PERSION™
PHARMACEUTICALS LLC

August 29, 2019

VIA ELECTRONIC SUBMISSION

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

Re: Citizen Petition Requesting That FDA Take Certain Actions With Respect to Generic Hydrocodone Bitartrate Extended-Release Capsules to Protect the Safety of Patients with Hepatic Impairment

Dear Sir or Madam:

On behalf of Persion Pharmaceuticals LLC ("Persion"), the undersigned hereby submits this Citizen Petition pursuant to sections 505(j) and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. §§ 355(j) and 355(q)) and 21 C.F.R. §§ 10.25, 10.30, 10.31 and 314.127 to request the Commissioner of Food and Drugs to take certain actions with respect to generic hydrocodone bitartrate extended-release capsules to protect the health and safety of patients with hepatic impairment.

Unlike virtually all other extended-release opioid products, ZOHYDRO® ER (hydrocodone bitartrate) extended-release capsules do not require dose adjustment in patients with mild or moderate hepatic impairment and may be used with careful dosing, titration and monitoring in patients with severe hepatic impairment. If a generic formulation fails to match ZOHYDRO ER's unique performance in hepatically impaired patients – and instead performs like the other extended-release opioids on the market – hepatically impaired patients who are switched to a generic version of ZOHYDRO ER and use it according to ZOHYDRO ER's labeling instructions could receive a dangerous overdose of hydrocodone. The risks of overdose are serious and include, among other things, life-threatening or fatal respiratory depression, ***which can be fatal based on a single dose***, increased likelihood of developing opioid use disorder ("OUD"), and increased risks of abuse, misuse and diversion.

To mitigate these serious risks, the Food and Drug Administration ("FDA") should ensure that generic hydrocodone bitartrate extended-release capsules perform in the same manner as ZOHYDRO ER in hepatically impaired patients. Specifically, FDA should require all new and pending Abbreviated New Drug Applications ("ANDAs") for generic hydrocodone bitartrate extended-release capsules to include data and information demonstrating that the proposed generic product is bioequivalent to the Reference Listed Drug ("RLD"), ZOHYDRO ER, in hepatically impaired subjects (not just healthy subjects). Bioequivalence testing in this special population is necessary because formulation differences that could impact hepatically impaired patients would not be expected to be detected by bioequivalence studies in healthy subjects alone.

Such testing is particularly crucial given the ongoing and devastating opioid crisis in the United States. FDA recently stated that when regulating opioids, "any action taken by the agency should be considered in light of the opioid crisis."[1] Persion agrees and believes this policy should extend to FDA's approval decisions for generic versions of extended-release opioids, which should not be approved in a manner that could exacerbate, rather than mitigate, the opioid crisis. Accordingly, in order to approve any generic hydrocodone bitartrate extended-release capsules, FDA must have complete assurance that such products do not pose significant new safety risks to hepatically impaired patients when used in accordance with required labeling instructions. The only way to gain this assurance is to require bioequivalence testing in hepatically-impaired subjects. The grounds for Persion's request are set forth in detail below.

I. Actions Requested

For the reasons that follow, Persion respectfully requests the Commissioner to:

1. Before granting final approval to any ANDA 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 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.

II. Statement of Grounds

A. Factual Background

1. ZOHYDRO® ER

Persion is the holder of a New Drug Application ("NDA") for ZOHYDRO ER (NDA 202880), which was approved on October 25, 2013 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."[2] ZOHYDRO ER contains the active ingredient hydrocodone bitartrate, a semi-synthetic opioid agonist, and is available in capsule strengths of 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg. ZOHYDRO ER was the first extended-release, single-entity hydrocodone product approved by FDA.

[1] Statement on the FDA's benefit-risk framework for evaluating opioid analgesics (June 20, 2019), *available at* https://www.fda.gov/news-events/press-announcements/statement-fdas-benefit-risk-framework-evaluating-opioid-analgesics.

[2] ZOHYDRO ER Prescribing Information, § 1 (Rev. 9/18), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202880s014s015lbl.pdf.

A new formulation of ZOHYDRO ER was approved on January 30, 2015, to incorporate BeadTek®, a technology intended to confer abuse-deterrent properties.[3] BeadTek adds an indistinguishable mixture of inactive beads to the previous mixture of active immediate-release hydrocodone beads and active extended-release hydrocodone beads in the ZOHYDRO ER formulation. The inactive beads remain inert and dissolve independently of the active hydrocodone beads. The inactive beads are specifically designed to form a viscous gel when crushed and dissolved in liquids and solvents. Importantly, this specialized technology does not change the 12-hour release properties of the formulation when taken as directed.

ZOHYDRO ER's unique formulation has another important characteristic: it significantly minimizes pharmacokinetic variation in patients with mild or moderate hepatic impairment compared to patients without such impairment. This medically relevant attribute was discovered in Study No. ZX002-1001, a pharmacokinetic study in healthy adults and adults with mild and moderate hepatic impairment. The study was conducted at the request of the Agency to determine the influence of hepatic impairment on the pharmacokinetics and relative bioavailability of hydrocodone and its metabolites following administration of a single oral dose of extended-release hydrocodone 20 mg under fasted conditions. The pharmacokinetic study included 30 subjects: 10 healthy adults; 10 adults with mild hepatic impairment; and 10 adults with moderate hepatic impairment. Severely impaired subjects were not studied because of the safety risks associated with overdose.

The results of Study No. ZX002-1001 unexpectedly demonstrated that plasma levels of hydrocodone did not vary significantly in subjects with mild or moderate hepatic impairment compared to healthy subjects. In particular, hydrocodone C_{max} values were only 8-10% higher in patients with mild or moderate hepatic impairment, respectively, while Area Under the Curve ("AUC") values were 10% and 26% higher in patients with mild and moderate hepatic impairment, respectively. According to FDA, these modest increases in exposure are not clinically relevant and thus do not warrant a dose adjustment in patients with mild or moderate hepatic impairment.[4]

As a result of these clinically significant study findings, the dosing instructions in ZOHYDRO ER's approved labeling state that "***No adjustment in starting dose with ZOHYDRO ER is required in patients with mild or moderate hepatic impairment.***"[5] Moreover, FDA concluded that Zohydro ER can be administered to patients with *severe* hepatic impairment if initiated on the lowest available dose (10 mg) and titrated and monitored carefully.[6]

These instructions for treating patients with hepatic impairment are repeated throughout ZOHYDRO ER's approved labeling[7] as follows:

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[3] ZOHYDRO ER Supplement Approval Letter (NDA 202880/S-003) (Jan. 30, 2015).
[4] FDA, ZOHYDRO ER Summary Review, p. 11 (Oct. 25, 2013), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202880Orig1s000SumR.pdf.
[5] ZOHYDRO ER Prescribing Information, § 2.4 (emphasis added).
[6] ZOHYDRO ER Prescribing Information, § 2.4.
[7] ZOHYDRO ER Prescribing Information.

HIGHLIGHTS OF PRESCRIBING INFORMATION

Patients with Severe Hepatic Impairment: Initiate dosing 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. (2.4)

FULL PRESCRIBING INFORMATION

2.4 Dosage Modifications 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 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)*].

2. <u>Opioid Use in Hepatically Impaired Subjects</u>

The dosing instructions for ZOHYDRO ER in hepatically impaired subjects are unusual and set ZOHYDRO ER apart from the vast majority of extended-release opioid products approved by FDA, including VANTRELA™ ER (hydrocodone bitartrate) extended-release tablets, another

extended-release hydrocodone bitartrate drug approved for 12-hour dosing.[8] As documented below, most extended-release opioid products require significant dose adjustments (*e.g.*, one third to one half the usual dose) when administered to hepatically impaired patients, including patients with mild or moderate hepatic impairment. Moreover, many extended-release opioid products are not recommended for use in patients with *severe* hepatic impairment – and some are even contraindicated in such patients.

The reason for this caution is twofold. First, hepatic impairment can significantly affect the pharmacokinetics of opioids. This is because the liver is the source of most opioid metabolism, the "major site for transformation of opioids from parent compounds to active or inactive metabolites."[9] When liver function is impaired, "reduced metabolism usually results in accumulation of the parent drug in the body with repeated administration."[10] Patients with hepatic impairment thus typically experience increased exposure to opioids – higher C_{max} and AUC and longer plasma half-life ($t_{1/2}$) – compared to patients without such impairment. For example, in a study performed on a *different formulation* of hydrocodone than ZOHYDRO ER on the effects of hepatic impairment, **"systemic exposure to hydrocodone was ~70% higher in subjects with moderate hepatic impairment vs normal hepatic function"** after administration of a 12-hour, extended-release tablet formulation.[11] In other words, the same dose of an opioid can lead to higher blood levels of the drug in hepatically impaired patients compared to non-impaired patients, meaning the hepatically impaired patient receives too much drug, *i.e.*, an overdose.

This leads directly to the second problem: opioids like hydrocodone entail serious and life-threatening safety risks related to dosing and overdosing, particularly sedation, respiratory depression, and, all too commonly, death. The opioid class of drugs, in fact, contains a boxed warning describing the serious risks associated with abuse, addiction, and fatal respiratory depression. Of special concern to patients with hepatic impairment, there is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, *and respiratory depression*. *See* Declaration of Christopher G. Gharibo, M.D., ¶ 11 (Aug. 16, 2019) ("Gharibo Decl.") (Exhibit 3). **Moreover, respiratory depression can be fatal based on a single dose.** *See* Declaration of Craig Antell, D.O., ¶ 20 (Aug. 20, 2019) ("Antell Decl.") (Exhibit 4). Studies have shown that "[h]igher doses of opioid analgesics were associated with increased overdose [mortality] risk."[12] For this reason, ZOHYDRO ER's approved labeling warns that "proper dosing and titration … are essential" to reduce the risk of respiratory depression.[13]

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[8] VANTRELA ER Prescribing Information, § 2.2 (Rev. 1/2017), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207975s000lbl.pdf.

[9] Johnson SJ. Opioid safety in patients with renal or hepatic dysfunction. *Pain Treatment Topics*. June 2007. Updated November 30, 2007. Available at http://paincommunity.org/blog/wp-content/uploads/Opioids-Renal-Hepatic-Dysfunction.pdf (last accessed Aug. 2, 2019) (Exhibit 1).

[10] Johnson SJ article.

[11] Bond M. Effects of renal impairment and hepatic impairment on the pharmacokinetics of hydrocodone after administration of a novel extended-release hydrocodone tablet formulated with OraGuard™ technology. *Pain Week Accepted Abstracts,* 2013 (Exhibit 2) (emphasis added); VANTRELA ER Prescribing Information, § 12.3 (Exhibit 9).

[12] Dasgupta N. et al. Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality. *Pain Medicine*. 2016; 17: 85-98, *available at* https://www.ncbi.nlm.nih.gov/pubmed/26333030 (Exhibit 5).

[13] ZOHYDRO ER Prescribing Information, § 5.3.

Hepatically impaired patients are particularly vulnerable to risks associated with the gradual onset of overdose. The effects of overdose are not always immediate and can build over time. Because patients with hepatic impairment are not able to clear opioids from their system efficiently, opioid levels tend to accumulate over time until, with little advance warning, a patient may experience severe respiratory depression from the elevated plasma levels. *See* Gharibo Decl. ¶ 21. This risk can be particularly acute in elderly patients, who generally are more vulnerable than younger patients, and in patients taking medications that depress the central nervous system ("CNS") (*e.g.*, OTC antihistamines and prescription anticonvulsants). *See* Antell Decl. ¶ 21; Gharibo Decl. ¶¶ 25-26. Many patients with hepatic impairment are elderly and taking concomitant medications that depress the CNS. *See* Antell Decl. ¶¶ 21-22.

Elderly patients are more vulnerable because the functioning of the liver, kidneys, and other organ systems naturally slows down during the aging process, which can add further reductions in hepatic function to reductions caused by liver disease. *See* Antell Decl. ¶ 21; *see* Gharibo Decl. ¶ 25-26. Moreover, co-administration of drugs like benzodiazepines that depress the CNS substantially increase the risks of death from overdose. *See* Antell Decl. ¶ 22; *see* Gharibo Decl. ¶ 27. In one study, for example, rates of overdose death were ten times higher in patients co-administered opioid analgesics and benzodiazepines versus opioid analgesics alone.[14] This is a signification risk because many patients are prescribed both opioid analgesics and benzodiazepines. *See* Antell Decl. ¶ 22. The approved labeling for ZOHYDRO ER contains an express boxed warning that concomitant use of opioids with benzodiazepines or other CNS depressants may result in "profound sedation, respiratory depression, coma, and death."[15]

Studies also have demonstrated that the risk of developing OUD increases with higher doses of opioids.[16] This risk is particularly pronounced in chronic opioid therapies (such ZOHYDRO ER), which is indicated for "daily, around-the-clock, long-term opioid treatment." One study published in 2014 found that "among individuals with chronic opioid use, *the likelihood of OUDs increased dramatically with increasing dose*, with ORs of 12.64, 24.00, and 107.25 for low, medium and high dose respectively."[17] The authors stated that their findings "suggest that if chronic opioid therapy is being used, low dose poses much less risk of OUDs than medium dose, and medium dose is much less risky than high dose."[18] These study results are likely due to the fact that the euphoric effects of opioids like hydrocodone are linked to dose: higher doses generally produce stronger euphoric effects. *See* Gharibo Decl. ¶ 23. Because patients with hepatic impairment receive what is essentially a higher dose than non-impaired patients, their risks of developing OUD would be expected to increase without appropriate dose adjustment. *See* Gharibo Decl. ¶ 23.

Because of these serious safety risks associated with opioids generally, treatment should always be initiated at "the lowest effective dosage for the shortest duration consistent with

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[14] Dasgupta N. et al article.
[15] ZOHYDRO ER Prescribing Information, Boxed Warning.
[16] Edlund MJ, Martin BC, et al. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. *Clin J Pain*. 2014;30(7):557-564. Author manuscript vailable at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4032801/ (Exhibit 6).
[17] Edlund et al. article.
[18] Edlund et al. article.

individual patient treatment goals."[19] Moreover, because of the above-described increases in systemic exposure, particular care must be used when prescribing opioids to hepatically impaired patients. For example, a 2007 review article recommended that codeine, methadone, meperidine, and propoxyphene not be used in patients with severe hepatic impairment and that, for hydrocodone and hydromorphone, the initial dose be decreased by 50% of the usual amount and patients be monitored carefully for symptoms of opioid overdose.[20]

These recommendations for significant dose reductions in hepatically impaired patients are consistent with the FDA-required labeling for the vast majority of approved extended-release opioid products, as described below:

> OxyContin® (oxycodone): The approved labeling recommends that, for patients with hepatic impairment, therapy should be initiated "at 1/3 to 1/2 the usual dosage and titrate[d] carefully" and that patients should be monitored carefully "for signs of respiratory depression, sedation, and hypotension."[21]
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> XTAMPZA® ER (oxycodone) extended-release capsules: The approved labeling recommends that, for patients with hepatic impairment, therapy should be initiated "at 1/3 to 1/2 the usual dosage and titrate[d] carefully" and that patients should be monitored carefully "for signs of respiratory depression."[22]
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> OPANA® ER (oxymorphone hydrochloride) extended-release tablets: The approved labeling requires initiation of patients with mild hepatic impairment at the lowest available dose (for opioid-naïve patients) or with a 50% dose reduction (for patients on prior opioid therapy), with careful titration and close monitoring for "signs of respiratory or central nervous system depression."[23] For patients with moderate or severe hepatic impairment, OPANA ER is contraindicated.[24]
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> MORPHABOND™ ER (morphine) extended-release tablets: The approved labeling states that, because "[m]orphine pharmacokinetics have been reported to be significantly altered in patients with cirrhosis[,]" patients should be started "with a lower than usual dosage of MORPHABOND ER and titrate[d] slowly while monitoring for signs of respiratory depression, sedation, and hypotension."[25]
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> EXALGO® (hydromorphone HCl) extended-release tablets: The approved labeling states that patients with moderate hepatic impairment should be started on 25% of the dose that would be prescribed to patients with normal hepatic function and then

[19] ZOHYDRO ER Prescribing Information, HIGHLIGHTS OF PRESCRIBING INFORMATION, § 2.1.
[20] Johnson SJ article.
[21] OXYCONTIN Prescribing Information, § 2.8 (Rev. 9/2018).
[22] XTAMPZA ER Prescribing Information, § 2.3 (Rev. 9/2018).
[23] OPANA ER Prescribing Information, § 2.5 (Rev. 9/2018).
[24] OPANA ER Prescribing Information, § 2.5. Targiniq® ER also is contraindicated in patients with moderate or severe hepatic impairment and requires a reduction of the starting dose to 1/3 to ½ the usual starting dose in patients with mild hepatic impairment. Targiniq ER Prescribing Information, §§ 2.5, 4 (Rev. 9/2018).
[25] MORPHABOND ER Prescribing Information, § 8.6 (Rev. 12/2018).

"closely monitor[ed] … for respiratory and central nervous system depression."[26] The use of EXALGO is not recommended in patients with severe hepatic impairment.

NUCYNTA® ER (tapentadol) extended-release tablets: The approved labeling states that patients with moderate hepatic impairment should be started on 50 mg no more than every 24 hours, which is half the dose recommended for patients with normal hepatic function (50 mg twice a day), and closely monitored for "respiratory and central nervous system depression."[27] Although no dosage adjustment is recommended in patients with mild hepatic impairment, the use of NUCYNTA ER is not recommended for patients with severe hepatic impairment.[28]

VANTRELA™ ER (hydrocodone bitartrate) extended-release tablets: The approved labeling states that patients with mild to moderate hepatic impairment should be started on one half of the recommended initial dose and monitored closely for "adverse events such as respiratory depression."[29] The use of VANTRELA ER is not recommended in patients with severe hepatic impairment.

Unlike the products described above, 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*.[30] Moreover, 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). The table below demonstrates that these differences exist even when ZOHYDRO ER is compared to other extended-release *hydrocodone* products, particularly VANTRELA ER, another approved extended-release hydrocodone intended for use for a 12-hour duration.

Because the VANTRELA ER formulation performs very differently than ZOHYDRO ER in hepatically impaired patients, ZOHYDRO ER's unusual labeling instructions for patients with hepatic impairment appear to be dependent on its unique formulation rather than the properties of hydrocodone itself. *See* Antell Decl. ¶ 9. If any of these products had not been required by FDA to perform a study on hepatically impaired patients, the dosing recommendations could have been different and could have put patients' lives at risk.

[26] EXALGO Prescribing Information, § 2.5 (Rev. 9/2018).
[27] NUCYNTA ER Prescribing Information, § 2.4 (Rev. 9/2018).
[28] NUCYNTA ER Prescribing Information, § 2.4.
[29] VANTRELA ER Prescribing Information, § 2.3.
[30] HYSINGLA™ ER (hydrocodone bitartrate) extended-release tablets is one of the other extended-release opioids that does not require an adjustment in starting dose in patients with mild or moderate hepatic impairment. HYSINGLA ER Prescribing Information, § 8.6 (Rev. 9/2018). However, HYSINGLA ER is intended for once-daily administration (every 24 hours) rather than twice-daily (every 12 hours).

TABLE 1: Comparison of ER Hydrocodone Products

	ZOHYDRO ER	VANTRELA ER	HYSINGLA ER
Active moiety	Hydrocodone	Hydrocodone	Hydrocodone
Dosage Form	ER Capsules	ER Tablets	ER Tablets
Strengths	10, 15, 20, 30, 40 and 50 mg	15, 30, 45, 60, and 90 mg	20, 30, 40, 60, 80, 100, and 120 mg
Duration	12-hours	12-hours	24 hours
Mild or Moderate Hepatic Impairment	No dosing adjustment	Initiate with ½ recommended initial dose	No dosing adjustment
Severe Hepatic Impairment	Initiate on lowest available dose	Not recommended for use	Initiate with ½ initial dose

3. Proposed Generic Versions of ZOHYDRO ER

In 2017, FDA tentatively approved two ANDAs seeking approval to market generic versions of ZOHYDRO ER, including ANDA 206952 submitted by Actavis Laboratories FL, Inc. ("Actavis") and ANDA 206986 submitted by Alvogen Pine Brook, Inc. ("Alvogen"). These tentative approvals were granted after FDA denied (without substantive comment) Pernix Therapeutics' ("Pernix") Citizen Petition regarding labeling requirements for generic versions of ZOHYDRO ER.[31] In particular, Pernix asked the Agency to refrain from approving any ANDA for a generic version of ZOHYDRO ER if it omitted from its proposed labeling certain safety-related information concerning administration of the drug to patients with mild or moderate hepatic impairment (see labeling language cited in section II.A.1 above). The FDA's denial was *pro forma* and did not reach the merits of Pernix's petition.

Prior to granting tentative approval to the above-identified ANDAs, FDA issued a draft bioequivalence guidance for hydrocodone bitartrate extended-release capsules that recommends two bioequivalence studies: (1) a fasting, single-dose, two-way crossover study using the 10 mg strength; and (2) a fed, single-dose, two-way cross-over study using the 10 mg strength.[32] Significantly, the patient population recommended for both studies is normal healthy males and non-pregnant females from the general population.

Persion assumes that the above-described ANDAs were tentatively approved based, in part, on bioequivalence testing conducted in accordance with the draft guidance. Because of ZOHYDRO ER's unique and clinically meaningful pharmacokinetic profile in subjects with

[31] FDA Petition Response, FDA-2016-P-0713 (July 22, 2016).
[32] FDA, Draft Guidance on Hydrocodone Bitartrate (Oct. 2016), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/psg/Hydrocodone%20bitartrate_oral%20ER%20cap_RLD%20202880_RC09-16.pdf.

hepatic impairment, however, Persion is concerned that the bioequivalence testing recommendations in the draft guidance cannot provide sufficient assurance that a generic product will perform the same as ZOHYDRO ER when administered, without dosage adjustment, to patients with hepatic impairment per the labeled directions. In other words, given ZOHYDRO ER's unique formulation, bioequivalence studies in healthy subjects would not necessarily detect clinically significant differences between the formulations of ZOHYDRO ER and a proposed generic product in hepatically impaired patients.

Accordingly, a proposed generic product with a different formulation could be bioequivalent to ZOHYDRO ER when studied in healthy subjects but then behave like most other extended-release opioid products in hepatically impaired patients *by significantly increasing systemic exposure to hydrocodone*. Hepatically impaired patients taking such a generic without dosage adjustment thus risk receiving an overdose of hydrocodone, which could result in life-threatening adverse events, including respiratory depression, sedation and hypotension. *See* Gharibo Decl. ¶ 11; *see* Antell Decl. ¶¶ 9, 17-20. Approving such a generic drug not only would violate the FFDCA and its implementing regulations (as described below), but also would create unreasonable safety risks for hepatically impaired patients who may be switched to a generic hydrocodone bitartrate extended-release capsule without their knowledge or consent. *See* Gharibo Decl. ¶¶ 11, 29-30; *see* Antell Decl. ¶¶ 9, 17-25.

B. Statutory and Regulatory Background

The Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Amendments") amended the FFDCA to create abbreviated pathways for the approval of follow-on versions of previously approved, brand name drug products. Under section 505(j) of the FFDCA (21 U.S.C. § 355(j)) an applicant may submit an ANDA for approval of a generic version of a previously approved "listed drug." The ANDA applicant must identify the listed drug upon which it seeks to rely for approval, and that listed drug is referred to as the RLD. The ANDA approval process allows the ANDA applicant to rely upon FDA's previous findings of safety and effectiveness for the RLD rather than independently demonstrating the safety and effectiveness of the proposed generic drug through rigorous clinical testing, such as "adequate and well-controlled" clinical trials.

To rely upon the previous findings of safety and effectiveness of the RLD, the ANDA applicant must demonstrate that its proposed generic product is bioequivalent to the RLD. In addition, the ANDA applicant must show that its proposed drug product is "the same as" the RLD in many other respects, including active ingredient, dosage form, strength, route of administration, and, with certain exceptions, labeling. The bioequivalence and "same labeling" requirements for ANDA approval are particularly relevant for purposes of this petition.

The FFDCA provides that a generic drug is bioequivalent to a RLD if:

> The rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the [RLD] when administered at the same molar dose of the therapeutic

> ingredient under similar experimental conditions in either a single dose or multiple doses . . .

21 U.S.C. § 355(j)(8)(B)(i).[33] Bioequivalence can be demonstrated through a variety of *in vivo* and/or *in vitro* tests depending upon the purpose of the study, the analytical methods available, and the nature of the drug product. 21 C.F.R. § 320.24(a). FDA regulations describe the following acceptable test methods in descending order of accuracy, sensitivity, and reproducibility: (1) *in vivo* PK test in humans measuring absorption into the bloodstream; (2) *in vivo* test in humans measuring urinary excretion; (3) *in vivo* PD tests in humans; (4) comparative clinical trials with safety and effectiveness endpoints; (5) *in vitro* studies, and (6) any other approach deemed adequate by FDA. *Id*. § 320.24(b). ANDA applicants generally are required to use the "most accurate, sensitive, and reproducible approach available" among those specified in the regulations. *Id*.

In addition to meeting the bioequivalence requirement, an ANDA generally cannot be approved unless the proposed generic product has the same labeling as the RLD. 21 U.S.C. § 355(j)(4)(G); 21 C.F.R. §314.127(a)(7). This requirement helps to ensure that an approved generic drug product is as safe and effective as the RLD when generic substitution occurs. Although there are some exceptions to this general rule, they are narrow. In particular, a generic drug can have different labeling from the RLD if: (a) the ANDA is submitted pursuant to a suitability petition; (b) labeling is omitted because it is protected by exclusivity or a listed patent; or (c) minor labeling changes reflect permissible differences between the ANDA and its RLD (*e.g*., different inactive ingredients, container-closure systems, shape or color). 21 U.S.C. §§ 355(j)(2)(A)(v), (j)(2)(A)(viii), (j)(4)(G); 21 C.F.R. §§ 314.94(a)(8)(iv), 314.127(a)(7).[34] *Labeling changes that introduce new or increased risks or that otherwise render the proposed generic less safe or effective than the RLD are not permitted and will result in refusal to approve the ANDA.* 21 C.F.R. §314.127(a)(7).[35]

Drug products that satisfy the approval requirements under section 505(j) of the FFDCA, including the bioequivalence and "same labeling" requirements, generally will be considered by FDA to be "therapeutically equivalent" to the RLD. Drug products are considered to be therapeutic equivalents only if they are "pharmaceutically equivalent"[36] and can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling (which would include the demonstration of bioequivalence). 21 C.F.R. § 314.3 (definition of "therapeutic equivalents"). Thus, products classified as therapeutically equivalent

[33] FDA's regulations similarly define "bioequivalence" as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." 21 C.F.R. § 320.1(e).

[34] *See also* FDA Response to Xyzal Petition, Docket No. FDA-2010-P-0545, pp. 7-8 (Feb. 24, 2011).

[35] S*ee also* FDA Response to King Petition, Docket No. FDA-2009-P-0040, at 7 (July 29, 2009).

[36] The term "pharmaceutically equivalent" is defined as "drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, *i.e.,* the same salt or ester of the same therapeutic moiety, …; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates." 21 C.F.R. § 314.3.

can be substituted with the expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed brand name drug.[37]

C. FDA Should Require Bioequivalence Testing in Hepatically Impaired Subjects

FDA should require that any ANDA for a generic version of ZOHYDRO ER contain data and information demonstrating that the proposed generic product is bioequivalent to ZOHYDRO ER in hepatically impaired subjects before granting final approval. Testing in this special population 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, *i.e.*, without dose adjustment. In the absence of such testing, there can be no assurance that a generic product will have the same clinical effect and safety profile as ZOHYDRO ER when administered to patients with hepatic impairment.

Although FDA generally recommends that bioequivalence testing be conducted in healthy subjects,[38] additional testing in hepatically impaired subjects is necessary in this case to detect differences in formulation between ZOHYDRO ER and a proposed generic product that may be clinically significant for this special population. It is well-established that hepatic impairment significantly affects the pharmacokinetics of opioids, including hydrocodone, because of the liver's major role in opioid metabolism. For example, in a clinical study of immediate-release hydromorphone tablets, *four-fold increases* in plasma levels of hydromorphone were observed in patients with moderate hepatic impairment.[39] Likewise, in a study of an extended-release formulation of hydrocodone (*i.e.*, VANTRELA ER) that differs from ZOHYDRO ER, **"[t]otal systemic exposure to hydrocodone was up to 70% higher in subjects with … moderate hepatic impairment than in subjects with normal organ function."**[40] As a result, most extended-release opioid products require significant dose reductions for patients with hepatic impairment, and many are not recommended for use, or are even contraindicated, in patients with severe hepatic impairment (see section II.A.2 above).

ZOHYDRO ER is clinically different. It employs a special formulation that unexpectedly minimizes the pharmacokinetic differences between normal subjects and those with hepatic impairment. The contrast between ZOHYDRO ER and other extended-release opioid products is perhaps most evident in comparisons to VANTRELA ER, another approved extended-release hydrocodone product that, like ZOHYDRO ER, is intended for 12-hour, twice-daily dosing. In a pharmacokinetic study, VANTRELA ER resulted in significantly increased total exposure (70%) and C_{max} (30%) in patients with moderate hepatic impairment versus healthy patients.[41] These increases were deemed to be clinically significant and resulted not only in significant dosage adjustments for mild or moderate hepatic impairment (50% reduction) but also in a specific labeling recommendation *against* use in patients with severe hepatic impairment.[42]

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[37] FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations*, p. viii (39th ed., 2019).
[38] *FDA Guidance: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* [Draft], p. 3 (Dec. 2013).
[39] EXALGO Prescribing Information, §8.6.
[40] Bond article (emphasis added).
[41] VANTRELA ER Prescribing Information, § 12.3.
[42] VANTRELA ER Prescribing Information, § 2.3.

ZOHYDRO ER, by contrast, produced much lower increases in total systemic exposure (26%) and C_{max} (10%) when administered to patients with moderate hepatic impairment.[43] These increases were so modest, in fact, that FDA determined they were not clinically significant.[44] Unlike VANTRELA ER, therefore, ZOHYDRO ER is labeled for use in patients with mild to moderate hepatic impairment *without any dosage adjustment*. This allows such patients to be dosed and titrated more predictably (and thus safely) by their physicians. *See* Gharibo Decl. ¶¶ 14-16; *see* Antell Decl. ¶ 13. Moreover, ZOHYDRO ER is recommended for use even in patients with *severe* hepatic impairment if initiated at the lowest available dose (10 mg) and then titrated and monitored carefully.

These striking pharmacokinetic differences between similar twice-daily, extended-release hydrocodone products strongly suggests that the effects of hepatic impairment on the pharmacokinetics of ZOHYDRO ER are related to the *formulation* itself rather than to the active ingredient hydrocodone bitartrate. *See* Antell Decl. ¶ 9. Indeed, because of the role of the liver in the metabolism of hydrocodone, one would expect a hydrocodone product to result in significantly increased blood levels in hepatically impaired patients versus healthy subjects, as occurs with VANTRELA ER. *See* Gharibo Decl. ¶¶ 12-16. The ZOHYDRO ER formulation, however, appears to modify the usual pharmacokinetic profile of hydrocodone by limiting the expected increases in total systemic exposure in patients with hepatic impairment to levels that are not clinically significant. This result is unexpected and, as demonstrated above, highly unusual.

Because the pharmacokinetic profile of ZOHYDRO ER in hepatically impaired subjects appears to be formulation-based, the effects of hepatic impairment on the bioequivalence of a proposed generic product cannot be predicted based upon studies in healthy subjects alone. The wide and unexpected variations between ZOHYDRO ER and VANTRELA ER – and between ZOHYDRO ER and other extended-release opioid products – in hepatically impaired patients underscores that conclusion. Different formulations can exhibit significantly different pharmacokinetic profiles in subjects with hepatic impairment compared to healthy subjects, and there is no way to predict or know this without conducting bioequivalence tests in subject to hepatic impairment. Accordingly, bioequivalence studies in healthy subjects, as recommended in the current draft Bioequivalence Guidance, must be supplemented by studies in subjects with hepatic impairment. Bioequivalence testing in this special population is necessary because formulation differences that could impact hepatically impaired patients would not be expected to be detected by bioequivalence studies in healthy subjects alone.

This additional testing is particularly critical because of the significant safety risks involved with administering opioids to hepatically impaired patients, including the risk of respiratory depression and death from overdosing. ZOHYDRO ER carries a boxed warning, and other warnings and precautions, regarding the risk of life-threatening respiratory depression from even a single dose.[45] This can be caused by acute overdosage of hydrocodone.[46] The labeling thus

[43] ZOHYDRO ER Prescribing Information, § 12.3.
[44] FDA, ZOHYDRO ER Summary Review, p. 11 (Oct. 25, 2013), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202880Orig1s000SumR.pdf.
[45] "Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death." ZOHYDRO Prescribing Information, § 5.3.
[46] ZOHYDRO Prescribing Information, § 10.

states that "[t]o reduce the risk of respiratory depression, *proper dosing and titration of ZOHYDRO ER are essential*. Overestimating the ZOHYDRO ER dose when converting patients from another opioid can result in fatal overdose with the first dose."[47]

If a proposed generic product with a different formulation fails to perform like ZOHYDRO ER in hepatically impaired patients, and instead performs like most other extended-release opioid products, it could create significant safety risks, including risks associated with overdose, such as life-threatening or fatal respiratory depression and increased risks of developing OUD. *See* Gharibo Decl. ¶¶ 17-19; *see* Antell Decl. ¶¶ 19-25. This is because patients with hepatic impairment who receive a generic product without any dosage adjustments likely would experience dangerous increases in total systemic hydrocodone exposure – similar to those seen with other extended-release opioid products, such as VANTRELA ER (*i.e.*, ~70% higher AUC and ~30% higher Cmax). *See* Gharibo Decl. ¶ 18; *see* Antell Decl. ¶ 19. Moreover, because such a generic will be approved as "therapeutically equivalent" to ZOHYRDRO ER, neither the prescribing physician nor the dispensing pharmacist will know to alter the dose.

Because proper dosing of extended-release hydrocodone products is essential to its safe use, this type of overdosing in hepatically impaired patients could have dire safety consequences. This is especially important given that ZOHYDRO ER has been prescribed by physicians since 2015, and the unique hepatic profile has allowed physicians to use ZOHYDRO ER in their care continuum for the hepatically impaired patient. The unchecked substitution to a generic with unproven safety in hepatically compromised patients puts those patients in jeopardy.

The numbers are staggering and could affect millions of patients in the United States with hepatic impairment who have been prescribed an opioid. It has been estimated that approximately 15% of the population in the United States has chronic liver disease.[48] Among individuals with chronic liver disease, approximately 25% are prescribed an opioid drug product.[49] If one assumes that the United States population in 2019 currently is approximately 329,275,000 people, then approximately 12 million individuals with hepatic impairment could be prescribed a generic opioid product. Even if all 12 million are not candidates for a generic version of ZOHYDRO ER, Persion believes that the potential patient population that could be subjected to the overdose risks from a non-bioequivalent version of ZOHYDRO ER numbers in the millions. The risks are especially acute for elderly patients, patients with other acute conditions (such as renal impairment) and patients taking other drug products that depress the central nervous system. *See* Gharibo Decl. ¶¶ 24-27; *see* Antell Decl. ¶¶ 21-23. In sum, this is a massive risk.

The approval of a generic product that provides an "overdose" in hepatically impaired patients also could increase the rates of abuse, misuse and diversion of extended-release hydrocodone products. *See* Antell Decl. ¶ 25. Because such an overdose is more likely to increase the euphoric effects of the generic product in hepatically impaired patients, such patients are more

[47] ZOHYDRO Prescribing Information, § 5.3 (emphasis added).
[48] Younossi ZM, Stepanova M, Afendy M, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol* 2011;9:524–530. Abstract available at https://www.ncbi.nlm.nih.gov/pubmed/21440669 (Exhibit 7).
[49] Rogal SS, Winger D, et al. Pain and opioid use in chronic liver disease. *Dig Dis Sci*. 2013;58(10):2976-2985. Author manuscript available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3751995/ (Exhibit 8).

likely to actively seek out the generic version for abuse and misuse, thereby creating an increased risk of diversion. *See* Antell Decl. ¶ 25.

To avoid these significant safety risks, FDA must require all ANDA applicants for generic versions of ZOHYDRO ER to conduct bioequivalence testing in subjects with hepatic impairment to ensure that the generic product performs the same as ZOHYDRO ER in such patients. Although Persion is not aware of any prior situation in which FDA has required bioequivalence testing in a special patient population (absent safety concerns with administering the drug to healthy volunteers), it has become an area of growing concern in the last few years. Indeed, in 2016, FDA awarded a grant to Auburn University to assess therapeutic interchangeability between brand name and generic products in special patient populations.[50] The study found evidence of pharmacokinetic differences between brand and generic products in some special populations, including the need for dosage adjustments when taking a generic, and recommended additional studies to further explore the problem.[51]

In this case, the safety risks associated with an extended-release opioid product for patients with hepatic impairment are too significant to ignore or to wait for additional research. Moreover, the ongoing opioid crisis demands that the Agency exercise increased vigilance in approving generic versions of extended-release opioids. The nation is in the middle of a growing opioid epidemic.[52] In 2015 alone, more than 12 million people misused prescription opioids and more than 33,000 people died from opioid drug overdoses.[53] And these numbers are on the rise: in 2017, the number of opioid-related deaths was six times higher than in 1999.[54] Recent data suggest that more than two million Americans currently suffer from opioid-related substance-use disorders.[55] The approval of generic extended-release hydrocodone bitartrate products that increase the risk of overdose in patients with hepatic impairment – potentially affecting millions of such patients – will only exacerbate these grim statistics.

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[50] FDA, FY 2016 Awarded GDUFA Regulatory Research Contracts and Grants, Award U01FD005875, *available at* https://www.fda.gov/media/101243/download.

[51] Kiptanui Z. Ogbenna B et al. A Systemic Review of Generic Drug Substitution in Special Populations, Poster at the American Public Health Association Annual Meeting and Expo, Atlanta GA, *available at* https://www.impaqint.com/work/papers-and-presentations/systematic-review-generic-drug-substitution-special-populations.

[52] In October 2017, the President declared the opioid crisis a Nationwide Public Health Emergency. WHITE HOUSE, Press Release, *President Donald J. Trump is Taking Action on Drug Addiction and the Opioid Crisis* (Oct. 26, 2017), https://bit.ly/2VBqPfU. That same month, officials from the U.S. Department of Health and Human Services ("HHS") and the FDA testified before Congress and reiterated the administration's commitment to addressing the crisis. *See* SENATE HEALTH, EDUCATION, LABOR AND PENSIONS COMMITTEE, *The Federal Response to the Opioid Crisis: Written Testimony on Behalf of Witnesses from HHS* (Oct. 5, 2017), https://bit.ly/2RHrPjv. As part of its five-point strategy to address the opioid epidemic, HHS has pledged to "[i]mprove access to prevention, treatment, and recovery support services to prevent the health, social, and economic consequences associated with opioid addiction and to enable individuals to achieve long-term recovery." HHS, *Strategy to Combat Opioid Abuse, Misuse, and Overdose*, at 3, https://bit.ly/2R5bhPv.

[53] 2015 National Survey on Drug Use and Health (SAMSHA); Monthly Morbidity Weekly Report (MMWR), 2016; 65(50-51); 1445-1452 (Center for Disease Control).

[54] CENTERS FOR DISEASE CONTROL AND PREVENTION, *Opioid Overdose: Understanding the Epidemic* (Dec. 19, 2018), https://bit.ly/2jEOHfs.

[55] FDA 158, 162; *see also* NATIONAL INSTITUTE ON DRUG ABUSE, *Opioid Overdose Crisis*, https://bit.ly/2j6YEE1 (last updated Jan. 2019).

FDA has taken a number of actions to address the opioid crisis, including issuing a draft guidance in June 2019 on considerations for the benefit-risk assessment of new opioid analgesic drugs.[56] Although the Draft Guidance applies specifically to new drug applications, the principles announced therein are equally applicable to the approval of generic drugs. For example, FDA has stated that it will consider whether the "formulation and/or excipients pose risks to patients" and whether there are "characteristics of the drug that increase or decrease the risk for respiratory depression, sedation, or development of opioid use disorder in patients."[57] The Agency also states that it will consider whether the benefit-risk balance may be unfavorable in special populations.[58] In this case, the specific formulation of a proposed generic could pose special risks to patients with hepatic impairment by increasing the risk for respiratory depression, sedation, or development of opioid use disorder if the generic drug does not have the same pharmacokinetic profile in subjects with hepatic impairment.

When issuing the Draft Guidance, FDA stated that when regulating opioids, "any action taken by the agency should be considered in light of the opioid crisis."[59] This policy is sound and furthers the interests of the public health. However, it cannot and should not be limited to FDA's regulation of new brand name opioid drug products. Rather, FDA must apply it equally to approval decisions affecting generic opioid drug products. In this case, FDA must act now to ensure that a generic version of ZOHYDRO ER will be safe for use in patients with mild or moderate hepatic impairment *without dosage adjustment* and safe for use in patients with severe hepatic impairment with the dosage adjustment recommended in ZOHYDRO ER's labeling. This requires supplementing the current bioequivalence study requirements in healthy volunteers with additional testing requirements in subjects with hepatic impairment.

This action is particularly important because FDA is the only party that can protect patients from the above-described safety risks. For the reasons discussed below, a generic applicant cannot modify the labeling of its generic drug even if it becomes aware of new safety risks, even new risks that apply solely to its generic drug. *See Pliva, Inc. v. Mensing*, 564 U.S. 604 (2011) (deferring to FDA interpretation concluding that labeling changes unilaterally made to strengthen a generic drug's warning label would violate statutory and regulatory "same labeling" requirements). The generic labeling typically must match the RLD's labeling. But if the safety issue only applies to the generic drug, the RLD's labeling typically will not address it. *See Wyeth v. Levine*, 555 U.S. 555 (2009) (requiring RLD manufacturer to update labeling to address newly discovered risks). Consequently, the only way to protect hepatically impaired patients against the serious risks described above and in the attached declarations is for FDA to require bioequivalence testing in subjects with hepatic impairment to ensure that the generic performs the same as the RLD in this special patient population.

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[56] FDA, Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework [draft] (June 2019), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/opioid-analgesic-drugs-considerations-benefit-risk-assessment-framework-guidance-industry ("Draft Benefit-Risk Guidance").

[57] Draft Benefit-Risk Guidance, p. 4.

[58] Draft Benefit-Risk Guidance, p. 6.

[59] Statement on the FDA's benefit-risk framework for evaluating opioid analgesics (June 20, 2019), *available at* https://www.fda.gov/news-events/press-announcements/statement-fdas-benefit-risk-framework-evaluating-opioid-analgesics.

D. FDA Should Require Any ANDA to Contain ZOHYDRO ER's Approved Labeling Instructions Regarding Administration of the Drug to Patients With Hepatic Impairment

In its February 25, 2016 Citizen Petition, Pernix explained why 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 removal of such information from the labeling would deny physicians and patients critical information necessary to the safe and effective use of generic hydrocodone bitartrate extended-release capsules in violation of 21 C.F.R. 314.127(a)(7).

Likewise, FDA cannot approve a generic version that *revises* such labeling instructions without violating the "same labeling" requirement set forth in the statute and FDA regulations. For example, if FDA were to determine that a proposed generic product requires dose adjustment in patients with mild or moderate hepatic impairment, or should not be used in patients with severe hepatic impairment, the Agency could not approve an ANDA for such a generic product with labeling reflecting those dosing modifications because it would have different labeling than ZOHYDRO ER. 21 U.S.C. § 355(j)(4)(G); 21 C.F.R. §314.127(a)(7). Moreover, this different labeling would create increased risks of overdosage and death because patients switched to the generic will assume they can use it just like ZOHYDRO ER, *i.e.*, without dose adjustment.[60]

Accordingly, for the reasons set forth in the Pernix petition, which is incorporated herein by reference, FDA should require any ANDA for generic hydrocodone bitartrate extended-release capsules to contain the same labeling instructions as the RLD concerning administration of the drug to patients with mild or moderate hepatic impairment.

E. Conclusion

In summary, FDA should require all ANDAs for generic versions of ZOHYDRO ER to include data from bioequivalence studies conducted in patients with hepatic impairment. Without such testing, there can be no assurance that a generic product will be safe for use in patients with hepatic impairment when used as recommended in ZOHYDRO ER's labeling. In addition, FDA should require any such ANDA to contain the same labeling instructions regarding the administration of hydrocodone bitartrate extended-release capsules to patients with hepatic impairment as ZOHYDRO ER.

III. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

IV. Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

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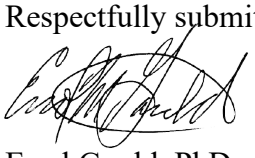
[60] *See* King Petition Response, p. 7 (refusing to approve a generic product if it cannot be substituted for the prescribed brand product without additional physician intervention or retraining).

V. Certification

I certify that, to my best knowledge 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, 2019 (Declarations of Drs. Antell and Gharibo); June 21, 2019 (FDA Draft Guidance on Benefit-Risk Assessment Framework); April 30, 2019 (Draft Bioequivalence Guidance for Hydrocodone Bitartrate); July 1, 2019 (comparison of labeling language among ER opioid products); April 30, 2019 (journal articles regarding opioid pharmacokinetics); April 30, 2019 (journal articles regarding opioid risks); April 30, 2019 (journal articles regarding prevalence of chronic liver disease and opioid use). 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: Persion Pharmaceuticals LLC. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



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