KINSEY S. REAGAN
PETER R. MATHERS
ANTHONY L. YOUNG
ANNE V. MAHER
BONNIE A. BEAVERS
DANIEL R. DWYER
SCOTT M. LASSMAN
STACY L. EHRLICH
JENNIFER A. DAVIDSON
JAMES WILLIAM WOODLEE
CYNTHIA L. MEYER

LAW OFFICES
KLEINFELD, KAPLAN AND BECKER, LLP
1140 NINETEENTH STREET, N.W.
WASHINGTON, D.C. 20036-6606
TELEPHONE (202) 223-5120
FACSIMILE (202) 223-5619
www.kkblaw.com

OF COUNSEL:
WILLIAM J. HARDY

April 9, 2013

Via Hand Delivery

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

CITIZEN PETITION

Dear Sir/Madam:

The undersigned, on behalf of Rhodes Technologies ("Rhodes"), submit this Citizen Petition pursuant to 21 C.F.R. §§ 10.30, 10.115, Parts 210, 211, and 314, and Sections 505 and 701 of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 355 and 371. Rhodes is the approved supplier of oxycodone hydrochloride active pharmaceutical ingredient to Purdue Pharma L.P. ("Purdue") for use in the manufacture of OxyContin® (oxycodone hydrochloride extended-release) Tablets, a twice-a-day oral formulation of oxycodone covered by New Drug Application # 22-272. Rhodes was also an approved supplier of API for New Drug Application # 20-553 for the original formulation of OxyContin, which has been discontinued.

Due to safety concerns about 14-hydroxycodeinone, an impurity found in the active pharmaceutical ingredient ("API") oxycodone, FDA has for over ten years been requesting that manufacturers of oxycodone API reduce levels of 14-hydroxycodeinone in their products. Since at least 2010, the Agency has required, as a condition of approval, that sponsors seeking to market single-entity oxycodone products use API containing not more than ("NMT") 10 parts per million of 14-hydroxycodeinone, or submit data adequately qualifying the impurity for safety. In response to FDA requirements, several manufacturers have modified their commercial processes and now offer to supply oxycodone API containing NMT 10 ppm 14-hydroxycodeinone.

In the fall of 2012, data on the genotoxicity of 14-hydroxycodeinone were presented at a professional conference. While these data indicate that 14-

hydroxycodeinone may not be genotoxic, these data do not establish that levels greater than 10 ppm of 14-hydroxycodeinone should be allowed in API used in single-entity oxycodone drug products. As discussed below and in the accompanying expert declaration, the current NMT 10 ppm limit in oxycodone API for use in single-entitly drug products should be maintained for two reasons. First, in accordance with long-standing FDA policy, impurities in API should be limited to the lowest levels that can consistently be achieved in their synthesis, regardless of whether or not those impurities have been identified as carcinogenic or otherwise harmful. Second, 14-hydroxycodeinone is an electrophile which is highly reactive and toxic to cells. In fact, 14-hydroxycodeinone was the eighth most potent cytotoxic compound among approximately 70,000 compounds screened for testing in *in vitro* experiments published in *Proceedings of the National Academy of Sciences of the United States of America.* At the very least, FDA should not consider relaxing the current NMT 10 ppm limit without first initiating a public process soliciting comment on whether the totality of the scientific data pertaining to 14-hydroxycodeinone warrants such a change.

Action Requested

Rhodes requests that the Food and Drug Administration take the following actions with respect to14-hydroxycodeinone impurity in oxycodone HCl API approved by FDA for use in drug products:

(1) Maintain the current limit of NMT 0.001% of API (10 ppm) for the acceptable level of 14-hydroxycodeinone impurity in oxycodone HCl API approved by FDA for use in single-entity oxycodone drug products; and

(2) If the Agency considers relaxing the current limit of NMT 0.001% of API (10 ppm) for 14-hydroxycodeinone: (a) publicly announce that the Agency is considering such a change, and (b) establish a public process through which the Agency solicits and considers the views of interested parties, prior to adopting any change to the current limit of NMT 0.001% of API (10 ppm).

Statement of Grounds

I. Factual Background

A. Agency Requirements Concerning 14-Hydroxycodeinone

Opioid products, including oxycodone, that are derived from thebaine contain a structural alert for mutagenicity described as an α, β-unsaturated ketone ("ABUK"). The ABUK moiety has been demonstrated to be reactive with DNA, resulting in potential

genotoxicity and mutagenicity.[1] Because exposure to potentially genotoxic compounds could result in the formation of tumors and cancer, the FDA's policy is that potentially genotoxic substances should be assessed for their genotoxic potential or reduced to acceptable levels.

Over ten years ago, in 2002, FDA first confirmed the presence of an impurity containing an ABUK moiety in oxycodone: 14-hydroxycodeinone. Upon review of the literature, FDA determined that ABUKs (including 14-hydroxycodeinone) had the potential to be reactive with DNA, resulting in potential genotoxicity and mutagenicity. The Agency also determined that 14-hydroxycodinone tested positive in the *in vitro* chromosome aberration assay. Based on these data, the Agency concluded that 14-hydroxycodeinone was a clastogen, meaning it causes chromosomal damage which may lead to mutagenesis or carcinogenesis.[2]

Because 14-hydroxycodeinone is an intermediate in the synthesis of oxycodone, and not a degradation product, the Agency determined that lowering the level of this impurity would require changes to the API manufacturing process. Recognizing that most applicants seeking approval to market drug products purchase API from a third party and do not directly control the API manufacturing process, FDA requested that applicants work with their API suppliers to reduce the level of 14-hydroxycodeinone.

From 2002 to 2006, in private communications with applicants and API suppliers, the FDA requested that 14-hydroxycodeinone levels be lowered to NMT 0.01% of oxycodone API (100 ppm) when used in combination drug products, and to NMT 0.001% of oxycodone API (10 ppm) when used in single-entity oxycodone drug products.[3] Consistent with this approach, when Purdue sought approval from FDA in 2004 to use oxycodone HCl API manufactured by Rhodes[4] to manufacture Purdue's

---

[1] *See* Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. FDA to P. Strassburger and E. Mahony (March 24, 2008), Docket FDA-2007-P-0183, at p. 3, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2007-P-0183-0005 (*citing* Eder et al., Molecular mechanisms of DNA damage initiated by alpha, beta-unsaturated carbonyl compounds as criteria for genotoxicity and mutagenicity, Environ. Health Perspect., 88, 99-106 (1990); Eder et al., The possible role of alpha, beta-unsaturated carbonyl compounds in mutagenesis and carcinogenesis, Toxicol. Lett., 67, 87-103 (1993)).

[2] *See* Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. FDA to R. Barto (Nov. 8, 2010), Docket No. 2010-P-0243, p. 4, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2010-P-0243-0003.

[3] *See* Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. FDA to P. Strassburger and E. Mahony (March 24, 2008), Docket FDA-2007-P-0183, at pp. 3-4, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2007-P-0183-0005.

[4] Purdue and Rhodes are independent associated companies.

approved oxycodone HCl drug products, Purdue and Rhodes were informed that approval of the Rhodes API would be contingent on successfully addressing the presence of 14-hydroxycodeinone , *i.e.,* providing data establishing the safety of the impurity or reducing the level to NMT 10 ppm. Purdue and Rhodes agreed to an intermediate limit of 500 ppm of 14-hydroxycodeinone, and committed to FDA to develop process improvements to enable the consistent production of oxycodone HCl API meeting a specification of NMT 10 ppm. Purdue and Rhodes successfully followed through on their commitment, qualifying and submitting a request on November 12, 2004 for FDA approval to use Rhodes' API containing of NMT 10 ppm of 14-hydroxycodeinone. A supplemental application was approved by FDA on March 15, 2005, and since that date Rhodes has consistently supplied Purdue with oxycodone HCl API containing NMT 10 ppm 14-hydroxycodeinone. The innovative development work underlying Rhodes' improvement resulted in the issuance of U.S. patents that are co-owned by Rhodes, including patents listed in the Orange Book by Purdue for OxyContin.

During the 2002 to 2006 timeframe, the Agency continued to approve other products that did not contain oxycodone API meeting the established 100 ppm (combination products) and 10 ppm (single-entity products) limits, so long as applicants committed to an aggressive timeline to reduce 14-hydroxycodeinone to the requested levels. FDA determined that it was appropriate to afford manufacturers some flexibility in meeting the limits because different drug substance manufacturers employed different synthetic processes and faced different technical challenges as they implemented new processes to reduce the level of 14-hydroxycodeinone . Thus, during this time, oxycodone drug products with varying levels of 14-hydroxycodeinone continued to be approved.[5]

Starting in 2007, the Agency began advising applicants and API suppliers of even more stringent limits on impurities containing the ABUK moiety, including 14-hydroxycodeinone. Based on international standards for potentially genotoxic impurities, the FDA advised that the impurity specification should be set at the equivalent of NMT 1.5 mcg/day for impurities that contain a structural alert for genotoxicity or carcinogenicity, or have tested positive in genotoxicity or carcinogenicity studies.[6] The

---

[5] *See* Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. FDA to P. Strassburger and E. Mahony (March 24, 2008), Docket FDA-2007-P-0183, at p. 4, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2007-P-0183-0005.

[6] *See* Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. FDA to P. Strassburger and E. Mahony (March 24, 2008), Docket FDA-2007-P-0183, at p. 5, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2007-P-0183-0005; Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. FDA to D. Rosen, B.S. Pharm., J.D. (Nov. 21, 2011), Docket No. FDA-2011-P-0433, p 6, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0433-0005.

rationale for this more stringent limit was detailed in a 2008 draft guidance.[7] FDA advised Purdue and Rhodes of this new limit in the course of its review of NDA # 22-272 for reformulated OxyContin.

For most drug products, the percentage limit for impurities in API may be calculated using the maximum daily dose of the product. In the case of single-entity opioids that typically have no established maximum daily dose and may be administered in increasingly higher doses, it is difficult to calculate a percentage limit on impurities using the generally applicable 1.5 mcg/day impurity intake limit. The FDA has, however, determined a maximum theoretical dosage per day ("MTDD") of 1.5 grams/day for single-entity oxycodone products. At this very high 1.5 grams/day MTDD, the ABUK specification would have to be set at 0.0001% to remain below the generally applicable 1.5 mcg/day intake limit on genotoxic and carcinogenic impurities. While NMT 1.5 mcg/day is therefore a target limit for impurities containing the ABUK moiety, FDA has not imposed this limit because it is not believed to be technically feasible at this time. Instead, the Agency has said it will continue to work with applicants and API suppliers to meet the 1.5 mcg/day limit.[8]

By 2010, FDA determined that API suppliers had been provided sufficient time to refine their manufacturing processes to reduce levels of 14-hydroxycodeinone. Accordingly, FDA publicly stated that new applications for single-entity oxycodone products were then expected to meet the NMT 0.001% (10 ppm) limit for 14-hydroxycodeinone, or provide data adequately qualifying the impurity for safety.[9]

---

[7] *Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* (December 2008) (Draft), U.S. FDA, Center for Drug Evaluation and Research, p. 7, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079235.pdf

[8] *See* Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. FDA to D. Rosen, B.S. Pharm., J.D. (Nov. 21, 2011), Docket No. FDA-2011-P-0433, pp. 6-7, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0433-0005.

[9] FDA first announced this more rigid limit for 14-hydroxycodeinone in a response to a Citizen Petition concerning ABUK impurities in another opioid, oxymorphone, which contains 14-hydroxycodeinone as well as another ABUK. *See* Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. FDA to R. Barto (November 8, 2010), Docket FDA-2010-P-0243, p. 4, available at http://www.regulations.gov/#!documentDetail;D=FDA-2010-P-0243-0003. That Citizen Petition Response uses different language to characterize the data required to qualify 14-hydroxycodeinone, *e.g.*, "adequately qualified for safety" (p. 4), "adequate safety qualification that indicates the impurities are not expected to be human carcinogens" (p. 5). The 2011 Citizen Petition response also uses varying language to characterize the data required to qualify 14-hydroxycodeinone, *e.g.*, "submit toxicology studies confirming that the impurities are not expected to be carcinogenic or mutagenic" (p. 2), "adequately qualified for safety" (p. 2), "adequate safety qualification of the impurities indicating that they were not expected to be human carcinogens" (p. 6), "adequately qualified for safety

Several companies are marketing oxycodone API consistent with the NMT 10 ppm standard.

B. Recent Data Concerning 14- Hydroxycodeinone

A poster presented at the Genetic Toxicology Association Meeting in October 2012 provided information on genotoxicity testing of 14-hydroxycodeinone. The abstract available online states:

> Purified 14-hydroxycodeinone was tested in a battery of genetic toxicology assays. Specifically, neat 14 hydroxycodeinone was tested for point mutations (mutagenicity) in an Ames Assay and chromosome rearrangements (clastogenicity) in a chromosome aberration assay using primary human peripheral blood lymphocytes. The Ames test was negative demonstrating an absence of mutagenic potential for purified 14-hydroxycodeinone. Clastogenicity was however observed in the in vitro chromosomal aberration assay. As a follow-up to the in vitro chromosomal aberration finding, an in vivo bone marrow micronucleus study was conducted in ICR mice to evaluate the potential for in vivo clastogenicity. The in vivo micronucleus study was clearly negative for clastogenicity at doses up to 320 mg/kg/bw (the MTD). An in vivo mouse comet assay analyzing both glandular stomach and liver was conducted to evaluate the potential for in vivo clastogenicity/DNA damage. This assay confirmed negative result observed in mouse bone marrow assay. The overall result of testing indicates that 14-hydroxycodeinone is not a genotoxic agent. Therefore 14-hydroxycodeinone has been qualified as a non genotoxic impurity per the appropriate guidelines (ICH Q3A & ICH Q3B) designed for qualifying the safety risks of impurities.[10]

A poster accompanying the abstract provides additional information on the rationale for the studies, as well as some of the study data.[11]

---

prior to the approval of the drug product" (p. 7), and "adequate toxicological data to qualify the impurities as nongenotoxic" (p. 9). *See* Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. FDA to D. Rosen, B.S. Pharm., J.D. (Nov. 21, 2011), Docket No. FDA-2011-P-0433, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0433-0005.

[10] *See,* Poster Abstract #17, *An evaluation of the potential genotoxicity of the impurity 14-hydroxycodeinone*, O'Neill P *et al., available at:* http://www.gta-us.org/scimtgs/2012Meeting/posters2012.html.

[11] *See* Poster entitled, *An evaluation of the potential genotoxicity of the impurity 14-hydroxycodeinone*, O'Neill P *et al.*, attached hereto as Exhibit A.

II. Regulatory Background Concerning FDA's Policy That Impurities In API Must Be Controlled To The Extent Feasible

Under the Agency's Good Manufacturing Practice Regulations, manufacturers of finished pharmaceuticals must adopt specified processes and controls to assure the quality of their products, including "the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity."[12] APIs, as components of finished pharmaceuticals, are subject to this requirement, and must be subject to scientifically sound and appropriate specifications.[13]

The quality standards applied to the production and control of APIs call for limiting impurities to the lowest levels that can consistently be achieved in their synthesis, regardless of whether or not those impurities have been identified as carcinogenic or otherwise harmful.[14] Thus, in order for an API to be acceptable for use in a finished pharmaceutical, specifications for impurities must reflect the manufacturer's demonstrated ability to control those impurities in previously manufactured batches, taking into consideration a reasonable range of expected analytical and manufacturing variability. In accordance with this approach, during review of NDAs and ANDAs, FDA routinely objects to proposed acceptance criteria for impurities in API that exceed impurity levels achieved in manufactured batches by more than an amount thought by the Agency to be necessary to account for such expected analytical and manufacturing variability.

FDA's approach to the control of impurities is described in the International Conference on Harmonization Guidance, *Impurities in New Drug Substances.*[15]

> 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 the analytical capability.

---

12 21 C.F.R. § 211.160(b).

13 21 C.F.R. § 211.3; 21 C.F.R. §§ 210.3(b)(3), (b)(7).

14 *Q3A Impurities in New Drug Substances,* ICH, June 2008, Revision 2, at p. 6, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073385.pdf; *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, 65 Fed. Reg. 83041 (Dec. 29, 2000), Decision Tree #1.

15 *Q3A Impurities in New Drug Substances,* ICH, June 2008, Revision 2, at p. 6, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073385.pdf.

> Where there is no safety concern, impurity acceptance criteria should be based on data generated on batches of a new drug substance manufactured by the proposed commercial process, allowing sufficient latitude to deal with normal manufacturing and analytical variation and the stability characteristics of the new drug substance.

The manner in which specific acceptance criteria are derived from the impurity content of previously manufactured batches is described in the International Conference on Harmonization Guidance, *Specifications: Test Procedures and Acceptance Criteria For New Drug Substances and New Drug Products: Chemical Substances, Q6A* (Oct. 1999).[16]

FDA's strict approach to impurities reflects their negative risk-to-benefit ratio. As the FDA has explained in a recent citizen petition response impurities convey only risk with no associated benefit:

> In general, impurities provide some risk and no benefit. Even in cases where data on the risk of an impurity is lacking, the lack of data itself conveys some risk of adverse effects. Further, if an impurity conveys essentially no benefit, the exposure to risk is high compared to the benefit (if any), resulting in a substantially negative risk/benefit ratio. Consequently, the general principal that FDA applies is that impurities should be minimized.[17]

---

[16] *See Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, 65 Fed. Reg. 83041 (Dec. 29, 2000), Decision Tree #1. The pertinent Decision Tree is more easily viewed on the version of the Guidance available on the ICH website at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf.

[17] Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. FDA to G. Levitt (Nov. 30, 2012), Docket No. FDA-2012-P-0583, p. 6, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0583-0009. This same point is made by FDA officials in a published article. *See* Jacobson-Kram, D and McGovern, T, *Toxicological overview of impurities in pharmaceutical products,* Advan Drug Deliv Rev, 59 (2007) 38-42.

III. Argument

A. FDA Should Maintain The Current NMT 10 ppm Limit For 14-Hydroxycodeinone in Oxycodone API For Use In Single-Entity Products

1. Application Of The FDA Requirement That Impurities Be Controlled To The Extent Feasible Necessitates Continuing The NMT 10 ppm Limit For 14-Hydroxycodeinone In Oxycodone API

Despite the recently presented genotoxicity data on 14-hydroxycodeinone, the current NMT 10 ppm limit should be maintained in accordance with FDA's requirement that impurities in API be limited 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.

As noted above, FDA first began advising applicants and DMF holders of the need to reduce levels of 14-hydroxycodeinone over a decade ago, in 2002. Initially, FDA instructed applicants that API used in single entity oxycodone products must contain NMT 10 ppm 14-hydroxycodeinone. Later, starting in 2007, applicants were advised of even more stringent targets.

For several years FDA afforded API manufacturers flexibility in meeting these limits but, in 2010, FDA publicly announced that sufficient time had passed to allow manufacturers to make the necessary process changes. Accordingly, FDA stated that it expected that new applications for opioid products will meet the specification limit for API with NMT 10 ppm 14-hydroxycodeinone.[18] Consistent with this firm Agency requirement, several API manufacturers are currently offering to supply oxycodone API that satisfies the NMT 10 ppm standard for 14-hydroxycodeinone. Moreover, several applications for single-entity oxycodone products have been approved by FDA since its 2010 announcement that API for use in such products must contain NMT 10 ppm 14-hydroxycodeinone, further evidencing the technical capabilities of manufacturers of oxycodone API.[19]

---

[18] *See* Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. FDA to R. Barto (Nov. 8, 2010), Docket FDA-2010-P-0243, p. 5, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2010-P-0243-0003; Letter from J. Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. FDA to D. Rosen, B.S. Pharm., J.D. (Nov. 21, 2011), Docket No. FDA-2011-P-0433, p. 7 available at: http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0433-0005.

[19] According to the Orange Book, applications for single-entity oxycodone products submitted by six companies other than Rhodes (Coastal, Vistapharm, Alvogen, Aurolife, King, and Sun) have been

Given that manufacturers have demonstrated the ability to manufacture commercial quantities of oxycodone API containing NMT 10 ppm 14-hydroxycodeinone, application of FDA's general requirements for impurities necessitates that the limit remain 10 ppm, regardless of the specific safety risks associated with the compound.

2. The Current NMT 10 ppm Limit Should Be Maintained As A Prudent Precautionary Measure

As detailed in the paragraphs that follow, 14-hydroxycodeinone is highly cytotoxic. In light of the potential risks associated with 14-hydroxycodeinone, the current NMT 10 ppm limit in oxycodone API for use in single-entity products should be maintained.

In order to characterize the potential risks associated with 14-hydroxycodeinone, Rhodes has consulted with Brent R. Stockwell, Ph.D.[20] Dr. Stockwell is an Early Career Scientist of the Howard Hughes Medical Institute, and an Associate Professor at Columbia University with joint appointments in the Department of Biological Sciences and the Department of Chemistry. He is also a member of the Motor Neuron Center and the Cancer Center at Columbia Medical School. Prior to joining the faculty of Columbia University, he was an independent Fellow at the Whitehead Institute for Biomedical Research, where he directed his own laboratory, developing new tools to enable the exploration of biology with small molecules. He is currently the principal investigator of the Stockwell Laboratory at Columbia University,[21] supervising postdoctoral scientists, graduate students, undergraduate students and technicians. For over thirteen years, Dr. Stockwell's research focus has been on the molecular and cellular mechanisms of cell death, and he has expertise in that aspect of toxicology that specifically relates to these cell death mechanisms.

Dr. Stockwell and his colleagues have developed a methodology for systematically characterizing compounds that are toxic to cells, based on the manner in which they cause cell death, and have published their results in *Proceedings of the*

---

approved since FDA's 2010 announcement that API for use in such products must contain NMT 10 ppm 14-hydroxycodeinone. In addition, an application by Lehigh Valley was approved just before FDA's public announcement, and Lehigh states in its citizen petition that it was required to use API containing NMT 10 ppm 14-hydroxycodeinone. Citizen Petition, Docket FDA-2011-P-0433 (May 31, 2011), at pp. 2-3, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0433-0003.

[20] The declaration of Brent R. Stockwell, Ph.D. is attached hereto as Exhibit B.

[21] http://www.columbia.edu/cu/biology/faculty/stockwell/StockwellLab/index/.

National Academy of Sciences of the United States of America.[22] The method, called "modulatory profiling," systematically analyzes the changes in the cytotoxicity of a compound when used in combination with each member of a panel of cell death modulators. These modulators are chemical and genetic perturbations to cells that influence specific cell death mechanisms. Among the compounds that have been assessed using this methodology is 14-hydroxycodeinone.[23]

14-hydroxycodeinone was selected for these experiments due to its level of cytotoxicity. Dr. Stockwell and his colleagues screened approximately 70,000 candidate compounds and selected the 23 most potent cytotoxic compounds, based on their ability to kill cells at the lowest possible concentrations, for inclusion in the modulatory profiling experiments. Not only was 14-hydroxycodeinone was one of the 23 most potent cytotoxic agents among the approximately 70,000 candidates screened, but it was also among the 8 most potent in the set of 23 compounds selected for the experiments.[24]

Tested compounds were grouped based on their modulatory profiles, which correlated well with their mechanisms of action. Based on the modulatory profile of 14-hydroxycodeinone, it was found to cluster with a series of other reactive electrophilic compounds that killed cells in a relatively non-specific manner. Thus, the cell death modulators had a relatively low impact on the cytotoxicity of 14-hydroxycodeinone and the related compounds in the same cluster, compared to the impact of modulators on other cytotoxic compounds.[25]

Dr. Stockwell concludes that, in light of available data on the toxicity of 14-hydroxycodeinone, FDA should maintain the current NMT 10 ppm limit:

> In my view, the appropriate course of action, consistent with the FDA's mission to protect the public health, is to maintain the current FDA limits on the presence of 14-hydroxycodeinone in oxycodone API, *i.e.*, NMT 0.001% (10 ppm) of API for use in single-entity oxycodone drug products. Given that manufacturers have been able to produce commercial quantities of oxycodone API meeting the NMT 10 ppm 14-hydroxycodeinone limit, I do not believe that there would be any benefit to health of relaxing the

---

22 *See* Wolpaw AJ *et al., Modulatory Profiling Identifies Mechanisms of Small Molecule-Induced Cell Death.* Proc Natl Acad Sci 2011 Sep;108(39): E771-80, with accompanying supplementary material, provided as attachment 3 to the declaration of Dr. Stockwell (Exhibit B).

23 Exhibit B, ¶ 11.

24 Exhibit B, ¶ 12.

25 Exhibit B, ¶ 18.

limits on such a highly cytotoxic substance, the presence of which offers no public health benefit.[26]

Addressing FDA's general policy requiring that impurities be controlled to the extent feasible, Dr. Stockwell states that it would be inadvisable "to override this policy and loosen the standards for this particular impurity, despite the proven ability to consistently control it more tightly, when the available data continue to advise a high degree of caution."[27]

In sum, 14-hydroxycodinone is a highly reactive electrophile and a uniquely potent cytotoxic agent. Although tests like those reported in October 2012 are widely accepted as a measure of genotoxicity risk, Dr. Stockwell cautions that it would be dangerous to conclude it is safe for patients to consume higher levels of 14-hydroxycodeinone. Moreover, there is no justification for them doing so given the lack of any benefit to such exposure and the availability of low-ABUK material from several sources. Therefore, FDA should not consider relaxing the current 10 ppm limit for 14-hydroxycodeinone in oxycodone API for use in single-entity products, until, at a minimum, the unique toxicity of 14-hydroxycodeinone is better understood.

B. If FDA Determines It Is Appropriate To Consider Relaxing The Current NMT 10 ppm Limit, It Should Solicit Public Comment On This Issue Prior To Implementation

If FDA determines that it is appropriate to consider relaxing the current NMT 10 ppm limit on 14-hydroxycodeinone in API for use in single-entity oxycodone drug products, FDA should initiate a public process and invite comments on the scientific justification, if any, for a change to the current limit. Particularly because the scientific considerations are complex, and the issue impacts a large number of companies, public participation is needed prior to any decision to relax the current limit.

The Agency's good guidance practice ("GGP") regulations were adopted in 2000 in response to the requirements of the Food and Drug Administration Modernization Act (FDAMA), which provide that FDA "shall develop guidance documents with public participation."[28] Prior to passage of FDAMA, FDA had already taken steps to improve its procedures for the development, issuance, and use of guidance documents in response to a Citizen Petition. For instance, during the course of its initial, pre-FDAMA

---

[26] Exhibit B, ¶ 22.

[27] Exhibit B, ¶ 23.

[28] 21 U.S.C. § 371(h)(1)(A); *Administrative Practices and Procedures; Good Guidance Practices,* Final Rule, 65 Fed. Reg. 56468 (Sept. 19, 2000).

development of good guidance practices, stakeholders expressed concern about the Agency's potential use of speeches, editorials, and journal articles to announce regulatory expectations.[29] These concerns echo those of the United States Court of Appeals for the District of Columbia Circuit:

> Congress passes a broadly worded statute. The agency follows with regulations containing broad language, open-ended phrases, ambiguous standards and the like. Then as years pass, the agency issues circulars or guidance or memoranda, explaining, interpreting, defining and often expanding the commands in regulations. One guidance document may yield another and then another and so on. Several words in a regulation may spawn hundreds of pages of text as the agency offers more and more detail regarding what its regulations demand of regulated entities. Law is made, without notice and comment, without public participation, and without publication in the Federal Register or the Code of Federal Regulations.[30]

FDA itself acknowledged that good guidance practices were necessary to address a "big problem," namely, the Agency's use of multiple methods to announce policies, including "podium policy," "White Papers," "Points to Consider" papers, "Information Sheets," Phone and Fax , resulting in a situation where "[n]obody was sure what our policy really was."[31]

The regulations adopted following passage of FDAMA define guidance documents as "documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue." Documents concerning, among other things, "[t]he design, production, labeling, promotion, manufacturing, and testing of regulated products" and "the processing, content, and evaluation or approval of submissions" are considered guidance documents.[32]

The Agency's three Citizen Petition responses addressing limits on 14-hydroxycodeinone in API for use in single-entity oxycodone drug products describe the Agency's policy on a regulatory issue and concern the "manufacturing and testing of regulated products" as well as the "evaluation or approval of submissions." As such, those Citizen Petition responses fall within the definition of guidance document, and have

---

29 *The Food and Drug Administration's Development, Issuance, and Use of Guidance Documents,* Notice, 63 Fed. Reg. 8961 (Feb. 27, 1997).

30 *Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1019 (D.C. Cir. 2000).

31 Good Guidance Practices (GGPs), Presentation by Nancy Derr, CDER (2009), at slide 3, available at: http://www.fda.gov/downloads/Drugs/NewsEvents/UCM182502.pdf.

32 21 C.F.R. §§ 10.115(b)(1), (b)(2).

functioned as guidance documents since their issuance, despite the Agency's failure to label them as such.

FDAMA requires that FDA "ensure public participation prior to implementation of guidance documents" that set forth, among other things, "changes in interpretation or policy that are of more than a minor nature" or "complex scientific issues."[33] Guidance documents addressing these topics are considered "Level 1" guidance documents.[34] A relaxation of the current NMT 10 ppm limit for 14-hydroxycodeinone in API for use in single-entity oxycodone drug products would constitute a non-minor change in interpretation or policy, given that it would amount to a reversal of the Agency's decade old policy on 14-hydroxycodeinone and a dramatic shift from the Agency's more recent (2007) request that manufacturers meet even more stringent limits on impurities containing the ABUK moiety, including 14-hydroxycodeinone (NMT 1.5 mcg/day). Moreover, evaluation of the risks associated with14-hydroxycodeinone raises complex scientific questions, FDA consideration of which would be enhanced through scientific input from the public.

Because any proposed relaxation of the current NMT 10 ppm limit would constitute a Level 1 guidance, FDA must seek public comment on the proposal before implementation.[35] FDA could request public comment through a variety of means, including, for example, publication of notice of this petition, along with a request for comments. FDA followed this approach in 1997 when it sought comment on two citizen petitions requesting that the agency revise its policy concerning therapeutic equivalency ratings between tablets and capsules.[36] Regardless of the means, soliciting and carefully considering public input prior to any relaxation of the current limit is essential, given the complex scientific issues involved as well as the large number of companies affected.

---

[33] 21 U.S.C. § 371(h)(1)(C).

[34] 21 C.F.R. § 10.115(c)(1)(ii) (Level 1 guidance document include those that "[s]et forth changes in interpretation or policy that are of more than a minor nature").

[35] 21 U.S.C. § 371(h)(1)(C); 21 C.F.R. § 10.115(g)(1). FDA does not seek public input on Level 1 guidance documents if "prior public participation is not feasible or appropriate." 21 C.F.R. § 10.115(g)(2). The legislative history to FDAMA provides that this exception is to be narrowly construed. *See* H. Rep. 105-310 at 74 (Oct 7, 1997) ("The Committee intends that the Secretary will waive this requirement for prior public participation only in rare and extraordinary circumstances where there is a compelling rationale").

[36] *See Citizen Petitions Concerning Therapeutic Equivalency Ratings Between Tablets and Capsules; Request for Comments,* 60 Fed. Reg. 14917 (March 28, 1997).

III. Conclusion

The current NMT 10 ppm limit for 14-hydroxycodeinone in oxycodone API for use in single-entity drug products should be maintained, in accordance with FDA's policy requiring that impurities be controlled to the extent feasible, because several manufacturers of oxycodone API have been able to develop commercial processes for making oxycodone API that satisfies that NMT 10 ppm limit. Moreover, as demonstrated herein, questions regarding 14-hydroxycodeinone remain. In light of information relating to the highly reactive and cytotoxic nature of 14-hydroxycodeinone, relaxation of the current NMT 10 ppm limit is not warranted. Should FDA nevertheless consider relaxing the current limit, it should initiate a public process through which interested parties may submit their views on whether the totality of the scientific evidence justifies such a change.

IV. Environmental Impact

Petitioner claims a categorical exclusion from the requirements of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

V. Economic Impact

An economic impact statement will be submitted if requested by the Commissioner, pursuant to 21 C.F.R. § 10.30(b).

VI. 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 that 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:[37]

---

[37] Consistent with the example provided in the preamble to the proposed rule addressing Section 505(q) certifications, specific dates are not provided in this certification for the historical information and FDA precedents referenced herein. *Amendments to Regulations on Citizen Petitions, Petitions for Stay of Action, and Submission of Documents to Dockets*, 77 Fed. Reg. 25, 28 (Jan. 3, 2012). This information generally became known to Purdue employees and representatives on a contemporaneous basis as the referenced events occurred and the referenced findings were made. This historical information, although relied upon as providing part of the factual and legal underpinning for the Agency to take the action requested herein, is not considered to be the type of information covered by the certification requirement

November 22, 2012: Knowledge of online abstract describing the genotoxicity data presented at the Genetic Toxicology Association meeting in October 2012.

February 15, 2013: Knowledge of modulatory profiling data addressing 14-hydroxycodeinone.

March 4, 2013: Opinion of Dr. Brent Stockwell concerning the safety of 14-hydroxycodeinone.

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: Rhodes Technologies and/or Purdue Pharma L.P.

I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Jennifer A. Davidson
Counsel to Rhodes Technologies

Respectfully submitted,

Peter R. Mathers
Jennifer A. Davidson
Counsel to Rhodes Technologies

Kleinfeld, Kaplan and Becker, LLP
1140 Nineteenth Street, N.W.
Washington, DC 20036
Phone: 202-223-5120
Fax: 202-223-5619

---

of FFDCA Section 505(q). Moreover, a requirement for certification with respect to the dates such information became known to Petitioner would serve no purpose. Any such certification requirement, if applied to any information not specifically addressed in this certification statement, or the refusal by FDA to consider such information in addressing the issues raised herein, would be arbitrary and capricious in violation of the Administrative Procedures Act and the Fifth and Fourteenth Amendments of the United States Constitution and would unconstitutionally burden and infringe upon Petitioner's right to petition the Government, in contravention of the First Amendment of the United States Constitution.

Exhibits

O'Neill P *et al., An evaluation of the potential genotoxicity of the impurity 14-hydroxycodeinone*, Poster presented at the Genetic Toxicology Association meeting, October 2012	A
Declaration of Brent R. Stockwell, Ph.D., with accompanying Exhibits 1, 2, and 3	B