DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 1 6 2013

Jennifer A. Davidson
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Re: Docket No. FDA-2013-P-0425

Dear Ms. Davidson and Mr. Mathers:

This letter responds to the citizen petition (Petition) that you submitted on behalf of Rhodes Technologies (Rhodes or the Petitioner), which was received by the Food and Drug Administration (FDA or the Agency) on April 10, 2013. The Petition requests that FDA take the following actions with respect to the 14-hydroxycodeinone impurity in oxycodone hydrochloride (oxycodone HCl) active pharmaceutical ingredient (API) used in single-entity oxycodone products:

(1) Maintain the current limit of not more than (NMT) 0.001% of API (10 parts per million (ppm)) as the acceptable level of the 14-hydroxycodeinone impurity in oxycodone HCl API used in single-entity oxycodone products; and

(2) If the Agency considers relaxing the NMT 0.001% of API limit for 14-hydroxycodeinone used in single-entity oxycodone products: (a) publicly announce that the Agency is considering such a change; and (b) prior to adopting any change to the current limit, establish a public process through which the Agency solicits and considers the views of interested parties.

FDA has carefully considered the information submitted in your petition and other relevant data available to the Agency. Based on our review of these materials, and for the reasons described below, your petition is denied.

I. BACKGROUND

A. Oxycodone HCl

Oxycodone HCl is a potent opioid agonist, marketed in various forms since approximately 1926. Its principal therapeutic action is analgesia. It is a Schedule II controlled substance, with abuse liability similar to other opioid analgesics. The API in oxycodone and certain other opioid products derived from thebaine contains 14-hydroxycodeinone, an impurity that includes an α,β-unsaturated ketone (ABUK) moiety.

The Agency considers the ABUK moiety to be a structural alert[1] for potential genotoxicity and mutagenicity.[2] Exposure to genotoxic or mutagenic compounds can result in the formation of tumors and cancer in patients.

Rhodes is a subsidiary of Purdue Pharma LP (Purdue), and is the supplier of oxycodone HCl API to Purdue, for use in the manufacture of OxyContin (oxycodone HCl extended release) Tablets, an oral formulation of oxycodone approved under new drug application (NDA) 22-272. Rhodes also supplied oxycodone HCl API for Purdue's original formulation of OxyContin (NDA 20-553), the marketing of which has been discontinued, and the NDA withdrawn.[3]

B. History of FDA's Policy Related to ABUK Impurities

In 2002, during review of an individual oxycodone product's synthesis, FDA noted the presence of the ABUK-containing impurity 14-hydroxycodeinone, an intermediate in the synthetic pathway to oxycodone. Some ABUKs have been demonstrated to be reactive with DNA, resulting in potential genotoxicity and mutagenicity, as noted above.[4] FDA also determined that 14-hydroxycodeinone tested positive in an *in vitro* chromosome aberration assay,[5] further confirming its potential genotoxic effect.[6] Potentially genotoxic compounds present a safety concern, as they could result in the formation of tumors and cancer in patients exposed to the impurities. Since the discovery of ABUKs in oxycodone products in 2002, the Agency has been working with applicants and Drug

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[1] A "structural alert" is a "[c]hemical grouping which is known to be associated with a particular type of toxic effect, e.g. mutagenicity." *See* IUPAC Glossary of Terms Used in Toxicology, available at http://sis.nlm.nih.gov/enviro/iupacglossary/glossarys.html.

[2] *See e.g.*, Eder, E. C Hoffman, H Bastian, et al., 1990, Molecular mechanisms of DNA damage initiated by alpha, beta-unsaturated carbonyl compounds as criteria for genotoxicity and mutagenicity, Environ. Health Perspect., 88, 99-106; Eder, E, S Scheckenbach, C Deininger, et al., 1993, The possible role of alpha, beta-unsaturated carbonyl compounds in mutagenesis and carcinogenesis, Toxicol. Lett., 67, 87-103.

[3] 78 FR 48177 (August 8, 2013).

[4] *Id.*

[5] An *in vitro* chromosome aberration test identifies agents that cause structural changes in chromosomes, and that are therefore potentially genotoxic or carcinogenic. Mammalian cells are cultured *in vitro*, exposed to a test substance, harvested, and analyzed to determine the frequency of structural chromosome aberrations (e.g., chromosomal deletions, fragments, intrachanges, and interchanges). Evans, H.J. Cytological Methods for Detecting Chemical Mutagens. Chemical Mutagens, Principles and Methods for their Detection, Vol. 4, Hollaender, A. Ed. Plenum Press, New York and London, pp. 1-29 (1976); *see also,* 40 CFR 799.9537.

[6] Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research (CDER), FDA to P. Stassburger and E. Mahony (March 24, 2008) at 2, Docket No. 2007-P-0183.

Master File (DMF) holders to lower the levels of 14-hydroxycodeinone in oxycodone APIs.[7]

FDA's policy for potentially genotoxic compounds is outlined in FDA's 2008 draft guidance for industry *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* (Genotoxic Impurities Draft Guidance).[8] That guidance recommends an exposure level of NMT 1.5 micrograms (mcg) per person per day for impurities that contain a structural alert for genotoxicity or mutagenicity, or that have tested positive in genotoxicity or mutagenicity studies.[9] According to the draft guidance, any impurity found at a level below this threshold generally should not need further safety qualification for genotoxicity and carcinogenicity concerns.[10]

In general, FDA recommends that the level of impurities in a drug substance should be controlled according to the international model adopted in the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for industry on impurities in new drug substances and

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[7] FDA does not approve an API. Instead, API manufacturers may submit a DMF for the drug substance (API) to the Agency. *See* 21 CFR 314.420. A DMF is a submission to FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs or drug substances. An NDA or ANDA applicant may reference a DMF for a drug substance in its application, and FDA will deem the API/DMF acceptable (or deficient) for use in the particular NDA or ANDA. In cases in which a DMF holder is manufacturing oxycodone HCl API, the relevant information and specifications related to the API (including the level of 14-hydroxycodeinone) are contained in the DMF. As a result, FDA worked with both applicants and DMF holders to lower the levels of the 14-hydroxycodeinone impurity in oxycodone HCl API. However, because FDA does not approve DMFs, we cannot prevent manufacturers from submitting DMFs for oxycodone HCl API that contain more than 0.001% 14-hydroxycodeinone; we can only refuse to approve, as appropriate, an NDA or ANDA that references such a DMF.

[8] *Available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079235.pdf.

[9] The NMT 1.5 mcg/day per person exposure limit is based on a "threshold of toxicological concern" (TTC). The TTC refers to a threshold level, below which exposure to a compound does not pose a significant risk for carcinogenicity or other toxic effects. The TTC recognizes that complete elimination of a genotoxic impurity is generally impossible, and thus seeks to find a level of exposure that can be considered safe (based on standards for assessing lifetime cancer risk), but is also technologically feasible. Genotoxic Impurities Draft Guidance at 5, 7-9.

[10] *Id.* at 7.

products[11] and FDA's relevant guidances for industry on impurities in drug substances and products.[12] The ICH and FDA guidances are collectively referred to as the "Impurities Guidances" in this document. The Impurities Guidances provide a paradigm for control of impurities, and set specific thresholds for reporting, identification, and qualification for ordinary impurities.[13] They also describe a risk-based model for establishing these thresholds, stating, for example, that "higher or lower thresholds for qualification of impurities can be appropriate for some individual drugs, based on scientific rationale and level of concern, including drug class effects and clinical experience" [14] and "lower thresholds can be appropriate if the impurity is unusually toxic."[15] Consequently, because potentially genotoxic and carcinogenic impurities may be "unusually toxic," these impurities are subject to the lower qualification thresholds in the Genotoxic Impurities Draft Guidance.

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[11] ICH guidance for industry *Q3A(R2) Impurities in New Drug Substances* (June 2008), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127984.pdf (ICH Q3A(R2)); ICH guidance for industry *Q3B(R2) Impurities in New Drug Products* (July 2006), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128033.pdf (ICH Q3B(R2)). *See also*, ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000), *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm134966.htm (ICH Q6A). The ICH Q3 series of guidances have been adopted by FDA as Agency guidances for industry.

[12] FDA guidance for industry *ANDAs: Impurities in Drug Substances* (June 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079235.pdf (ANDA Drug Substance Impurities Guidance); FDA guidance for industry *ANDAs: Impurities in Drug Products* (November 2010), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf (ANDA Drug Product Impurities Guidance); FDA guidance for industry *NDAs: Impurities in Drug Substances* (February 2000), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070577.pdf (NDA Impurities Guidance).

[13] The reporting threshold is a limit above which the impurity should be reported (listed in the specification for the product). The identification threshold is a limit above which an impurity should be identified (i.e., the applicant should structurally characterize the impurity). The qualification threshold is a limit above which the impurity must be qualifed. Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. ICH Q3A(R2) at 9-10; ICH Q3B(R2) at Glossary 1-2. *See* ANDA Drug Substance Impurities Guidance at 2, 4; ANDA Drug Product Impurities Guidance at 2, 4; NDA Impurities Guidance.

[14] ICH Q3A(R2) at 7; ICH Q3B(R2) at 6. *See* ANDA Drug Substance Impurities Guidance at 5; ANDA Drug Product Impurities Guidance at 5; NDA Impurities Guidance.

[15] ICH Q3A(R2) at 11, note 3; ICH Q3B(R2) at Attachment 1, note 2. *See* ANDA Drug Substance Impurities Guidance at 8; ANDA Drug Product Impurities Guidance at 7; NDA Impurities Guidance.

Specifically, the Impurities Guidances recommend that above specified threshold limits, impurities should be qualified for safety,[16] and that acceptance criteria[17] should be "set no higher than the level that can be justified by safety data" and should also be consistent with "the level achievable by the manufacturing process and the analytical capability."[18] If the impurity is at or below the recommended qualification threshold, the Impurities Guidances indicate that the impurity needs no further safety qualification.[19]

The Agency has outlined the specific application of its impurities policy with respect to 14-hydroxycodeinone in opioid products in responses to several citizen petitions since 2008.[20] Initially we established higher acceptable limits for ABUKs in APIs, subsequently lowering these limits as compliance became technologically feasible, and correspondingly increasing our expectations of applicants seeking approval of opioid products. Most recently, FDA clearly stated its current policy in response to a citizen petition submitted in 2011.[21] In that document, the Agency reiterated that, prior to approval, we expect all applicants for single-entity opioid drug products, including single-entity oxycodone HCl products, to reduce ABUK impurities to acceptable levels (generally 10 ppm),[22] or to submit toxicology studies confirming that the impurities are not expected to be genotoxic or mutagenic.[23] This NMT 0.001% level is consistent with

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[16] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. ICH Q3A(R2) at 6; ICH Q3B(R2) at 6; ANDA Drug Substance Impurities Guidance at 4; ANDA Drug Product Impurities Guidance at 4; *see* NDA Impurities Guidance.

[17] Acceptance criteria are numerical limits, ranges, or other suitable measures indicating an acceptable level of an impurity in a drug product or API. ICH Q6A, Glossary.

[18] ICH Q3A(R2) at 6. *See* ICH Q3B(R2) at 6; ANDA Drug Substance Impurities Guidance at 4-5; ANDA Drug Product Impurities Guidance at 4-5; NDA Impurities Guidance.

[19] *Id.*

[20] Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research (CDER), FDA, to P. Stassburger and E. Mahony (March 24, 2008), Docket No. 2007-P-0183 (Purdue Response); Letter from J. Woodcock, M.D., Director, CDER, FDA, to R. Barto (November 8, 2010), Docket No. 2010-P-0243 (Endo Response); Letter from J. Woodcock, M.D., Director, CDER, FDA, to D. Rosen (November 21, 2011), Docket No. 2011-P-0433 (Lehigh Response). Given the level of detail in the three prior citizen petition responses, we see no need to explain at length in this response the development of the ABUK policy over the last decade. The Lehigh letter, in particular, includes a complete explanation of events on pages 6-7.

[21] Lehigh Response at 2; *see also*, Endo Response at 5.

[22] The acceptance criterion of NMT 10 ppm (0.001%) applies to oxycodone HCl API used in single-entity oxycodone drug products. An acceptance criterion of NMT 100 ppm (0.01%) is adequate for oxycodone HCl API used in combination oxycodone drug products (e.g., oxycodone and acetaminophen combinations).

[23] Lehigh Response at 2; *see also*, Endo Response at 5.

FDA's general approach to potentially genotoxic impurities, as explained in the Genotoxic Impurities Draft Guidance.[24]

C. Recent Data on the Safety of 14-Hydroxycodeinone

The Petition provided information on two separate studies concerning the safety of 14-hydroxycodeinone. The first study is documented in a poster presented at the Genetic Toxicology Association Meeting in October 2012 by employees of Janssen Pharmaceuticals, Inc., and Noramco Inc. (Petition Exhibit A). The poster describes the results of four toxicology studies assessing the genotoxicity of 14-hydroxycodeinone. According to the poster presentation, the overall findings of the study conclude that "14-hydroxycodeinone is not a genotoxic agent. Therefore, specification levels regarding 14-hydroxycodeinone levels do not need to be controlled from a genotoxicity standpoint" (Id.). To FDA's knowledge, the data and results from the studies described in the poster have not been published in a peer-reviewed scientific journal.

The second study is a publication in *Proceedings of the National Academy of Sciences of the USA* (PNAS) by Adam Wolpaw, Brent Stockwell, and colleagues at Columbia University (Petition Exhibit B.3) (Wolpaw and Stockwell study).[25] The publication describes the efforts of Drs. Wolpaw and Stockwell and their colleagues to categorize the mechanisms of xenobiotic-induced cell death via a method they refer to as "modulatory profiling." The goals of the experiments were to: 1) gain a better understanding of mechanisms mediating cell death; and 2) predict the potential cytotoxic mechanisms and potencies of certain test compounds to identify compounds with relevant mechanisms of action that could serve as viable therapeutic drug candidates. The study was not intended to specifically evaluate the safety of impurities; however, the study did test several opioid impurities, including 14-hydroxycodeinone, and indicates that 14-hydroxycodeinone is a cytotoxic agent, even at low concentrations.[26]

II. DISCUSSION

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[24] The Genotoxic Impurities Draft Guidance recommends an exposure of NMT 1.5 mcg per person per day for impurities that contain a structural alert for genotoxicity or mutagenicity. Converting the TTC of 1.5 mcg/day to a percentage-based impurity limit in API for opioids would require setting the ABUK acceptance criterion to NMT 0.0001% of API, which may not be technically achievable. Lehigh Response at 6-7. FDA stated in the Lehigh Response that although it is continuing to work with sponsors to reach the 1.5 mcg/day per person exposure limit, the NMT 0.001% of API limit is deemed acceptable, because it is as low as reasonably possible. Lehigh Response at 7. The Agency considers this limit in line with the Genotoxic Impurities Draft Guidance, given that the guidance encourages a "flexible approach...informed by the feasibility of controlling impurity levels and the capabilities of the current process." Genotoxic Impurities Draft Guidance at 12.

[25] Wolpaw A J, K Shimada, R Skouta, et al., 2011, Modulatory Profiling Identifies Mechanisms of Small-Molecule Induced Cell Death, *Proc Natl Acad Sci USA* 108:E771-E780.

[26] Wolpaw and Stockwell Study at p. 2 of Supplementary Text.

A. FDA Intends to Maintain Its Current Policy With Respect to Appropriate Levels of 14-Hydroycodeinone in Oxycodone HCl API

The Petition requests that we enforce a strict limit of NMT 0.001% (10 ppm) of 14-hydroxycodeinone in oxycodone HCl API approved for use in single-entity oxycodone products. The petitioner argues that this strict limit is necessary because: 1) FDA's policy is to require applicants to limit impurities in API to "the lowest levels that can be consistently achieved in their synthesis, regardless of whether or not those impurities have been identified as harmful to humans" (Petition at 9); and 2) based on recent data, 14-hydroxycodeinone is "highly cytotoxic" and thus may continue to pose a safety risk to patients even if it is demonstrated to be non-genotoxic (Petition at 10).

For the reasons discussed below, FDA denies the petitioner's request to apply a strict NMT 0.001% limit of 14-hydroxycodeinone in oxycodone HCl API approved for use in single-entity oxycodone products. However, we will continue to maintain our stated policy with respect to appropriate levels of 14-hyroxycodeinone used in single-entity oxycodone HCl products: **the API must meet the NMT 0.001% limit for 14-hydroxycodeinone OR the applicant (or DMF holder) must submit appropriate data to qualify that 14-hyroxycodeinone is not genotoxic.**

If the applicant or DMF holder were to submit appropriate data qualifying 14-hydroxycodeinone as non-genotoxic, FDA would consider relaxing the NMT 0.001% limit for that specific API when used in finished single-entity oxycodone HCl products.[27] Under those circumstances, FDA would follow the Impurities Guidances for ordinary impurities and permit the API to contain 14-hydroxycodeinone at the levels for non-genotoxic compounds outlined in those documents, which are higher than 0.001% of API.

1. FDA's Policy With Respect to 14-Hydroxycodeinone Is Consistent With the Agency's General Impurities Policy

The Petitioner states that FDA's policy is to limit impurities in API to "the lowest levels that can be consistently achieved in their synthesis, regardless of whether or not those impurities have been identified as harmful to humans" (Petition at 9). Because manufacturers have demonstrated that the NMT 0.001% limit is feasible, the Petitioner argues that FDA must follow its impurities policy and limit 14-hydroxycodeinone to

[27] Each oxycodone HCl API that is used in an NDA or ANDA for a single-entity oxycodone HCl product must either meet the NMT 0.001% 14-hydroxycodeinone limit, or the applicant or DMF holder must submit data or adequate literature references qualifying the impurity as non-genotoxic. For example, an oxycodone DMF holder or applicant could submit to FDA for review data to support a finding that 14-hydroxycodeinone is not genotoxic. However, as long as those data remain proprietary, they may only be used by another DMF holder or applicant if that applicant or DMF holder has a letter of authorization from the owner of the data to reference the data. If the data is published in an appropriate format to allow substantive review by the Agency, all applicants and DMF holders would be permitted to reference the publication as evidence that 14-hydroxycodeinone is not genotoxic. Final determination of the adequacy of any publication to support an application can only be provided upon review of the submission.

NMT 0.001% of API, regardless of the specific safety risks of the product (Petition at 9-10).[28]

We disagree with the Petitioner's characterization of the Agency's general approach to impurities. We do not uniformly require impurities to be limited to the lowest levels that are technologically feasible, regardless of existing data. Rather, we follow the approach described in both the Genotoxic Impurities Draft Guidance and the ICH and FDA Impurities Guidances. Those guidances set general threshold safety levels for impurity qualification, but also note that lower thresholds may be justified for impurities with specific safety concerns, such as genotoxicity or carcinogenicity.[29] Likewise, the guidances indicate that higher qualification thresholds may also be appropriate when the level of concern for safety is less than usual based on factors such as patient population, drug class effects, and clinical considerations.[30] In addition, a higher impurity limit can be considered if there are adequate safety and/or clinical studies to support the proposed levels.[31] Alternative thresholds will be considered on a case-by-case basis.

The Impurities Guidances also clearly state that impurity levels should be tied to both safety and manufacturing capabilities: "acceptance criteria [for impurities] should be set no higher than the level that can be *justified by safety data* and should be consistent with the level achievable by the manufacturing process and analytical capability."[32] Furthermore, the Impurities Guidances allow for some flexibility in applying the qualification threshold in light of other factors (e.g., scientific rationale and level of concern, including drug class effects and clinical experience).[33] In other words, the threshold levels are recommended limits. When presented with safety data or other relevant information, the Agency may increase or decrease the qualification threshold for an impurity present in a specific product on a case-by-case basis.

More specifically, if the impurity is potentially genotoxic, FDA recommends a low impurity level in the drug product (or API) in accordance with the Genotoxic Impurities Draft Guidance. If a potentially genotoxic impurity has been demonstrated to be non-genotoxic, FDA treats the impurity as it would any other non-genotoxic/non-carcinogenic

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[28] FDA does not dispute that manufacturers have demonstrated that it is possible to manufacture oxycodone HCl API with NMT 0.001% 14-hydroxycodeinone.

[29] ICH Q3A(R2) at 11, note 3; ICH Q3B(R2) at Attachment 1, note 2. *See* ANDA Drug Substance Impurities Guidance at 8; ANDA Drug Product Impurities Guidance at 7; NDA Impurities Guidance.

[30] ICH Q3A(R2) at 7; ICH Q3B(R2) at 6. *See* ANDA Drug Substance Impurities Guidance at 5; ANDA Drug Product Impurities Guidance at 5; NDA Impurities Guidance.

[31] ICH Q3A(R2) at 6; *see* ICH Q3B(R2) at 6. *See* ANDA Drug Substance Impurities Guidance at 4-5; ANDA Drug Product Impurities Guidance at 4-5; NDA Impurities Guidance.

[32] *Id.*

[33] ICH Q3A(R2) at 7; ICH Q3B(R2) at 6. *See* ANDA Drug Substance Impurities Guidance at 5; ANDA Drug Product Impurities Guidance at 5; NDA Impurities Guidance.

impurity—i.e., subject to the reporting, identification, and qualification thresholds listed in the Impurities Guidances.

This is exactly the approach the Agency has taken, and will continue to maintain, with 14-hydroxycodeinone. It is consistent with our general and genotoxic impurities policies, and also with our treatment of potentially genotoxic impurities other than 14-hydroxycodeinone, including 14-hydroxymorphinone and codeinone, which are found in morphine and codeine API, respectively, and were identified as containing structural alerts for genotoxicity (ABUK moieties).[34]

FDA's long-standing policy with respect to 14-hydroxycodeinone, including any decision to relax the NMT 0.001% limit if presented with adequate data, is consistent with our general approach to impurities, as described above and as outlined in the Impurities Guidances. Although FDA agrees that, in general, impurities should be limited to the extent possible, we do not agree that our policy can be characterized, in the Petitioner's words, as uniformly attempting to "limit" impurities to the lowest level technologically feasible, regardless of safety concerns.[35] Our approach to impurities control takes into account the totality of the circumstances, including safety concerns, manufacturing capabilities, clinical experience with the product, and other factors. As such, our impurities policy does not necessitate, as the Petitioner contends, that we apply a strict and inflexible NMT 0.001% limit on 14-hydroxycodeinone simply because manufacturers have demonstrated that this level is technologically feasible. Instead, we intend to maintain our current policy with respect to 14-hydroxycodeinone as stated above. We therefore deny the Petitioner's request to impose a rigid NMT 0.001% limit without the possibility of relaxing the limit when presented with appropriate evidence.

2. The Wolpaw and Stockwell Study Is Not Persuasive Evidence to Support A Change in FDA's Current Policy With Respect to 14-Hydroxycodeinone

The Petitioner further argues that FDA should not relax the NMT 0.001% limit for 14-hydroxycodeinone, because recent data indicate that 14-hydroxycodeinone is "highly cytotoxic" at low concentrations. The Petitioner relies on the Wolpaw and Stockwell study, described above, for this conclusion, and includes in the Petition a declaration from Dr. Stockwell that FDA should enforce a NMT 0.001% limit for 14-hydroxycodeinone because he "does not believe that there would be any benefit to health of relaxing the limits on such a highly cytotoxic substance, the presence of which offers no public health benefit" (Petition Exhibit B, ¶ 22).

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[34] *See* Endo Response at 3 and 5.

[35] The policy that Petitioner suggests, which would focus solely on the lowest impurity level that was technologically feasible to achieve, would remove the incentive for a manufacturer to produce data that would show whether a higher level of that impurity was safe. Such a policy would also result in expenditures to reduce the level of an impurity – or block from the market producers that could not reduce that level – for no obvious purpose if the higher level had been shown to be safe.

FDA disagrees with the Petitioner's argument that the NMT 0.001% limit should be strictly enforced because 14-hydroxycodeinone is cytotoxic *in vitro*.

First, even if FDA were to relax the NMT 0.001% limit on 14-hydroxycodeinone after review of appropriate data demonstrating that the impurity is not genotoxic, 14-hydroxycodeinone would still be subject to certain tight controls—namely, the reporting, identification, and qualification thresholds in the Impurities Guidances. The paradigm developed in the Impurities Guidances is intended to control a patient's overall exposure to impurities (that are non-genotoxic) and, as explained below, was deemed to be adequate with respect to 14-hydroxycodeinone for many years before the discovery of the ABUK moiety and the imposition of the NMT 0.001% limit as a result of the potential for genotoxicity.

Second, Dr. Stockwell's finding that 14-hydroxycodeinone is cytotoxic is not surprising or novel. The Agency has been aware for many years that 14-hydroxycodeinone can induce cell death at the highest concentrations tested in *in vitro* chromosomal aberration assays. Cytotoxicity is also documented in the poster presentation by the Janssen and Noramco employees (Petition Exhibit A). Despite this knowledge, before the discovery of the ABUK moiety and the imposition of the policy that applicants must either meet the NMT 0.001% limit to control genotoxicity concerns or qualify the impurity for safety, FDA managed the impurity according to the Impurities Guidances (i.e., permitted 14-hydroxycodeinone at levels higher than 0.001% of API). At that point, 14-hydroxycodeinone had been present in some manufacturers' oxycodone HCl API for many years, such that the existing clinical experience with approved oxycodone HCl drug products was deemed adequate to support the safety of the impurity from a general toxicology perspective, if present at or below the qualification threshold levels outlined in the Impurities Guidances.

The Wolpaw and Stockwell publication confirms that 14-hydroxycodeinone is cytotoxic *in vitro*, but provides no evidence that this has *in vivo* or clinical implications that contradict the long history of safely marketing oxycodone HCl products with 14-hydroxycodeinone present at levels greater than 0.001% of API. Accordingly, neither the Wolpaw and Stockwell paper, nor Dr. Stockwell's affidavit, persuade the Agency to reconsider its approach to managing 14-hydroxycodeinone in oxycodone HCl API—we intend to continue our policy of requiring API to meet the NMT 0.001% limit, or be qualified as non-genotoxic. If 14-hydroxycodeinone is demonstrated to be non-genotoxic, FDA continues to believe that the paradigm for control of ordinary impurities in the Impurities Guidances is adequate from a safety standpoint, even in light of *in vitro* cytotoxicity concerns.

In summary, the Petitioner has not provided FDA with convincing evidence to depart from its long-standing policy with respect to 14-hydroxycodeinone—a policy that is consistent with FDA's general approach to controlling impurities in drug substances, and with our treatment of other compounds that are suspected to have genotoxic properties. FDA denies the Petitioner's request to apply a strict NMT 0.001% limit on the level of 14-hydryoxycodeinone in oxycodone HCl API used in single entity oxycodone HCl

products. Instead, FDA intends to maintain its current policy: the API must meet the NMT 0.001% limit for 14-hydroxycodeinone OR the applicant (or DMF holder) must submit appropriate data to qualify that 14-hyroxycodeinone is not genotoxic. If FDA determines that 14-hydroxycodeinone is not genotoxic, the acceptance criterion for 14-hydroxycodeinone in oxycodone HCl API may be controlled according to the Impurities Guidances.

B. FDA Will Not Create a New Venue for Public Input on 14-Hydroxycodeinone Levels in Addition to the Public Dockets for this Citizen Petition and for the Relevant Guidance Documents

The Petition requests that if the Agency considers relaxing the NMT 0.001% of API limit for 14-hydroxycodeinone in oxycodone HCl API, FDA should initiate a public process and invite comments on the scientific justification, if any, for the change (Petition at 12). The Petitioner argues that FDA announced its policy with respect to 14-hydroxycodeinone in three prior responses to citizen petitions,[36] which effectively function as a guidance document under the Agency's Good Guidance Practices (GGPs),[37] because they concern the "manufacturing and testing of regulated products," as well as the "evaluation or approval of submissions" (Petition at 13, citing GGPs).[38] The Petitioner further argues that relaxing the NMT 0.001% limit would be a significant change in policy that raises complex scientific issues (Petition at 14). As a result, this would constitute a "level 1 guidance document", and, therefore, necessitate an opportunity for "public participation" (Petition at 14, citing 21 U.S.C. 371(h)(1)(c)(i) and 21 CFR 10.115(c)(1) and (g)(1)). The Petitioner suggests that public participation could be achieved through a variety of means, such as publication of the Petition in the *Federal Register* with a request for public comment (Petition at 14).

FDA denies the Petitioner's request to create a new venue for public input prior to relaxing the NMT 0.001% limit for 14-hydroxycodeinone for several reasons. First, as discussed in the previous section, FDA is not changing its policy with respect to the 14-hydroxycodeinone impurity. As we have stated in two previous citizen petition responses, and again in this response, FDA's policy is as follows: oxycodone HCl API used in single-entity oxycodone HCl products must meet the NMT 0.001% limit for 14-hydroxycodeinone OR the applicant (or DMF holder) must submit appropriate data to qualify that 14-hyroxycodeinone is not genotoxic.[39] If a sponsor qualifies 14-

[36] See note 19, citing to the Purdue, Endo, and Lehigh Responses.

[37] The Food and Drug Administration Modernization Act (FDAMA) required that FDA "develop guidance documents with public participation" and promulgate a regulation describing "the policies and procedures of the Food and Drug Administration for the development, issuance, and use of guidance documents." 21 U.S.C. 371(h)(1)(A) and (h)(5). As a result of FDAMA, a final rule implementing the Agency's GGPs was published on September 19, 2000 (65 FR 56468). The GGPs are codified at 21 CFR 10.115.

[38] 21 CFR 10.115(b)(2).

[39] *See* note 19, citing to the Endo and Lehigh Responses.

hydroxycodeinone as non-genotoxic, FDA will regulate it according to the Impurities Guidances, and may therefore permit a level higher than 0.001%. Our response to this Petition does not alter or change that policy. As such, there is no requirement to create a new venue for public input on this issue, such as publishing a notice of this Petition in the *Federal Register* requesting public comment, or holding a public meeting on the topic.

Notwithstanding that FDA will not create a new venue for public comment on 14-hydroxycodeinone, we note that there are several existing mechanisms by which the public can offer input on this issue. For example, this Petition is a public document, assigned docket number FDA-2013-P-0425. Any citizen, company, organization, or other entity had the opportunity to submit a comment to the Petition docket while the Petition was pending. FDA reviews and considers all comments and supplements submitted to the petition docket when responding to citizen petitions. Although interested parties had more than four months to submit a comment to this Petition, no comments were submitted.

Furthermore, the Impurities Guidances and the Genotoxic Impurities Draft Guidance explain our general policy with respect to genotoxic and other impurities. Those documents are Agency guidance documents and are all subject to public comment, including comments discussing the application of the guidances to 14-hydroxycodeinone.[40] The Genotoxic Impurities Draft Guidance is still in draft form. The other guidance documents are now final; however, the public can comment on any guidance at any time.[41] Again, these dockets provide an opportunity for the public to offer input on appropriate levels of 14-hydroxycodeinone in oxycodone HCl API.

We also note that, while obtaining public comment on agency policies is appropriate, in the drug approval process the application of those policies to particular approval decisions is not a public process. This is because data that are developed by applicants or DMF holders to support approvals are in many cases proprietary. Just as FDA does not publicize and seek public comment on the data submitted by your client, Rhodes Technologies, in support of approval of the products that rely on its submissions, it is

[40] Comments on any FDA guidance may be submitted by visiting http://www.regulations.gov, entering the docket number for the relevant document, and following instructions for submitting electronic comments. The relevant guidances are assigned the docket numbers listed below. The citation for the *Federal Register* notice announcing the availability of the guidance, and providing additional information on submitting comments is also provided.

- ICH Q3A(R2): FDA-1994-D-0055 (formerly 94D-0325); 68 FR 6924 (Feb. 11, 2003)
- ICH Q3B(R2): FDA-1996-D-0048 (formerly 96D-0009); 68 FR 64628 (Nov. 14, 2003)
- ANDA Impurities Guidance (Drug Substances): FDA-1998-D-0021 (formerly 98D-0514); 74 FR 34359 (Jul. 15, 2009)
- ANDA Impurities Guidance (Drug Products): FDA-2010-D-0584; 75 FR 73108 (Nov. 29, 2010)
- NDA Impurities Guidance: FDA-1998-D-0277 (formerly 98D-1267); 65 FR 10097 (Feb. 25, 2000)
- Genotoxic Impurities Draft Guidance: FDA-2008-D-0629; 73 FR 76361 (Dec. 16, 2008).

[41] 21 CFR 10.115(g)(5).

unable to publicize and seek public comment on the data that your clients' competitors might submit to support approval of their products.

Given that FDA is not changing its policy with respect to how to determine the appropriate level of 14-hydroxycodeinone in products containing oxycodone HCl API, and the fact that opportunities for the public to comment on the Agency's 14-hydroxycodeinone policy, including this petition docket, were and are available, FDA is denying the Petitioner's request that FDA initiate a new public process inviting public comment on the issue.

III. Conclusion

For the reasons discussed above, the Petition is denied.

Sincerely,

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