U.S. FOOD & DRUG ADMINISTRATION

JAN 2 1 2020

Errol Gould, Ph.D.
Global Head of Clinical Development
and Medical Affairs
Persion Pharmaceuticals LLC
10 North Park Place
Suite 201
Morristown, NJ 07960

Re: Docket No. FDA-2019-P-4140

Dear Dr. Gould,

This letter responds to the citizen petition you submitted to the Food and Drug Administration (FDA or the Agency) dated August 29, 2019 (Petition). The Petition asks FDA to take "certain actions with respect to generic hydrocodone bitartrate extended-release capsules to protect the health and safety of patients with hepatic impairment."[1] More specifically, the Petition requests that:

1. Before granting final approval to any ANDA [abbreviated new drug application] for generic hydrocodone bitartrate extended-release capsules, require that the ANDA contain data and information demonstrating that the proposed generic product is bioequivalent to the RLD [reference listed drug] in hepatically impaired subjects; and

2. Before granting final approval to any ANDA for generic hydrocodone bitartrate extended-release capsules, require that the ANDA contain the same information in its labeling as in the labeling of the RLD concerning administration of the drug to patients with hepatic impairment.[2]

We interpret the first request to ask that any ANDA contain bioequivalence data from testing in hepatically impaired subjects.[3] We understand the second request as an effort to assure that any ANDA would need to challenge a patent that purports to claim the labeling information in question, thus delaying approval of a generic drug and competition for your product. We have carefully considered the Petition. For the reasons described below and consistent with FDA's statutory authority, regulations and policies, the Petition is denied.

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[1] Petition at 1.

[2] Petition at 2.

[3] As discussed below, FDA concludes that testing in healthy subjects may provide data and information demonstrating that the proposed generic product is bioequivalent to the RLD in hepatically impaired subjects.

I. BACKGROUND

A. Zohydro ER

On October 25, 2013, FDA approved new drug application (NDA) 202880 for Zohydro ER (hydrocodone bitartrate) extended-release capsules, 10 milligrams (mg), 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg.[4] NDA 202880 is currently held by Persion Pharmaceuticals LLC. Zohydro ER is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.[5] As with other opioid drug products, Zohydro ER's approved labeling advises prescribers to use the lowest effective dose for the shortest duration and individualize dosing based on severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse.[6] Zohydro ER is administered orally twice daily (every 12 hours).

On January 30, 2015, FDA approved a supplement to NDA 202880 (Supplement 3) for Zohydro ER that, among other changes, added two inactive ingredients, polyethylene oxide (PEO) and povidone, to the drug product formulation.[7] Labeling information regarding Zohydro ER's use by patients with hepatic impairment did not change as a result of the reformulation.

Relevant information from Zohydro ER's labeling with respect to its use in a hepatically impaired population includes:

> **2.4 Dosage Modification in Patients with Severe Hepatic Impairment**
> Patients with severe hepatic impairment may have higher plasma concentrations of hydrocodone than those with normal function. Therefore, initiate therapy with 10 mg every 12 hours and titrate carefully, while monitoring for respiratory depression, sedation, and hypotension. No adjustment in starting dose with ZOHYDRO ER is required in patients with mild or moderate hepatic impairment [*see Clinical Pharmacology (12.3)*].[. . .]
>
> **8.6 Hepatic Impairment**
> No adjustment in starting dose with ZOHYDRO ER is required in patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment may have higher plasma concentrations than those with normal hepatic function [*see Clinical Pharmacology (12.3)*]. Therefore, a dosage reduction is recommended for patients with severe hepatic impairment [*see Dosage and Administration (2.4)*]. Monitor patients with

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[4] Drugs@FDA, Zohydro ER Approval Letter, October 25, 2013, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/202880Orig1s000ltr.pdf (Zohydro ER NDA approval letter).

[5] Drugs@FDA, Zohydro ER Approved Labeling, September 18, 2018, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202880s014s015lbl.pdf (Zohydro ER labeling).

[6] See the DOSAGE AND ADMINISTRATION section of Zohydro ER's Prescribing Information, available on FDA's drugs@FDA searchable database, https://www.accessdata.fda.gov/scripts/cder/daf/.

[7] Drugs@FDA, Zohydro ER S-003 Supplement Approval Letter, January 30, 2015, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/202880Orig1s003ltr.pdf (Zohydro ER S-003 supplement approval letter)

severe hepatic impairment closely for respiratory depression, sedation, and hypotension [*see Clinical Pharmacology (12.3)*].[. . .]

12.3 Pharmacokinetics [. . .]
Hepatic Impairment
After a single dose of 20 mg ZOHYDRO ER in 20 patients with mild to moderate hepatic impairment based on Child-Pugh classifications, mean hydrocodone Cmax values were 25 ± 5, 24 ± 5, and 22 ± 3.3 ng/mL for moderate and mild impairment, and normal subjects, respectively. Mean hydrocodone AUC values were 509 ± 157, 440 ± 124, and 391 ± 74 ng·h/mL for moderate and mild impairment, and normal subjects, respectively. Hydrocodone Cmax values were 8-10% higher in patients with mild or moderate hepatic impairment, respectively, while AUC values were 10% and 26% higher in patients with mild and moderate hepatic impairment, respectively. Severely impaired subjects were not studied [*see Use in Specific Populations (8.6)*].[8]

II. STATUTORY AND REGULATORY BACKGROUND

A. Abbreviated New Drug Applications (ANDA) and the Bioequivalence Requirement

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to add, among other things, section 505(j) (21 U.S.C. 355(j)), which established an abbreviated approval pathway for generic drugs.[9] To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the RLD is safe and effective.[10] The ANDA applicant must identify the listed drug on which it seeks to rely and, with certain limited exceptions, a drug product described in an ANDA must contain the same active ingredient, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.[11]

An ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the RLD.[12] Under section 505(j)(8)(B)(i) of the FD&C Act, a drug is considered bioequivalent to a listed drug if:

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[8] Zohydro ER labeling.

[9] For purposes of this response, the term *generic drug* refers to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act.

[10] An *RLD* is the "listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA." 21 CFR 314.3(b). RLDs are identified in the Orange Book.

[11] Section 505(j)(2)(A) and (j)(4) of the FD&C Act (21 U.S.C. 355(j); see also § 314.94(a).

[12] See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (requiring "information to show that the new drug is bioequivalent to the listed drug"), § 314.94(a)(7) (requiring that an ANDA contain information to show that the drug product is bioequivalent to the RLD), and 21 CFR 314.127(a)(6)(i) (stating that FDA will refuse to approve an

> 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. . . .[13]

A showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of action at a rate and to an extent that is not significantly different from that of the RLD, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to perform the same way in the body as the RLD. Bioequivalence testing determines whether differences in formulation (e.g., differences in inactive ingredients) between a proposed generic drug and the RLD have an effect on the rate and extent to which the active ingredient becomes available at the site of action.

As discussed further below, the statute, regulations, and case law give FDA considerable flexibility in determining how the bioequivalence requirement is met. The testing methods may include in vivo data (data from a study on human subjects), in vitro data (data from laboratory studies), or a combination of in vivo and in vitro data.[14] This flexibility is reflected in FDA's regulations, which describe the types of evidence that may be used to establish bioequivalence:

> FDA may require *in vivo or in vitro testing, or both,* to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products . . . . The selection of the method used to meet an *in vivo* or *in vitro* testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.[15]

ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the RLD referred to in the ANDA).

[13] See also 21 CFR 314.3(b) and 21 CFR 320.23(b).

[14] See section 505(j)(7)(A)(i)(III) of the FD&C Act; see also *Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995) (noting that this provision "vests the FDA with discretion to determine whether *in vitro* or *in vivo* bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated application process").

[15] 21 CFR 320.24(a) (emphasis added). In the preamble to the final rule setting forth FDA's regulations for ANDAs, the Agency explained that, depending upon the drug, it would determine the appropriate bioequivalence methodology on a case-by-case basis: "Bioequivalence can be established by pharmacodynamic measurement as well as by in vitro techniques and bioequivalence studies with clinical endpoints. The preferred method for establishment of bioequivalence . . . *is determined on a case-by-case basis*, depending on the drug under study." Abbreviated New Drug Application Regulations, Final Rule (57 FR 17950 at 17972, April 28, 1992) (emphasis added).

The methods described in § 320.24(b) (21 CFR 320.24(b)) include (1) in vivo pharmacokinetic (PK) studies of the active ingredient, or when appropriate its active metabolites, in whole blood, plasma, serum, or other appropriate biological fluid or an in vitro test that has been correlated with and is predictive of in vivo bioavailability data; (2) in vivo studies in which urinary excretion of the active moiety and, when appropriate, its active metabolite(s) are measured as a function of time; (3) in vivo studies measuring acute pharmacodynamic effect; (4) comparative clinical endpoint studies; and (5) other in vitro studies acceptable to FDA (usually a dissolution rate test) that ensure human in vivo bioavailability.[16] In addition, consistent with section 505(j)(8)(C) of the FD&C Act, § 320.24(b)(6) of the regulations states that FDA has the authority to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence."[17]

For most systemically acting drug products, the rate and extent of systemic absorption of the drug is usually the most sensitive, accurate, and reliable indicator of the rate and extent to which the active ingredient becomes available at the site of drug action. The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption generally rests on a comparison of drug and/or metabolite concentrations in an accessible biological fluid, such as blood or urine, after administration of a single dose or multiple doses of each drug product to healthy volunteers.[18]

In general, bioequivalence (BE) PK studies are conducted using a two-treatment crossover study design, randomly separating a limited number of subjects into test and reference drug groups. Single doses of the test and reference drugs are administered, and blood or plasma/serum concentrations of the drug are measured over time. The rate and extent of absorption are statistically evaluated. The relevant PK parameters calculated from these data include the area under the plasma concentration versus time curve (AUC), calculated to the last measured concentration time (AUC_{0-t}), and AUC extrapolated to infinity (AUC_{∞}). These parameters represent the extent of absorption (i.e., how much of the drug in the given dose was absorbed). The other relevant PK parameter is the maximum or "peak" drug concentration (C_{max}). C_{max} is used to reflect the rate of absorption.

For in vivo PK BE studies, FDA generally considers two products to be bioequivalent when the 90-percent confidence interval for the log-transformed ratio of geometric means for the PK parameters, AUC and C_{max}, are entirely within an 80- to 125-percent acceptance interval.[19] The

[16] 21 CFR 320.24(b).

[17] § 320.24(b)(6).

[18] Section 505(j)(8)(B) of the FD&C Act; See generally, the draft guidance for industry *BE Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*, available on the FDA Drugs guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[19] See FDA guidance for industry *Statistical Approaches to Establishing Bioequivalence*, January 2001 (Establishing Bioequivalence Guidance). This guidance represents FDA's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

use of an 80- to 125-percent acceptance interval is a scientific judgment about the best statistical practices for bioequivalence determinations and reflects decades of scientific data on the variability of product characteristics (such as potency) within and between batches, as well as biological variability in patients. From these data, FDA has concluded that the variability in PK values allowed under this acceptance interval will not adversely affect clinical outcomes because this variability is within the range of differences that can already arise because of other product-specific and biological factors.[20]

B. Draft Product-Specific Guidance for Hydrocodone Bitartrate Extended-Release Oral Capsules

FDA's guidance for industry *Bioequivalence Recommendations for Specific Products* describes the Agency's process for making available to the public FDA's guidance on the design of bioequivalence studies for specific drug products.[21] Currently, FDA periodically publishes notices in the *Federal Register* announcing the availability of draft, revised draft, and final versions of product-specific guidances (PSGs). These documents are available on FDA's website.[22]

FDA considers comments received on PSGs when developing its final guidances. As with Agency guidance in general, these PSGs describe the Agency's current thinking and should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. Applicants following our PSGs have an expectation that FDA will agree that their approach to establishing bioequivalence is appropriate. However, applicants may confer with the Agency on using a different approach for establishing bioequivalence. Recommendations made in a draft or final guidance do not bind the Agency or the public. Further, even in the absence of a PSG, FDA has the authority to approve a product supported by bioequivalence data that meet the applicable statutory and regulatory requirements.

In October of 2016, FDA published a draft PSG on hydrocodone bitartrate extended-release oral capsules. The draft PSG recommends that two in vivo bioequivalence studies, which are of a single dose, two-way crossover design using the 10 mg strength under fasting and fed conditions in healthy males and non-pregnant females in the general population, be conducted.

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[20] Dighe, S.V., Adams, W.P., *Bioequivalence: A United States Regulatory Perspective*, Pharmaceutical Bioequivalence (Welling PG et al., eds.), pp. 347-380 (1991) (Regulatory Perspective on Bioequivalence Study)

[21] FDA guidance for industry *Bioequivalence Recommendations for Specific Products*, June 2010. This guidance states that the Agency intends to develop bioequivalence recommendations based on its understanding of the characteristics of the listed drug, information derived from published literature, and Agency research and consultations within different offices in FDA's Center for Drug Evaluation and Research (CDER) as needed based on the novelty or complexity of the bioequivalence considerations. Specific product recommendations may contain differing amounts of detail and background information depending on the product and will be revised as appropriate to ensure that the most up-to-date bioequivalence information is available to the public. Id. at 2-3.

[22] The Product-Specific Guidances for Generic Drug Development are available on FDA's website at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development.

Bioequivalence is determined based on plasma hydrocodone concentrations. In addition, the draft PSG provides information on dissolution test method and sampling times.[23]

C. "Same Labeling" Requirement for Products Approved in ANDAs and Permissible Carve-Outs

Section 505(j)(2)(A)(i) of the FD&C Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." Also, section 505(j)(2)(A)(v) of the FD&C Act requires that an ANDA contain:

> information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the FD&C Act] or because the new [generic] drug and the listed drug are produced or distributed by different manufacturers."[24]

A parallel provision appears in section 505(j)(4)(G) of the FD&C Act.[25]

Although the requirements set forth in sections 505(j)(2)(A)(v) and 505(j)(4)(G) of the FD&C Act are known as the "same labeling" requirements, they do not require that a generic drug's labeling be identical to that of the listed drug it references in every respect. Instead, these provisions reflect, among other things, Congress's intent that the generic drug be safe and effective for each condition of use prescribed, recommended, or suggested in the generic drug labeling without requiring that an ANDA be approved for each condition of use for which the listed drug is approved. In describing the Hatch-Waxman Amendments, Congress explicitly acknowledged that "the bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved."[26]

In interpreting the statutory exception to the same labeling requirement, which allows certain

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[23] Draft hydrocodone bitartrate extended-release oral capsule PSG, available at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development. As stated in the PSG, the draft guidance, once finalized, will represent the FDA's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you wish to discuss an alternative approach, contact the Office of Generic Drugs.

[24] See also 21 CFR 314.92(a)(1), 314.94(a)(4)(i), 314.94(a)(8)(iv), 314.127(a)(2), and 314.127(a)(7).

[25] Section 505(j)(4)(G) of the FD&C Act provides that FDA shall approve an ANDA unless, among other things, "the information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

[26] H.R. Rep. No. 98-857, pt.1, at 2; and 21 ("The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved.").

labeling differences because the proposed ANDA and the listed drug are "produced or distributed by different manufacturers," among other things, the regulations at § 314.92(a)(1) (21 CFR 314.92(a)(1)) explicitly state that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted".

Similarly, section 314.94(a)(8)(iv) (21 CFR 314.94(a)(8)(iv)) sets forth some examples of permissible differences in labeling that may result because the generic drug product and listed drug are produced or distributed by different manufacturers. Permissible differences include, but are not limited to, the following:

> [D]ifferences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the act.[27]

The regulations at § 314.127(a)(7) (21 CFR 314.127(a)(7)) further provide that, to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent, or by exclusivity*," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use" (emphasis added). In practice, when determining how to carve out language from an ANDA's labeling to give effect to the RLD's patent- or exclusivity-protection, FDA examines the current labeling of the RLD and makes any appropriate omissions of patent- or exclusivity-protected information.[28] It then determines whether the labeling with the protected information carved out remains safe and effective for the remaining non-protected conditions of use.[29] Thus, starting with the currently approved labeling for the RLD, these provisions specifically affirm that ANDA applicants may carve out from their proposed labeling any patent- or exclusivity-protected indication or other aspect of labeling and obtain approval for the remaining non-protected conditions of use as long as the ANDA remains safe and effective for the remaining non-protected conditions of use.

Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement. For example, in *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for use of the pioneer is a matter of indifference."[30] Similarly, in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288

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[27] 21 CFR 314.94(a)(8)(iv).

[28] 21 CFR 314.94(a)(8)(i), (iv).

[29] 21 CFR 314.127(a)(7).

[30] *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996). See also *Spectrum Pharm., Inc. v. Burwell*, 824 F.3d 1062, 1066 (D.C. Cir. 2016) (explaining that D.C. Circuit has "approved FDA's general approach

F.3d 141 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible labeling difference because of a difference in manufacturer.[31] Sigma-Tau Pharmaceuticals, Inc. (Sigma-Tau) argued that FDA was obligated to look beyond the labeling an ANDA applicant proposed to use in determining whether a generic drug would violate an innovator's exclusivity. The court stated that Sigma-Tau's argument would extend exclusivity beyond what Congress intended and "frustrate the longstanding practice of Congress, the FDA, and the courts not to interfere with physicians' judgments and their prescription of drugs for off-label uses."[32] The court reasoned that "[Sigma-Tau's theory] to bar the approval of generic drugs, even for unprotected indications. . . [would add] a huge evidentiary hurdle to the generic drug approval process [and] would be profoundly anti-competitive."[33]

Thus, the statute, regulations, and applicable case law permit the omission of an indication or other aspect of labeling protected by a listed patent or applicable exclusivity as an acceptable difference between the proposed generic drug and the RLD that are produced or distributed by different manufacturers if the omission does not render the proposed generic drug less safe or effective than the RLD for the non-protected conditions of use that remain in the labeling.

III. SUMMARY OF THE PETITION

The Petition contends that if a generic formulation fails to match Zohydro ER's performance in hepatically impaired patients then such patients who are switched to a generic version of Zohydro ER and use it according to Zohydro ER's labeling could receive a dangerous overdose of hydrocodone.[34] Accordingly, the Petition requests that FDA not approve an ANDA seeking approval of a generic hydrocodone bitartrate extended-release capsule (i.e., relying on Zohydro ER as its RLD) unless the ANDA includes data and information demonstrating that the proposed generic product is bioequivalent to the RLD in hepatically impaired subjects. The Petition claims that such testing "is necessary to ensure that the generic product is as safe and effective as Zohydro ER when administered to patients with hepatic impairment under the conditions specified in Zohydro ER's labeling[.]"[35]

Your Petition contends that Zohydro is "one of the few extended-release opioids that can be administered to patients with mild or moderate hepatic impairment *without dosage adjustments*."[36] You also note that Zohydro ER is "recommended for use even in patients with

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to labeling carve-outs as an acceptable interpretation of the [FDCA]" and upholding FDA's approval of a generic drug with an indication protected by orphan exclusivity carved out).

[31] *Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 148, n. 3 (4th Cir. 2002).

[32] Id. (citations omitted).

[33] Id.

[34] Petition at 1.

[35] Petition at 12.

[36] Petition at 8, emphasis in original.

severe hepatic impairment if initiated at the lowest available dose (10 mg) and then titrated and monitored carefully."[37] The Petition states that although "hepatic impairment significantly affects the pharmacokinetics of opioids, including hydrocodone,"[38] Zohydro ER's formulation "minimizes the pharmacokinetic differences between normal subjects and those with hepatic impairment."[39] The Petition asserts the minimized pharmacokinetic difference is evidenced by the results of Study No. ZX002-1001, which was included in NDA 202880 in support of Zohydro ER's initial approval and its labeling with respect to dosing for patients with mild, moderate and severe hepatic impairment.[40]

The Petition contrasts Zohydro ER's labeling regarding administration to patients with hepatic impairment with that of other approved extended-release opioid products, specifically focusing on Vantrela ER (NDA 207975). Vantrela ER is a hydrocodone bitartrate extended-release tablet[41] that is not currently marketed according to FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). The Petition seems to suggest that because patients with hepatic impairment are generally expected to experience increased plasma concentrations of hydrocodone, but the increase seen following administration of Zohydro ER in patients with mild and moderate hepatic impairment is relatively small (as seen in Study No. ZX002-1001), Zohydro ER's "special formulation" (and not Zohydro ER's PK profile or the properties of hydrocodone itself) allows Zohydro ER to be dosed and titrated more predictably and safely in patients with hepatic impairment.[42]

The Petition further concludes that the bioequivalence studies in healthy subjects, as recommended by FDA's current corresponding draft PSG, must be supplemented with bioequivalence testing in subjects with hepatic impairment because the Petition contends testing in healthy subjects alone is not sufficient to detect the impact of formulation differences on hepatically impaired patients.[43] In support of this contention, the Petition references a meta-analysis of studies examining generic substitution among specific populations, including patients with impaired liver function.[44] According to the Petition, "the study found evidence of pharmacokinetic differences between brand and generic products in some specific populations, including the need for dosage adjustments when taking a generic, and recommended additional studies to further explore the "problem".[45] The Petition goes on to assert that the approval of generic extended-release hydrocodone bitartrate products that increase the risk of overdose in

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[37] Petition at 13, emphasis in original.

[38] Petition at 12.

[39] Petition at 12; see also Petition at 3.

[40] Petition at 3.

[41] Petition at 8 and 12-13.

[42] Petition at 8 and 12-13.

[43] Petition at 13.

[44] Petition at 15.

[45] Petition at 15.

patients with hepatic impairment will further exacerbate the national opioid crisis. Accordingly, the Petition reasons that requiring generic extended-release hydrocodone bitartrate capsules to be supported by bioequivalence testing in individuals with hepatic impairment is consistent with FDA's draft guidance on Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework (Draft Benefit-Risk Guidance).[46]

Finally, the Petition asserts that it is especially important for FDA to ensure a generic product performs the same as Zohydro ER in hepatically impaired patients because the generic product must have the same labeling as the RLD.[47] As a result, the Petition also requests that FDA require an ANDA for a generic hydrocodone bitartrate extended-release capsule referencing Zohydro ER to have the same labeling as the RLD concerning administration of the drug to patients with mild or moderate hepatic impairment.[48]

IV. DISCUSSION

A. A demonstration of bioequivalence in healthy subjects as recommended in the hydrocodone bitartrate extended-release capsule draft PSG is appropriate to support approval of an ANDA.

As discussed above, the Petition's first request is that FDA not approve an ANDA relying on Zohydro ER as its RLD unless the ANDA includes data and information demonstrating that the proposed generic product is bioequivalent to the RLD in hepatically impaired subjects. Underlying this request is the petitioner's premise that Zohydro ER's *formulation* significantly minimizes PK variation in patients with mild or moderate hepatic impairment[49] and that a demonstration of bioequivalence in healthy subjects would not rule out clinically significant PK differences between Zohydro ER and a proposed generic product in hepatically impaired patients.[50]

1. The Petition provides no scientific support for its assertion that Zohydro ER's formulation plays a unique role in the PK of hydrocodone in hepatically impaired patients.

The Petition claims Zohydro ER "employs a special formulation that unexpectedly minimizes the pharmacokinetic differences between normal subjects and those with hepatic impairment."[51] However, the Petition offers no explanation or supporting references for how the formulation of Zohydro ER (either the original formula or the reformulation approved in 2015) minimizes such

[46] Petition at 16.

[47] Petition at 16.

[48] Petition at 17.

[49] Petition at 3.

[50] Petition at 10.

[51] Petition at 12.

PK differences. The Petition explains that the liver is the source of most opioid metabolism and that when liver function is impaired, "reduced metabolism usually results in accumulation of the parent drug in the body with repeated administration."[52] The Petition does not, however, explain how Zohydro ER's formulation minimizes this effect in individuals with hepatic impairment. The Petition seems to suggest, without explanation, that Zohydro ER's inactive ingredients impact the rate at which the released active ingredient, hydrocodone, is metabolized in individuals with hepatic impairment.

To support its contention that Zohydro ER is especially well suited for individuals with hepatic impairment, the Petition points to FDA-approved labeling for a variety of opioid products regarding administration to individuals with hepatic impairment. The Petition correctly notes that many opioid labels recommend downward dosing adjustments and careful titration in hepatically impaired individuals.[53] The Petition then asserts that Zohydro ER "is one of the few extended-release opioids that can be administered to patients with mild or moderate hepatic impairment *without dosage adjustments*" and that "unlike many other similar opioid products, ZOHYDRO ER can be used in patients with severe hepatic impairment (with some dose adjustment and careful titration and monitoring)."[54].

We disagree with your conclusion that Zohydro ER is *unexpectedly* well suited for individuals with hepatic impairment. FDA has approved three NDAs for extended-release, single active ingredient, hydrocodone products: Zohydro ER, Hysingla ER, and Vantrela ER. Of these three products, Zohydro ER and Hysingla ER have similar labeling regarding hepatic impairment. The labels of both Zohydro ER and Hysingla ER state that no adjustment in starting dose is required in patients with mild or moderate hepatic impairment, and that patients with severe hepatic impairment should receive a low starting dose followed by careful monitoring. Among FDA-approved extended-release, single ingredient hydrocodone products, Vantrela ER is the outlier, having more restrictive labeling regarding administration to patients with hepatic impairment. Thus, we do not agree that Zohydro ER has unexpected PK properties in individuals with hepatic impairment.

The Petition also points to PK studies in hepatically impaired subjects to support its contention that Zohydro ER is especially well suited for individuals with hepatic impairment. Specifically, the Petition refers to Study ZX002-1001,[55] which was used to inform Zohydro ER's labeling

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[52] Petition at 5, quoting, Johnson SJ. Opioid safety in patients with renal or hepatic dysfunction. *Pain Treatment Topics*. June 2007.

[53] Petition at 7-8.

[54] Petition at 8.

[55] Study ZX002-1001 was a Phase 1, open-label, single-dose, parallel study in subjects with mild or moderate hepatic impairment. Ten healthy subjects were matched to 20 (n=10 in mild, n=10 in moderate) hepatically-impaired subjects for age, body mass index, with some consideration for race and sex. Child-Pugh score was used in classifying as mild or moderate hepatic impairment subjects based on encephalopathy grade, ascites, serum bilirubin, serum albumin, and prothrombin time, as described in FDA's guidance for industry on *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (available at: https://www.fda.gov/media/71311/download).

regarding administration to hepatically impaired patients, and makes a cross study comparison of ZX002-1001 with a hepatic impairment study performed for Vantrela ER.[56] The Petition references the results from the ZX002-1001 hepatic impairment study that showed when comparing subjects with mild or moderate hepatic impairment to healthy subjects there was an 8-10% higher maximum plasma concentration of hydrocodone (C_{max} value) and a 10% and 26% higher area under the plasma concentration vs. time curve (AUC), respectively.[57] The Petition contends that FDA did not find these increases clinically relevant, and as a result no dose adjustment was necessary for patients with mild or moderate hepatic impairment, and Zohydro ER could be administered to patients with severe hepatic impairment at the lowest dose while titrated and monitored carefully.[58] The Petition goes on to reason that Zohydro ER's formulation must account for this minimal PK variation.[59]

The Petition notes that a PK study in patients with hepatic impairment described in the labeling of Vantrela ER resulted in a 30% increase in C_{max} and 70% increase in AUC for individuals with moderate hepatic impairment compared to healthy subjects, resulting in Vantrela ER's more restrictive labeling regarding administration to patients with hepatic impairment.[60] Thus, the Petition reasserts its conclusion that observed minimal differences in pharmacokinetics between healthy subjects and patients with mild or moderate hepatic impairment in Study ZX002-1001 is attributable to Zohydro ER's formulation and not the active ingredient hydrocodone bitartrate.[61]

While we do not disagree with the Petition's summary of the results of the hepatic impairment studies for Zohydro ER and Vantrela ER or that there are differences between the two products in terms of labeled dosing instructions for patients with hepatic impairment, the Petition offers no scientific explanation for why or how Zohydro ER's formulation accounts for such differences. In addition, the Petition takes the results and differences in labeling and draws conclusions that go beyond what the hepatic impairment PK studies were designed to examine. For example, the hepatic impairment PK studies for each product had different sets of conditions, ranging from differences between the products themselves (e.g, dosage form and potentially different release mechanism), the dose strengths studied (15 mg for Vantrela ER and 20 mg for Zohydro ER), and a limited and different number of subjects with hepatic impairment in each of the hepatic impairment groups (8 subjects with moderate hepatic impairment for Vantrela ER and 20 patients with mild to moderate hepatic impairment for Zohydro ER).[62] Given the

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[56] Petition at 3, 7-8, 12-14.

[57] Petition at 3; see also, Zohydro ER labeling, Section 12.3.

[58] Petition at 3.

[59] Petition at 3 and 12.

[60] Petition at 12-13; *see also* drugs@FDA, Vantrela ER approved labeling, January 17, 2017, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207975s000lbl.pdf (Vantrela ER labeling).

[61] Petition at 12-13.

[62] See drugs@FDA, Zohydro ER Medical Review, October 25, 2013, available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202880Orig1s000MedR.pdf (Zohydro ER medical review); *see also* drugs@FDA, Vantrela ER Medical Review, January 17, 2017, available at:

differences described above and the lack of bioavailability studies comparing these extended-release products under controlled conditions, relying on a cross study/labeling comparison of hepatic impairment PK information to conclude that Zohydro ER's unique formulation significantly minimizes PK variation in patients with mild or moderate hepatic impairment compared to patients without such impairment is not scientifically reasonable.

2. *The Petition does not support its view that bioequivalence testing in healthy subjects does not sufficiently account for any formulation effects on pharmacokinetics in patients with hepatic impairment; nor does it acknowledge that bioequivalence testing in patients with hepatic impairment was not required to support Zohydro ER's reformulation in 2015.*

After contending that Zohydro ER's formulation "minimizes the pharmacokinetic differences between normal subjects and those with hepatic impairment,"[63] the Petition goes on to reason that an ANDA seeking approval of a generic product relying on Zohydro ER as its RLD must include not only the bioequivalence tests described in FDA's draft PSG, but, in addition, must include a bioequivalence test in patients with hepatic impairment.[64] The Petition claims the bioequivalence testing recommended in the draft PSG would not be sufficient to assure a generic product will perform the same as Zohydro ER when administered to patients with hepatic impairment per the labeled directions, and that such an assurance must come from bioequivalence testing in a hepatically impaired population.[65]

The Petition presents no reason to expect that a generic product found to be bioequivalent to Zohydro ER through PK testing in healthy subjects, consistent with FDA's draft PSG, would not be bioequivalent to Zohydro ER in patients with hepatic impairment. FDA's draft PSG provides recommendations on the design of studies for establishing that a generic hydrocodone extended-release capsule drug product is bioequivalent to Zohydro ER (NDA 202880). Specifically, it recommends two in vivo bioequivalence studies, of a single-dose, two-way crossover design using the 10 mg strength, under fasting and fed conditions in healthy males and non-pregnant females in the general population.[66] Additional bioequivalence studies in other populations, such as in those with any organ dysfunction, are not recommended.

The purpose of a bioequivalence evaluation is to determine if there is a significant difference in the rate and extent of absorption of the therapeutic ingredient between the test product and its

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https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/207975Orig1s000MedR.pdf (Vantrela ER medical review).

[63] Petition at 12.

[64] Petition at 13.

[65] Petition at 13-14.

[66] See the draft PSG, available at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development.

RLD when administered at the same molar dose under similar experimental conditions.[67] In bioequivalence studies, potential differences in PK resulting from formulation differences between test and reference products are evaluated. Bioequivalence testing compares bioavailability of the test and reference products using the PK metrics. Although the PK metrics (AUC, C_{max}) are post-absorption values (i.e., they are based on concentrations of the drug measured in whole blood, plasma, serum, or other appropriate biological fluid after the drug has been absorbed), they are determined by absorption. If there were differences in drug release and dissolution between test and reference products that can affect absorption, those differences can be detected in healthy subjects. As such, bioequivalence studies are generally recommended to be conducted in healthy subjects because healthy subjects have lower PK variability with less confounding factors and are thus more sensitive to detect any formulation differences as compared to specific patient populations. The extent of PK differences between healthy subjects and patients with hepatic impairment are expected to be similar for both test and RLD products when bioequivalence is demonstrated in healthy subjects. In other words, if there are differences in PK due to disease conditions, we expect to see similar effects both in test and RLD products if bioequivalence is established in healthy subjects. We do not have data to suggest otherwise. Therefore, it is a common practice to assess bioequivalence in healthy subjects. This practice reflects our current scientific thinking and is consistent with the recommendations in FDA's draft guidance entitled "Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA."[68]

The Petition cites the above-mentioned hepatic impairment PK studies conducted on Zohydro ER and Vantrela ER, and Zohydro ER's labeling for hepatically impaired patients, to assert that bioequivalence testing in hepatically impaired subjects is necessary and such testing is necessary because the PK profile of Zohydro ER in hepatically impaired subjects appears to be formulation-based.[69] The results of the hepatic impairment PK studies of Zohydro ER and Vantrela ER—which involve two drugs that have not been shown to be bioequivalent—do not provide a reason to expect that a generic product found to be bioequivalent to Zohydro ER in healthy subjects would not be bioequivalent to Zohydro ER in patients with hepatic impairment. The Petition provides no data nor mechanistic understanding (i.e., factors or processes such as interactions due to excipients in a formulation) to suggest that a bioequivalence outcome will be different between healthy subjects and patients with hepatic impairment. Without data or evidence that suggests otherwise, a demonstration of bioequivalence in healthy subjects for Zohydro ER generic drug products as recommended in the draft PSG is appropriate to satisfy the bioequivalence requirement for approval of an ANDA that refers to Zohydro ER. An additional bioequivalence study in patients with hepatic impairment for generic hydrocodone extended-release products is not warranted.

In fact, we note that Zohydro ER's own formulation change was approved without PK data in hepatically impaired individuals, the very data the Petition seeks to require for any ANDA for a

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[67] https://www.fda.gov/media/87219/download

[68] https://www.fda.gov/media/87219/download.

[69] Petition at 13.

generic version of Zohydro ER. On January 30, 2015, FDA approved a formulation change of Zohydro ER that added two new excipients, polyethylene oxide and povidone. This change in formulation was permitted based on in vitro data and the application of an established in vitro in vivo correlation (IVIVC) showing the predicted bioavailability of the new formulation to the bioavailability of the original formulation was within bioequivalence limits. The IVIVC, in turn, was based on testing of Zohydro ER in healthy subjects, not in hepatically impaired subjects. If testing of the reformulated Zohydro ER formulation in hepatically impaired subjects was necessary to show bioequivalence, then there would not have been a basis to approve the currently marketed Zohydro ER formulation.

Specifically, consistent with FDA's guidance for industry on SUPAC-MR: Modified Release Solid Oral Dosage Forms,[70] the two newly added excipients were considered non-release controlling level 3 excipients, with "level 3" meaning the change is likely to have a significant impact on formulation quality and performance.[71] For a level 3 change involving non-release controlling excipients, the SUPAC-MR guidance recommends a demonstration of bioequivalence based on a single-dose bioequivalence study but notes this study can be waived in the presence of an established IVIVC.[72] Of note, the SUPAC-MR guidance does not recommend a bioequivalence test in any relevant specific population. Accordingly, because Zohydro ER had an established IVIVC from its original approval, the supplement was supported by the in vitro data and IVIVC in lieu of a bioequivalence test.[73] Moreover, a demonstration of bioequivalence in patients with hepatic impairment was not recommended or required.

Even if Zohydro ER had been reformulated to add what the SUPAC-MR guidance would characterize as release-controlling level 3 excipients, the bioequivalence documentation recommended by the SUPAC-MR guidance would have been the same, and a bioequivalence study in hepatically impaired individuals would not have been recommended or required.[74]

Thus, absent additional information, there is no reason to expect that a generic product found to be bioequivalent to Zohydro ER through bioequivalence testing in healthy subjects would not be bioequivalent to Zohydro ER in patients with hepatic impairment, which is in fact consistent with what was required to support approval of the reformulation of Zohydro ER in 2015.[75]

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[70] https://www.fda.gov/media/70956/download.

[71] SUPAC-MR guidance at 7.

[72] SUPAC-MR guidance at 8.

[73] We note that all the data submitted by the holder of NDA 202880 in support of Zohydro ER's new formulation involved healthy subjects and not hepatically impaired subjects.

[74] SUPAC-MR Guidance at 15.

[75] We note that the exhibits included and referenced in the Petition indicate that hepatic impairment can affect the pharmacokinetics of opioids. However, the exhibits, including referenced declarations, do not indicate that a bioequivalence outcome will be different in patients with hepatic impairment if bioequivalence of the generic to Zohydro ER is demonstrated in healthy subjects.

3. FDA-approved labeling for hydrocodone bitartrate extended-release products already includes various measures aimed to address the concerns raised in the Petition regarding increased plasma concentrations of hydrocodone in patients with hepatic impairment.

We recognize the Petition's concerns that hepatic impairment affects the PK of hydrocodone and could lead to increased plasma concentrations of hydrocodone, which in turn could lead to an increased risk of adverse events including opioid use disorder.[76] Such concerns[77] are in part why products such as Zohydro ER are labeled with numerous opioid related warnings.[78] In addition, while the labeling of Zohydro ER may not recommend any dose adjustment for patients with mild or moderate hepatic impairment, the dosing instructions, in general, include limitations such as "[u]se the lowest effective dosage for the shortest duration consistent with individual patient treatment goals."[79] In fact, for patients that are opioid-naive or opioid non-tolerant, the initial dosing recommendation, "initiate with 10 mg capsules orally every 12 hours[,]"[80] is very similar to the modified dosing recommendation for patients with severe hepatic impairment, "initiate therapy with 10 mg every 12 hours and titrate carefully, while monitoring for respiratory depression, sedation, and hypotension."[81] Thus, as with Zohydro ER, a generic to Zohydro ER will have these same warnings and general dosing restrictions that are aimed to minimize the opioid related safety concerns.

In addition, the Petition references an FDA grant to assess therapeutic interchangeability between brand name and generic products in specific patient populations and claims the "study found evidence of pharmacokinetic differences between brand and general products in some special populations . . . and recommended additional studies to further explore the problem." (Petition at 15 and FN 50 and 51). While the referenced poster is not available from the website provided in the Petition, it is FDA's understanding that the examples the Petition mentioned in this statement appear to be tacrolimus or cyclosporine, not products related to the subject of this Petition (i.e., hydrocodone extended-release products) and that the systematic review did not yield consistent evidence of barriers for brand to generic switching in specific populations.

[76] Petition at 4-7.

[77] The Petition suggests principles from FDA's draft guidance for industry on Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework (June 2019; available at: https://www.fda.gov/media/128150/download), should apply to FDA's approval of generic drugs. Regardless of whether the principles do or do not apply to the approval of generics, the guidance is not relevant to the request in this Petition because for the reasons discussed above an additional bioequivalence study in patients with hepatic impairment for generic hydrocodone extended-release capsules is not necessary to demonstrate bioequivalence between a generic hydrocodone bitartrate extended-release capsule and its RLD.

[78] See for example, Zohydro ER labeling.

[79] Section 2.1 Important Dosage and Administration Information, Zohydro ER labeling.

[80] Section 2.2 Initial Dosage, Zohydro ER labeling.

[81] Section 2.4 Dosage Modifications in Patients with Severe Hepatic Impairment, Zohydro ER labeling.

B. Whether an ANDA for a hydrocodone bitartrate extended-release capsule must contain the same information in its labeling as in the labeling of the RLD concerning administration of the drug to patients with hepatic impairment will be evaluated consistent with the corresponding statutory and regulatory requirements.

The Petition requests that FDA require an ANDA for generic hydrocodone bitartrate extended-release capsules referencing Zohydro ER as its RLD to contain the same labeling instructions as the RLD concerning administration of the drug to patients with mild or moderate hepatic impairment.[82] In support of this request the Petition references and incorporates a previous petition submitted by Pernix Ireland Pain Limited, previous holder of NDA 202880 for Zohydro ER, on February 25, 2016. In that petition, Pernix argued that FDA could not approve a generic version of Zohydro ER with labeling that omits approved labeling instructions for administering the drug to patients with hepatic impairment. The Petition contends that removal of such information from the labeling would deny critical information necessary to the safe and effective use of generic hydrocodone bitartrate extended-release capsules and that under 21 CFR 314.127(a)(7), such a labeling carve-out would not be permissible.[83]

Today, FDA is providing final approval of an ANDA for hydrocodone bitartrate extended-release capsules that references Zohydro ER; this ANDA contains the same labeling instructions for administering its drug to patients with hepatic impairment as Zohydro ER. Therefore, with respect to this ANDA, the Agency did not have the occasion to evaluate a proposed omission of any labeling instructions for administering a generic version of Zohydro ER to patients with hepatic impairment.

We deny the Petition's request that FDA categorically require an ANDA for a hydrocodone bitartrate extended-release capsule referencing Zohydro ER as its RLD to contain the same information in its labeling as in the labeling of the RLD concerning administration of the drug to patients with hepatic impairment. As discussed above in section II.C, the statute, regulations, and applicable case law permit the omission of an indication or other aspect of labeling protected by a listed patent or applicable exclusivity as an acceptable difference between the proposed generic drug and the RLD that are produced or distributed by different manufacturers if the omission does not render the proposed generic drug less safe or effective than the RLD for the non-protected conditions of use that remain in the labeling.

Whether an exception to the "same labeling" requirements applies to an application for a generic hydrocodone bitartrate extended-release capsule and, if so, whether the differences render the proposed product less safe or effective than the listed drug for all remaining, nonprotected conditions of use is evaluated by FDA based on the particular facts that are applicable to an application at the time of the decision. As we discussed in our response to the February 25, 2016 petition, such decisions are made by the Agency on a case-by-case basis in the normal course of the review process.

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[82] Petition at 2 and 17.

[83] Petition at 17.

V. CONCLUSION

For the reasons described above, the Petition is denied.

Sincerely,

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