



4164-01-P

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; 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 final guidance for industry entitled “Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products.” The document provides guidance about 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 related chronic indications. This guidance finalizes the draft guidance of the same name issued August 6, 2018.

DATES: The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit either electronic or written comments on Agency guidances 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.” 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, 240-402-7500.

- 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.govinfo.gov/content/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, 240-402-7500.

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

Submit written requests for single copies of this 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 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 final guidance for industry entitled “Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products.” The recommended nonclinical assessment as outlined in the guidance addresses safety of novel chemicals of the drug product formulation, novel chemicals generated from any chemical of the drug product formulation by the delivery system, and novel impurities. As used in the guidance, the phrase novel chemicals of the drug product 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 related chronic indications 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 chemicals 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. 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 guidance finalizes the draft guidance of the same name issued August 6, 2018 (83 FR 38315). Changes from the draft to the final include the following:

- More information to guide the nonclinical development of an active ingredient in addition to nicotine
- Clarification on absorption, distribution, metabolism, and excretion studies, consistent with previous reference to the International Council for Harmonisation guidance for industry entitled “M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals” (January 2010)
- Reference to the draft guidance for industry entitled “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA [Prescription Drug User Fee

Amendments] Products” (December 2017), which describes the process through which sponsors can request meetings

- Clarification on how sponsors can compare the exposure to nicotine in an approved drug by providing pharmacokinetic information (e.g., C_{max} , T_{max} , area under the curve) from the proposed drug product
- An example of how systemic toxicity could be addressed by a nonclinical toxicity study conducted with a noninhalation route of exposure
- Clarification that local effects in oral or respiratory tract tissues are best addressed with a nonclinical inhalation study

This guidance is being issued consistent with FDA’s good guidance practices regulation (21 CFR 10.115). The guidance represents 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.

II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521) is not required for this guidance. The previously approved collections of information are subject to review by OMB under the PRA. 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 guidance at either
<https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs> or
<https://www.regulations.gov>.

Dated: October 23, 2020.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

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