development experience with Ofirmev®, it is highly likely that such a product would not protect against these degradation processes to the same extent as the approved Ofirmev® formulation.

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[4] P. David Josephy, et al., *Oxidation of p-Aminophenol Catalyzed by Horseradish Peroxidase and Prostaglandin Synthase*, 23 Molecular Pharmacology 461 (1982) (Attachment 2); L. Lerner, *Identity of a Purple Dye Formed by Peroxidic Oxidation of p-Aminophenol at Low pH*, 115 J. Physical Chemistry 9901 (2011) (Attachment 3).

3. The Ofirmev® Formulation

The components of the Ofirmev® formulation were carefully chosen to maximize the stability of the commercial product. These components include buffering agents to prevent excursions of pH both below and above the optimum pH of the formulation, along with cysteine and mannitol to serve as free radical scavengers.

a. pH Control with Buffering Agents

Cadence has determined that the optimal pH for an aqueous acetaminophen solution is at or very near 5.5. Maintaining this pH level is crucial to ensuring a minimal rate of acetaminophen hydrolysis. Excursions in either direction—either an increase or decrease in pH from 5.5—will accelerate the rate of hydrolysis, and therefore, the rate of *p*-aminophenol formation.[5] These excursions can occur as a result of chemical reactions in the solution or from reactions of the solution with the container closure system, among other causes. It is difficult to predict the various circumstances that may drive an increase or decrease of the pH and, as a result, the use of buffers that will resist changes in pH is essential.

The phosphate buffer used in the Ofirmev® formulation has three ionizable hydrogen atoms, two of which have pK_as (acid strengths) that bracket the 5.5 pH level, one at 2.12 and the other at 7.1, thus resisting pH changes in either direction. Similarly, the cysteine used in Ofirmev® has three ionizable hydrogen atoms with pK_as of 2, 8, and 10, causing it to likewise resist pH changes above and below 5.5. These ingredients in the Ofirmev® solution effectively resist hydrolysis and *p*-aminophenol formation to maintain the stability and purity of the Ofirmev® drug product.

b. Free Radical Control with Cysteine and Mannitol

In an acetaminophen solution, the compound cysteine can scavenge molecular oxygen with subsequent formation of the compound cystine. A portion of the very small amount of oxygen remaining in the solution after manufacturing can be scavenged by this process and, for any remaining oxygen in the solution that could generate free radicals, cysteine is strongly reactive toward free radicals and can terminate the polymerization reaction. These beneficial properties make cysteine the optimum antioxidant among the seven commonly used and tested during development of Ofirmev®. In addition, mannitol also acts as a radical scavenger and helps prevent product degradation.

The Ofirmev® development program showed that a combination of buffering agents and antioxidants, along with careful control of the level of residual oxygen in the solution, dramatically slow the rate of acetaminophen degradation. By basically eliminating this reaction, the presence of *p*-aminophenol is also significantly reduced, preventing its ability to induce *p*-aminophenol-related toxicities or cause polymerization reactions during the shelf life of the product.

4. Potential Toxicity of Acetaminophen Polymeric Degradents

Very little is known about the structure or properties of the polymeric degradents that form from improperly formulated or improperly manufactured solutions of acetaminophen. Nonetheless, comparisons can be made with other known polymers that share common characteristics. One example is melanin, a complex, heterogeneous polymer that is largely responsible for producing pigmentation throughout the animal kingdom. Although melanin is formed from the polymerization of the amino acid

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[5] Koshy & Lach, *supra* note 2.

tyrosine (unrelated to acetaminophen), it may have structural similarities with the polymers formed from *p*-aminophenol in aqueous acetaminophen solutions, which would suggest that it may have similar properties. Polymers formed from chemical oxidation of acetaminophen alone, although not utilizing *p*-aminophenol as the free radical initiator, possess an electron paramagnetic resonance ("EPR") signal almost identical to that found in various forms of melanin.[6] Thus, it is reasonable to assume that polymers formed from initiation by *p*-aminophenol and incorporation of acetaminophen from the solution into the polymer structure will have similar ESR properties.

It is generally presumed that melanin polymers have a protective function, but some forms have been shown to possess toxic properties. Intermediates in the natural synthesis of melanin can be cytotoxic,[7] and melanin can also bind pharmaceutical compounds, leading to either dangerously high pharmaceutical concentrations in specific tissues or altered drug actions within the body.[8] In addition, melanin polymers may affect the immune response to fungal infections, thereby rendering such infections more virulent.[9] Synthetic melanin can also have toxic properties.

Neither the structures of melanin polymers nor the structures of the polymers formed in improperly formulated acetaminophen solutions are well characterized. Nonetheless, important parallels can be drawn between these species with respect to product safety. Given the potential harmful properties of cytotoxicity and drug binding associated with melanin polymers, and the fact that much less is known about the colored polymers formed in acetaminophen solutions as compared to melanin polymers, a new acetaminophen solution that does not contain the protective components present in the Ofirmev® formulation raises safety and efficacy concerns. Accordingly, FDA must require that any acetaminophen solution that does not contain the same pH buffers and antioxidants found in Ofirmev® be fully evaluated and tested to ensure that the product demonstrates the same quality, stability, safety, and effectiveness as Ofirmev®.

B. Legal Background

1. FDA Drug Approval Process

An NDA submitted for FDA approval of a new drug must contain, among other items, full reports of investigations demonstrating the drug's safety and effectiveness for its intended use.[10] When an NDA is submitted under Section 505(b)(1) of the FDCA, these investigations are conducted by or for the NDA applicant. When an NDA is submitted under Section 505(b)(2) of the FDCA, these investigations are not conducted by or for the applicant, nor has the applicant obtained a right of reference

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[6] David W. Potter, et al., *Identification of Acetaminophen Polymerization Products Catalyzed by Horseradish Peroxidase*, 260 J. Biological Chemistry 12,174 (1985) (Attachment 4).

[7] Peter Heiduschka, et al., *Melanin Precursor 6,6-Dihydroxyindol: Protective Effects and Cytotoxicity on Retinal Cells In Vitro and In Vivo*, 35 Toxicologic Pathology 1030 (2007) (Attachment 5).

[8] Peter Dayhaw-Barker, *Retinal Pigment Epithelium Melanin and Ocular Toxicity*, 21 Int'l J. Toxicology, 451 (2002) (Attachment 6); Robert J. D'Amato, et al., *Evidence for Neuromelanin Involvement in MPTP-Induced Neurotoxicity*, 327 Nature 324 (1987) (Attachment 7).

[9] Gary B. Huffnagle, et al., *Down-Regulation of the Afferent Phase of T Cell-Mediated Pulmonary Inflammation and Immunicity by a High Melanin-Producing Strain of* Cryptociccus Neoformans, 155 J. Immunology 3507 (1995) (Attachment 8).

[10] 21 U.S.C. § 355(b)(1).

or use from the person by or for whom the investigations were conducted.[11] Therefore, 505(b)(2) applications provide an alternate regulatory pathway for the approval of both new chemical entities and changes to previously approved drug products by permitting applicants to rely, in part, on published literature or FDA's previous finding of safety and effectiveness for an existing product. In some cases, a 505(b)(2) applicant may be required to conduct nearly the same amount of preclinical and clinical testing as that required for a traditional NDA, and in other cases substantially less work may be required. In either case, applicants are ultimately responsible for demonstrating the safety and effectiveness of their proposed new drugs to the satisfaction of FDA.

The ANDA process for approval of generic drugs is separate and distinct from the new drug approval process. When submitting an ANDA, applicants are not required to provide independent evidence of the safety and effectiveness of a proposed generic product. Rather, an ANDA applicant must show that its proposed generic drug is the "same as" a listed drug, i.e., a drug that has been approved under Section 505(b) of the FDCA and appears in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book").[12] Ordinarily, the listed drug to which an ANDA applicant must demonstrate sameness is the drug product selected by FDA as the reference standard for conducting bioequivalence testing, also known as the reference listed drug ("RLD").[13] In this way, an ANDA applicant obtains approval of a new generic drug by demonstrating that it is the same as the RLD and relying upon FDA's previous finding that the RLD is safe and effective for the particular intended use.[14]

2. Approval of Parenteral Drug Products

As discussed above, a generic drug must generally be the same as a listed drug. The term "same as," in this context, means "identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use."[15] Although, based on this definition, generic drugs may differ from their RLDs in inactive ingredients, applicants are nonetheless required to identify and characterize the specific inactive ingredients included in a generic drug and "provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product."[16]

Generic versions of parenteral drug products are an exception to this general rule—they are ***not*** permitted to differ in inactive ingredients from the approved RLD. Rather, a generic drug product intended for parenteral use must contain "the same inactive ingredients and in the same concentration as the [RLD]."[17] However, there is an exception to this exception. Applicants may seek approval of a generic drug product intended for parenteral use that differs from the RLD only with respect to preservatives, buffers, and antioxidants and only if the applicant "identifies and characterizes the

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[11] *Id.* § 35(b)(2).

[12] 21 U.S.C. § 355(j)(2)(A)(i); 21 C.F.R. §§ 314.92(a)(1), 314.94(a)(3).

[13] 21 C.F.R. § 314.94(a)(3).

[14] FDA has stated that applicants should file a 505(b)(2) application if they are seeking approval of a change to an approved drug that would not be permitted under the ANDA approval process because approval will require the review of clinical data. Likewise, applicants should not file a 505(b)(2) application for duplicates of approved products that are eligible for approval in an ANDA. *See* FDA, *Guidance for Industry: Applications Covered by Section 505(b)(2)* (Draft Guidance, 1999), at 3-4; 21 C.F.R. § 314.54.

[15] 21 C.F.R. § 314.92(a)(1).

[16] *Id.* § 314.94(a)(9)(ii).

[17] *Id.* § 21 C.F.R. § 314.94(a)(9)(iii).

differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product."[18]

Ultimately, FDA may withhold approval of an ANDA if information submitted in the application or any other information available to the Agency shows that "[t]he inactive ingredients of the drug product are unsafe for use . . . under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug product," or that "[t]he 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."[19] Specifically, "FDA will consider an inactive 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."[20]

Similarly, while a 505(b)(2) applicant may seek approval of a new drug product or a change to a previously approved drug product in reliance on safety and effectiveness studies not conducted by the applicant and to which the applicant has not obtained a right of reference, the applicant must still supply all of the information necessary to support approval of the proposed new product.[21] As with all NDAs, FDA must refuse to approve a 505(b)(2) application if the investigations included in an application fail to show that the drug product is safe and effective for its intended use.[22] Thus, if an applicant submits a 505(b)(2) application for approval of changes to a previously approved parenteral drug product, the applicant must provide sufficient nonclinical and clinical data—whether referenced or obtained by or for the applicant—to permit FDA to make the requisite finding of safety and effectiveness for approval.

C. FDA Must Not Approve Any New Acetaminophen Product for Parenteral Use that Does Not Have an Identical Inactive Ingredient Composition as Ofirmev® Without Nonclinical Studies and Adequate and Well-Controlled Clinical Trials Demonstrating the Product Is as Safe and Effective as Ofirmev®

As discussed above, hydrolysis and free radical oxidation are reactions that occur naturally within all aqueous acetaminophen solutions, making the inactive ingredient profile for such products crucial to maintaining their integrity. The degradents found in improperly formulated acetaminophen solutions have never been tested for safety or efficacy, and the polymers' similarity to melanin polymers indicates that they may likewise be associated with harmful properties. Given these serious concerns, FDA must rigorously review any application for a new acetaminophen solution that differs in inactive ingredients from the approved Ofirmev® formulation.[23]

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[18] *Id.*

[19] 21 U.S.C. § 355(j)(4)(H); 21 C.F.R. § 314.127(a)(8)(i).

[20] 21 C.F.R. § 314.127(a)(8)(ii)(B).

[21] 21 U.S.C. § 355(b)(2); 21 C.F.R. § 314.54(a).

[22] 21 U.S.C. § 355(d)(2), (5); 21 C.F.R. § 314.125(b)(3), (5).

[23] As a subsidiary matter, FDA must also refuse to approve any new acetaminophen product for parenteral use that does not contain an identical inactive ingredient profile as Ofirmev® absent adequate in vivo bioavailability and bioequivalence testing. The regulations contemplate waivers from the in vivo

1. FDA Must Not Approve an ANDA for a Generic Drug Referencing Ofirmev® that Differs in Inactive Ingredients from the RLD Without Additional Nonclinical and Clinical Testing and Data

Pursuant to FDA's regulations, the Agency must not approve a new generic drug intended for parenteral use that differs from its RLD in anything but a preservative, buffer, or antioxidant and, even then, FDA must find that any difference in a preservative, buffer, or antioxidant does not affect the safety or efficacy of the proposed generic drug product.[24] In order to approve an ANDA for a proposed generic drug that references Ofirmev® as its RLD but which differs from the approved Ofirmev® formulation in preservative, buffer, or antioxidant, FDA must determine that the differences do not affect the safety or efficacy of the product; in other words, FDA must find that the proposed generic drug is at least as safe and effective as Ofirmev®. Given the dearth of nonclinical and clinical research into alternative acetaminophen solution formulations, along with the serious safety concerns surrounding the degradation products that are formed in substandard formulations, adequate nonclinical and clinical studies are required for FDA to make this requisite safety and effectiveness determination. FDA must require that any generic drug submitted for approval in an ANDA that references Ofirmev® as its RLD is either identical to the Ofirmev® formulation, or contains test data sufficient to demonstrate its comparable safety and effectiveness.

2. FDA Must Not Approve a 505(b)(2) Application for a New Acetaminophen Injection Product that Differs in Inactive Ingredients from Ofirmev® Without Additional Nonclinical and Clinical Testing and Data

The ANDA approval process differs from the NDA approval process with respect to the essential showing that is required for each pathway. Where an ANDA may be approved by demonstrating sameness to the RLD, an NDA—whether a traditional NDA or 505(b)(2) application—must always demonstrate the safety and effectiveness of the proposed new drug. FDA has broad discretion under the FDCA to determine whether evidence submitted in an NDA demonstrates the safety and effectiveness of a new drug, but its review must ensure that the new drug meets the requisite statutory standard for approval.

With respect to changes to previously approved products, FDA regulations permit a 505(b)(2) applicant to rely on FDA's previous finding of safety and effectiveness to the extent such reliance would be permitted under the generic drug approval process.[25] Thus, FDA's prior determination of safety and effectiveness that would support the approval of a generic drug is also available to an applicant who modifies an approved drug. Nonetheless, it is within the Agency's authority and mandate to determine whether and to what extent the information submitted in a 505(b)(2) application supports approval of the product change. In this regard, FDA must require sufficient nonclinical and clinical data

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requirement (biowaivers) in several instances, including for parenteral solutions which contain the same active and inactive ingredients in the same concentration as an NDA- or ANDA-approved drug. 21 C.F.R. § 320.21(b)(1). The corollary to this is that biowaivers are not contemplated—and in vivo bioavailability or bioequivalence testing is therefore required—for parenteral drug products which fail to match an approved product in both active and inactive ingredients. For such products, in vivo bioavailability or bioequivalence is not considered "self-evident," as such products are not identical to a previously approved drug. Accordingly, FDA must require in vivo bioavailability or bioequivalence testing for any acetaminophen injection 505(b)(2) NDA or ANDA which contains inactive ingredients different from those in the approved Ofirmev® formulation.

[24] *Id.* § 314.127(a)(8)(ii)(B).

[25] *Id.* § 314.54(a).

in any 505(b)(2) application submitted for an acetaminophen injection product to ensure that the product is safe and effective. As a result, FDA must ensure that sufficient testing is performed on any new product formulation with inactive ingredients different from those in Ofirmev®, because the safety and effectiveness of such a solution has never been clinically tested. FDA should recognize that the safety of degradation products formed from pH-driven hydrolysis and oxidation that may occur as a result of changes to the Ofirmev® formulation must be clearly established before an altered solution can be administered to patients. The protection of the public health warrants nothing less.

D. Prior Cases where FDA Permitted Changes to the Inactive Ingredient Profiles of Generic Parenteral Drug Products Are Inapplicable to Acetaminophen Solutions Referencing Ofirmev®

FDA has, in the past, permitted certain generic drug products intended for parenteral use to include changes in their inactive ingredient profiles from their respective RLDs, including changes that go beyond the general exception for preservatives, buffers, and antioxidants. However, this past precedent is inapplicable to any new generic product referencing Ofirmev® as its RLD, and as such, should be considered immaterial to the present issues. Each of these past cases has been the result of a citizen petition submitted by a generic manufacturer requesting that FDA apply its general ANDA waiver authority[26] to permit marketing of a drug formulation that FDA had previously determined to be safe and effective in an approved an NDA. In contrast to these cases, however, no such generic manufacturer citizen petition has been submitted with respect to Ofirmev®, nor could there be, since there has been no prior independent safety and effectiveness review and FDA approval of acetaminophen solutions that differ in any respect from the approved Ofirmev® formulation.[27] As detailed further below, this fact renders these prior instances irrelevant to the issues Cadence raises in this citizen petition.

In the first case, Ben Venue Laboratories filed a citizen petition asking FDA to permit its ANDA to reference the discontinued formulation of Sandostatin Injection, which used sodium chloride as a tonicity agent and a glacial acetic acid/sodium acetate buffer system. This differed from the currently marketed formulation, which uses mannitol as a tonicity agent and a lactic acid/sodium buffer system. FDA granted the citizen petition, explicitly characterizing it as a situation in which "an ANDA applicant [sought] approval to market a previous formulation of a drug product that FDA had approved as safe"—a situation far from analogous to that of generic products referencing Ofirmev®.[28]

Likewise, several citizen petitions were filed by ANDA applicants requesting permission to reference the originally approved formulation of Zosyn (piperacillin sodium and tazobactam sodium for injection), which did not contain the inactive ingredients edetate sodium and citric acid found in the reformulated product. The NDA holder, Wyeth Pharmaceuticals, also submitted a citizen petition requesting that FDA require any ANDA referencing Zosyn to exhibit the same compatibility profile as reformulated Zosyn with respect to these specific inactive ingredients. FDA granted the former citizen petitions and denied the latter, approving ANDAs for the drug products that excluded edetate sodium and citric acid. However, again, FDA's decision was limited to a drug product that had been NDA-approved

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[26] *Id.* § 314.99(b).

[27] In each of the cases cited, FDA also determined that the original formulation of the RLD had been withdrawn from the market for reasons *other than* safety or effectiveness.

[28] *See* FDA Citizen Petition Response re: Sandostatin, Docket Nos. 2001P-0574 and 2005P-0061 (Mar. 25, 2005).

in both its original and reformulated versions, thus the differences in inactive ingredients were deemed safe when each version of the product was adequately labeled.[29]

Finally, two citizen petitions were recently submitted requesting opposing determinations from FDA regarding whether to accept ANDAs referencing Acetadote (acetylcysteine injection) products containing disodium edetate ("EDTA") which was not present in the reformulated version of the RLD. FDA granted the generic applicant's petition and denied the innovator Cumberland Pharmaceuticals' petition, stating that the Agency may approve an ANDA for acetylcysteine injection that duplicates the original Acetadote formulation containing EDTA. Again, FDA had approved NDAs for both the original and reformulated versions, rendering this precedent immaterial to an examination of generic drugs referencing Ofirmev®. Indeed, FDA cautioned that any "differences in the ANDA formulation relative to the RLD formulation that are shown to be unsafe based on available information will preclude ANDA approval."[30]

As the cases described above demonstrate, FDA has only permitted changes between a generic parenteral drug and its RLD if the changes either (1) meet the requirements of the exception for changes to preservatives, buffers, or antioxidants, including a sufficient demonstration of safety and effectiveness for the inactive ingredient change; or (2) have been previously reviewed and determined to be safe and effective by FDA through the approval of an NDA. This further highlights the potential adverse consequences of approving a follow-on product to Ofirmev® with differing inactive ingredients of unknown safety and efficacy. FDA should recognize that adequate testing prior to approval of such products is essential for the protection of the public health.[31]

III. ENVIRONMENTAL IMPACT

On behalf of Cadence, Craig Pharma Solutions LLC claims a categorical exclusion from the requirement to submit an environmental assessment pursuant to 21 C.F.R. § 25.31(a).

IV. CERTIFICATION

On behalf of Cadence Pharmaceuticals, Inc., Craig Pharma Solutions LLC makes the following certification pursuant to section 505(q)(1)(H) of the FDCA: I certify that, to my best knowledge

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[29] *See* FDA Citizen Petition Response re: Zosyn, Docket Nos. FDA-2005-P-0003, FDA-2006-P-0019, FDA-2006-P-0331, and FDA-2006-P-0319 (Sept. 15, 2009).

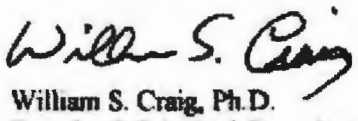
[30] *See* FDA, Citizen Petition Response re: Acetadote, Docket Nos. FDA-2011-P-0339, FDA-2012-P-0507 (Nov. 7, 2012).

[31] A recent citizen petition submitted by Merchant & Gould requests approval to submit an ANDA for a proposed generic product referencing Pfizer's Vfend I.V. (voriconazole injection) which contains an inactive ingredient that differs from the RLD, and that is not a preservative, buffer, or antioxidant. *See* Merchant & Gould, Citizen Petition re: Vfend I.V., Docket No. FDA-2013-P-0203 (Feb. 19, 2013). Unlike the cases cited above, this drug formulation has not previously been approved through the NDA process. Rather, the petitioner is seeking approval to market a voriconazole injection product containing sulfuobutyl ether B-cyclodextrin sodium as a solubilizing agent instead of the RLD's hydroxypropyl B-cyclodextrin solubizing agent. Although we would caution FDA against using its general ANDA waiver authority lightly, we also recognize that each drug is different. We would emphasize, however, that approval of a generic drug referencing Ofirmev® that has different ingredients than the RLD without nonclinical studies and adequate well controlled clinical trials demonstrating safety and effectiveness would present potentially significant risks, counseling against waiving the sameness requirements for such products, even if FDA determines that it is appropriate for generic drugs referencing Vfend I.V.

and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: August 10, 2012 (information that an ANDA referencing Ofirmev® might include a different formulation than Ofirmev®). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Cadence Pharmaceuticals, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

On behalf of Cadence Pharmaceuticals, Inc., Craig Pharma Solutions LLC makes the following certification pursuant to 21 C.F.R. § 10.30(b): 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 which are unfavorable to the petition.

Respectfully submitted,



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