DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–D–2583]

Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled ''Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products.'' The document provides guidance regarding the nonclinical information FDA recommends to support development and approval of orally inhaled nicotine-containing drug products, including electronic nicotine delivery systems intended for smoking cessation and other chronic uses.

DATES: Submit either electronic or written comments on the draft guidance by October 5, 2018 to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2018–D–2583 for ''Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products; Draft Guidance for Industry; Availability.'' Received comments will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993–0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Alina Salvatore, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 5418, Silver Spring, MD 20903–0002, 240–402–0379.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled ''Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products.'' This document provides guidance on the nonclinical information FDA recommends to support development and approval of orally inhaled nicotine-containing drug products for smoking cessation and other chronic uses.

The recommended nonclinical assessment as outlined in the guidance addresses safety of novel components of the drug product formulation, novel chemicals generated from any component of the drug product formulation by the delivery system, and novel impurities. As used in the guidance, the phrase *novel component of the formulation* refers to active and inactive ingredients intentionally added to the drug product that have not been approved in drugs at an equal or greater dose, for an equal or greater duration of use, or by a relevant route of administration sufficient to characterize toxicity via local and systemic exposure. FDA expects that in many cases use of the delivery system will generate novel chemicals (*e.g.,* heat-generated products).

Orally inhaled nicotine-containing drug products developed for smoking cessation and other chronic uses are expected to involve continuous use or chronic intermittent use resulting in 6

months or more exposure over a lifetime. Because of the duration of use, the nonclinical assessment for marketing approval should include general toxicity studies, developmental and reproductive toxicity studies, an assessment of carcinogenic potential, and supporting toxicokinetic and pharmacokinetic studies.

FDA is aware of the serious risk associated with smoking and is committed to facilitating the development of therapies to support smoking cessation efforts. This guidance focuses on novel components of the drug product formulation, heat-generated products, and impurities that are generally not well characterized. Orally inhaled nicotine-containing tobacco products, including electronic nicotine delivery systems currently marketed in the United States, have already been associated with toxicity concerns (Refs 1–4). An adequate nonclinical assessment, as described in this guidance, can address the potential toxicity of chemicals from orally inhaled nicotine-containing drug products. As noted in the guidance, sponsors can use an alternative approach if that approach provides adequate safety information.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on nonclinical testing of orally inhaled nicotine-containing drug products. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. This guidance is not subject to Executive Order 12866.

II. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The collections of information in 21 CFR part 312 have been approved under OMB control number 0910–0014. The collections of information resulting from special protocol assessments have been approved under OMB control number 0910–0470.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at either *https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm* or *https://www.regulations.gov.*

IV. References

The following reference marked with an asterisk (*) is on display at the Dockets Management Staff (see **ADDRESSES**) and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it also is available electronically at *https://www.regulations.gov.* References without asterisks are not on display because they have copyright restriction, or they are available as published articles and books. Please contact the person identified in the **FOR FURTHER INFORMATION CONTACT** section to schedule a date to inspect references without asterisks.

1. Madsen, L.R., N.H. Vinther Krarup, T.K. Bergmann, et al., 2016, ''A Cancer That Went Up in Smoke: Pulmonary Reaction to E-Cigarettes Imitating Metastatic Cancer,'' *Chest,* 149(3):e65–67.
2. Ghosh, A., R.C. Coakley, T. Mascenik, et al., 2018, ''Chronic E-Cigarette Exposure Alters the Human Bronchial Epithelial Proteome,'' *American Journal of Respiratory and Critical Care Medicine,* epub ahead of print February 26, 2018, doi: 10.1164/rccm.201710–2033OC.
* 3. Olmedo, P., W. Goessler, S. Tanda, et al., 2018, ''Metal Concentrations in E-Cigarette Liquid and Aerosol Samples: The Contribution of Metallic Coils,'' *Environmental Health Perspectives,* 126(2): doi: 10.1289/EHP2175.
4. Rubinstein, M.L., K. Delucchi, N.L. Benowitz, and D.E. Ramo, 2018, ''Adolescent Exposure to Toxic Volatile Organic Chemicals From E-Cigarettes,'' *Pediatrics,* epub ahead of print March 5, 2018, doi: 10.1542/peds.2017–3557.

Dated: July 31, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–16726 Filed 8–3–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Findings of Research Misconduct

AGENCY: Office of the Secretary, HHS.

ACTION: Notice.

SUMMARY: Notice is hereby given that on July 13, 2018, the U.S. Department of Health and Human Services (HHS) Debarring Official, on behalf of the Secretary of HHS, issued a final notice of debarment based on an Administrative Law Judge's findings of research misconduct against Christian Kreipke, Ph.D., former Research Associate Professor, Wayne State University. Dr. Kreipke engaged in research misconduct in research supported by National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), grants R01 NS039860 and R01 NS064976–01A2. The administrative actions, including five (5) years of debarment, were implemented beginning on July 13, 2018, and are detailed below.

FOR FURTHER INFORMATION CONTACT:

Wanda K. Jones, Dr.P.H., Interim Director, Office of Research Integrity, 1101 Wootton Parkway, Suite 750, Rockville, MD 20852, (240) 453–8200.

SUPPLEMENTARY INFORMATION:

Christian Kreipke, Ph.D., Wayne State University: ORI issued a charge letter enumerating findings of research misconduct and proposing HHS administrative actions. Dr. Kreipke (''Respondent'') subsequently requested a hearing before an Administrative Law Judge (ALJ) of the Departmental Appeals Board to dispute these findings. A hearing before the ALJ was held on July 10–12, 2017. On May 31, 2018, the ALJ issued his recommended decision, finding that Respondent recklessly caused or permitted twenty-three (23) instances of research misconduct in his three (3) grant applications, two (2) articles on which he was the first listed author, and two (2) posters on which he was the first listed author. The ALJ held that appropriate administrative actions included a five-year debarment from any contracting or subcontracting with any agency of the United States and from eligibility for or involvement in nonprocurement programs of the United States referred to as ''covered transactions.'' 2 CFR parts 180 and 376. The ALJ held it was an appropriate administrative action to also impose a five-year prohibition from serving in any capacity to the U.S. Public Health Service (PHS), including but not limited to, service on any PHS advisory committee, board, or peer review committee, or as a consultant. The ALJ noted that ORI also had proposed that the publisher of certain articles be notified of the need to retract those articles and that retraction had already occurred by the time of his recommended decision.

Under the regulation, the ALJ's recommended decision went to the Assistant Secretary for Health, who did not modify it and forwarded it to the HHS Debarring Official, who is the deciding official for the debarment. The ALJ decision constituted the findings of fact to the HHS Debarring Official in accordance with 2 CFR 180.845(c). On July 13, 2018, the HHS Debarring Official issued a final notice of debarment to begin on July 13, 2018, and end on July 12, 2023.