Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmacology/Toxicology

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Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
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Contains Nonbinding Recommendations

Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. 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. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides sponsors with recommendations on the nonclinical information to support development and approval of orally inhaled nicotine-containing drug products,[2] including electronic nicotine delivery systems intended for smoking cessation and related chronic indications.[3]

This guidance focuses on novel chemicals of the drug product formulation,[4] novel chemicals generated from any chemical of the drug product formulation by the delivery system[5] (e.g., heat-generated chemicals), and novel impurities from the drug product formulation and delivery system. This guidance does not address nonclinical toxicity studies that may be requested by the Center for Devices and Radiological Health to support use of the delivery system (e.g., biocompatibility studies).

[1] This guidance has been prepared by the Office of Nonprescription Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] The term *drug* is defined in section 201(g)(1) the Federal Food, Drug, and Cosmetic Act (FD&C Act).

[3] An orally inhaled nicotine-containing product can be regulated as either a medical product or a tobacco product depending on the intended use. See 21 CFR 1100.5, which describes when a product made or derived from tobacco will be subject to regulation as a drug, device, or combination product.

[4] In this 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 by FDA 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.

[5] The products addressed by this guidance are generally drug and device combination products with a drug primary mode of action.

An adequate nonclinical toxicity assessment can address the potential toxicity of chemicals from orally inhaled nicotine-containing drug products. Some of these products have already been associated with toxicity concerns.[6,7,8,9,10]

Orally inhaled nicotine-containing drug products developed for smoking cessation and related chronic indications[11] are expected to involve continuous use or chronic intermittent use resulting in 6 months or more exposure over a lifetime. The recommendations for nonclinical toxicity assessment in this guidance are intended to support the indication of smoking cessation and related chronic indications in an adult population for either prescription or nonprescription use.

These recommendations for nonclinical testing of orally inhaled nicotine-containing drug products are based on FDA's current scientific understanding of toxicity evaluation of orally inhaled drug products for chronic use. In addition, the recommendations are intended to complement the recommendations for nonclinical toxicity assessment of drug products in the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) and the guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (May 2005).[12]

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[6] Madsen LR, Vinther Krarup NH, Bergmann TK, Bærentzen S, Neghabat S, Duval L, and Knudsen ST, 2016, A Cancer That Went Up in Smoke: Pulmonary Reaction to e-Cigarettes Imitating Metastatic Cancer, Chest, 149(3):e65–e67.

[7] Ghosh A, Coakley RC, Mascenik T, Rowell TR, Davis ES, Rogers K, Webster MJ, Dang H, Herring LE, Sassano MF, Livraghi-Butrico A, Van Buren SK, Graves LM, Herman MA, Randell SH, Alexis NE, and Tarran R, 2018, Chronic E-Cigarette Exposure Alters the Human Bronchial Epithelial Proteome, Am J Respir Crit Care Med, epub ahead of print February 26, 2018, doi: 10.1164/rccm.201710-2033OC.

[8] Olmedo P, Goessler W, Tanda S, Grau-Perez M, Jarmul S, Aherrera A, Chen R, Hilpert M, Cohen JE, Navas-Acien A, and Rule AM, 2018, Metal Concentrations in e-Cigarette Liquid and Aerosol Samples: The Contribution of Metallic Coils, Environ Health Perspect, 126(2): doi: 10.1289/EHP2175.

[9] Rubinstein ML, Delucchi K, Benowitz NL, and Ramo DE, 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.

[10] References are not intended to be an exhaustive list of studies that characterize toxicity in e-cigarettes.

[11] Nicotine replacement therapy (NRT) drug products can be developed for the following chronic indications: smoking cessation and reduction in risk of relapse. NRT drug products that first have demonstrated effectiveness for smoking cessation or reduction in risk of relapse can also include additional information in labeling by demonstrating effectiveness in the following secondary endpoints: reduction of urge to smoke, relief of cue-induced craving in former smokers, and relief of withdrawal symptoms not associated with a cessation attempt. See the draft guidance for industry *Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products* (February 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[12] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

FDA will consider existing clinical and nonclinical information that characterizes the safety of novel chemicals, to the extent that such data reflect current scientific standards and sponsors own or have a right of reference[13] to the data. In this case, such data should adequately provide the toxicity information that the FDA-recommended studies (see section II. B., Recommendations for Nonclinical Development) are designed to provide. Sponsors are encouraged to meet with FDA to discuss drug development plans before initiating studies.[14]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. NONCLINICAL DEVELOPMENT

A. Key Considerations

A thorough nonclinical toxicity assessment is integral to the benefit-risk assessment of orally inhaled nicotine-containing drug products. Sponsors should consider the following:

- FDA does not recommend new nonclinical data to characterize the toxicity of nicotine alone if one of the following applies:

  - For smoking cessation, sponsors can consider if the nicotine exposure is within the range of exposure expected from lawfully marketed combustible tobacco products based on local and systemic exposures relevant to the proposed orally inhaled nicotine-containing drug product.

  - Sponsors can rely on the exposure to nicotine in an approved listed drug to inform the nonclinical toxicity evaluation for this purpose under an abbreviated approval pathway.[15] If sponsors rely on FDA's finding of safety for an approved listed drug, that drug should provide exposure[16] equal to or higher than the exposure anticipated from the proposed orally inhaled nicotine-containing drug product, considering the conditions of use proposed in labeling. For example, a relevant approved drug is one that has conditions of use similar to the proposed orally inhaled nicotine-containing drug product, including the dose, duration, route of administration, and the indicated population.

[13] See 21 CFR 314.50(g) regarding right of reference for an NDA under section 505(b) of the FD&C Act.

[14] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). When final, this guidance will represent the FDA's current thinking on this topic.

[15] See section505(b)(2) of the FD&C Act (21 U.S.C. 355(b)(2)).

[16] The pharmacokinetic parameters (e.g., C_{max}, T_{max}, area under the curve) of the new inhaled product should be compared with the relied-upon listed drug.

- Sponsors should submit toxicity information for all chemicals of the drug product formulation, heat-generated products, and impurities to support clinical use.

  – In many cases, use of the delivery system will alter chemicals from the formulation or device, creating new chemicals (e.g., heat-generated products). If an active ingredient in addition to nicotine is proposed, sponsors should refer to the nonclinical development recommended in ICH M3(R2) to complement the recommendations below.

- Sponsors should properly characterize the risks from orally inhaled nicotine-containing drug products. Orally inhaled nicotine-containing drug products result in local and systemic exposure to nicotine and other chemicals, including heat-generated chemicals, via the inhalation, buccal, and oral routes of administration. Some chemicals may be novel, not found in relevant, previously approved drug products, or may not have adequate toxicity information available. Local and systemic exposure should be addressed in the nonclinical toxicity assessment. For example, nonclinical toxicity studies of a chemical administered subcutaneously would not address local effects in oral or respiratory tract tissues. Consequently, additional information relevant to these tissues may be warranted.

- All drugs have risks. FDA weighs the benefits and risks with respect to the proposed indication and patient population.[17]

B. Recommendations for Nonclinical Development

The nonclinical toxicity assessment appropriate for marketing approval should include general toxicity studies, developmental and reproductive toxicity studies, an assessment of carcinogenic potential, and supporting toxicokinetic and nonclinical pharmacokinetic studies[18] in both sexes (see Appendix A). Whether genetic nonclinical toxicity studies should be conducted depends on the tobacco use and smoking status of clinical trial subjects. The following recommendations outline general principles for conducting nonclinical toxicity studies.[19]

[17] For information on benefit-risk assessment, see the guidance for industry *Premarketing Risk Assessment* (March 2005). See also the FDA Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making available at https://www.fda.gov/media/112570/download.

[18] See the ICH guidance for industry *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies* (March 1995).

[19] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

1. General Principles

Following are FDA recommendations for general principles that apply to developing orally inhaled nicotine-containing drug products:

- We recommend a full chemical analytical characterization of the aerosol, including heat-generated chemicals, using the proposed delivery system, to identify the substances that can be generated by an orally inhaled nicotine-containing drug product. The device and system used to generate the aerosol should be fully described, including the settings used.

- FDA does not recommend pharmacology studies to address the mechanism of action if nicotine is the only active ingredient. FDA recommends that sponsors provide justification that any proposed inactive ingredients do not have pharmacological activity. If an additional active ingredient is proposed, sponsors should characterize its pharmacology as recommended in ICH M3(R2).

- To inform the benefit-risk assessment, nonclinical toxicity studies can benefit from the inclusion of a testing group or groups exposed to aerosol from the proposed formulation or formulations heated in a relevant delivery system, compared with a reference testing group exposed to cigarette smoke. Adequate negative controls should be included in all studies. See section II. B. 1. 2. for adequate negative control groups (e.g., sham air control group, vehicle control group).

- Heat-generated chemicals should be evaluated as a mixture in nonclinical toxicity studies. Novel chemicals (e.g., heat-generated products) and chemicals that are a safety concern should be identified by quantitative dosing analysis and measurement of exposure (e.g., toxicokinetics) in nonclinical toxicity studies. Quantitative dosing analysis in nonclinical toxicity studies should measure the level of chemicals as they are being administered to animals. For example, the dose is measured at the site of administration (e.g., the nose for rats) in nonclinical inhalation studies. The resulting systemic exposure is determined based on toxicokinetic data.

- In general, FDA recommends inhalation studies to support the use of novel chemicals because systemic toxicity studies by other routes do not sufficiently model drug deposition in the lung (i.e., bronchi, bronchioles, and alveoli) that occurs following oral inhalation exposure. Sponsors should conduct inhalation studies with an aerosol generated using the proposed delivery system.

- Toxicokinetic measurements are usually obtained during ongoing nonclinical toxicity studies rather than through separate studies.

- FDA recognizes that metabolism may affect toxicity. Sponsors should collect toxicokinetic information for active ingredients in nonclinical toxicity studies. Regarding nicotine, full characterization of absorption, distribution, metabolism, and excretion (ADME) is generally not necessary because of existing information. However, for other active ingredients, sponsors should conduct full ADME characterization as recommended

in ICH M3(R2) and the guidance for industry *Safety Testing of Drug Metabolites* (November 2016). ADME of excipients should be characterized as described in the guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients.* Sponsors should also address the safety of metabolites from heat-generated chemicals, following the principles in the excipients guidance and the drug metabolites guidance.

- Sponsors should follow available guidance on assessing drug substance and drug product impurities[20] and consider if the nicotine derived from plant-based products may be associated with genotoxic impurities. Nicotine-specific impurities that are present at higher levels than in approved drug products, considering the route of administration, population, dose, and duration, are a concern if the impurities also exceed relevant ICH-recommended limits. FDA will assess such impurities on a case-by-case basis.

- To support marketing approval, sponsors should submit a nonclinical toxicity assessment of extractables and leachables of the delivery system and any container/closure system. Sponsors should consider the level of these impurities under different conditions, including when overheating occurs to produce a dry puff.

2. General Toxicity Studies

Following are FDA recommendations for a general toxicity assessment:

- For general toxicity studies to address novel chemicals, FDA recommends studies in rodent and nonrodent species (see Appendix A), consistent with international standards for pharmaceutical development.[21] FDA strongly recommends that both species be dosed by the inhalation route of administration, provided that this route of administration results in systemic exposure in at least one species sufficient to assess toxicity compared with the anticipated clinical systemic exposure. Inhalation studies should include adequate control groups (e.g., sham air control group, vehicle control group) and a full panel of tissues, not just tissues of the respiratory tract, to address route-dependent systemic toxicity. For information about a positive control group exposed to cigarette smoke, see section 1, General Principles.

  - If systemic exposure is not sufficient after inhalation, we recommend that:

    - The rodent species be dosed by a noninhalation route to allow for systemic toxicity assessment. Rodents are primarily nose breathers and may not receive

[20] For impurities and degradants of the drug substance and drug product, see the ICH guidances for industry *Q3A(R2) Impurities in New Drug Substances* (June 2008), *Q3B(R2) Impurities in New Drug Products* (July 2006), and *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (March 2018). For solvents and elemental impurities, see the ICH guidances for industry *Q3C Impurities: Residual Solvents* (December 1997) and *Q3D Elemental Impurities* (September 2015).

[21] See ICH M3(R2).

adequate buccal and oral exposure to the drug relevant to clinical use of orally inhaled nicotine-containing drug products.

- Because the nonrodent species, in contrast, are not exclusive nose breathers, they should be dosed by the inhalation route of exposure using a method (e.g., a face mask) that allows for oral and nasal inhalation of chemicals, resulting in buccal and oral exposure to the drug, to model oral inhalation in humans.

- The relevant mucosa be evaluated macroscopically and microscopically.

3. Developmental and Reproductive Toxicology

FDA recommends developmental and reproductive toxicity studies[22] for novel chemicals for which adequate toxicity data are not available. Sponsors should conduct these studies using a route of administration that results in systemic exposure and exposure to the reproductive organs. Following are FDA recommendations for a developmental and reproductive toxicity assessment:

- Sponsors should consider FDA's general recommendations (see Appendix A) and refer to ICH M3(R2) for more specific recommendations on the timing of developmental and reproductive toxicity studies.

- Timing of developmental and reproductive toxicity studies can also be affected by findings that are a cause for concern (e.g., when male reproductive organs are identified as target organs in general toxicity studies).

- ICH M3(R2) also describes nonclinical data recommended to minimize the risk of unintentional exposure of the embryo or fetus when including women of childbearing potential in clinical trials.

4. Carcinogenicity

Following are FDA recommendations for a carcinogenicity assessment:

- FDA recommends that sponsors conduct carcinogenicity studies in two rodent species for novel chemicals for which adequate toxicity data are not available, consistent with international standards for pharmaceutical development.[23] In general, sponsors should conduct a carcinogenicity study that involves administering novel chemicals by the inhalation route to mice or rats for 2 years. Sponsors should also conduct a second carcinogenicity study by a route that produces adequate systemic exposure. This study

[22] See the ICH guidance for industry *S5(R2) Detection of Toxicity to Reproduction for Medicinal Products Toxicity to Male Fertility* (November 2005).

[23] See the ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* (March 1996).

can be a 2-year study or a shorter (usually 6 months) alternative carcinogenicity model accepted by FDA, but either study should be conducted in a species different from that used in the inhalation carcinogenicity study.[24] Therefore, at a minimum, one species should be dosed by the inhalation route, and the second species should have systemic exposure to adequately assess systemic toxicity. Regardless of the route of administration, all carcinogenicity studies should address a full panel of tissues.[25] See section II. B. 1. 2. for adequate negative control groups (e.g., sham air control group, vehicle control group).

- Carcinogenicity studies by the oral route in two different rodent species (e.g., mouse and rat) can be sufficient (i.e., no inhalation carcinogenicity study) for novel chemicals when proliferative or preneoplastic changes in the respiratory tract are not observed in chronic inhalation toxicity studies and when adequate local buccal and airway exposure by the oral route is demonstrated.[26]

5. Genetic Toxicology

Following are FDA recommendations for a genetic toxicology assessment:

- FDA's recommendation for genetic toxicity studies of novel chemicals depends on the tobacco use and smoking status of subjects in the proposed clinical trials because of the differential cancer risks in these populations.

  - FDA recommends genetic toxicity studies, as described in ICH M3(R2), to assess the toxicity of novel chemicals if clinical trials are conducted in subjects who are not current smokers.

  - In general, FDA does not recommend genetic toxicity studies to support clinical trials in current smokers because this population is already at risk for cancer, and genetic toxicity studies do not provide organ-specific risk assessment for cancer relevant to current smokers.

[24] See the ICH guidance for industry *S1B Testing for Carcinogenicity of Pharmaceuticals* (July 1997).

[25] FDA recommends submitting the carcinogenicity study protocol or protocols for review in concurrence with the Center for Drug Evaluation and Research's Executive Carcinogenicity Assessment Committee before initiating the studies. For further guidance regarding carcinogenicity studies, see the guidance for industry *Carcinogenicity Study Protocol Submissions* (May 2002).

[26] This is consistent with the guidance for industry and review staff *Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route* (October 2015).

APPENDIX A

Table 1: Milestones and Pivotal Nonclinical Toxicity Studies Recommended for Novel Chemicals[1,2,3]

Milestones and toxicity studies	Drug product development phase			
	Phase 1	**Phase 2**	**Phase 3**	**Phase 4**
Clinical Characteristics	Small number of subjects and short duration of treatment	Larger number of patients and longer duration of treatment	Larger number of patients and long-term duration of treatment	Large number of patients and limited control on dose and duration
General toxicity	Short-term studies in rodent and nonrodent species (adequate dose/duration)	Maximum 6-month rodent, 9-month nonrodent studies (adequate dose/duration	Chronic studies (6-month rodent, 9-month nonrodent)	Toxicity-specific mechanistic studies, if recommended
Developmental and reproductive toxicity	Not necessary	Not necessary	Effects on fertility and early embryonic development (rodent study) and embryofetal development (rodent and nonrodent studies)	Effects on pre- and post-natal development (rodent study)

continued

[1] Section II. B.1. of this guidance provides additional recommendations regarding the assessment of impurities, including assessment of extractables and leachables of the delivery system of any container/closure system.

[2] If an active ingredient other than nicotine is proposed, sponsors should refer to the nonclinical development recommended in the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) to complement the recommendations above.

[3] Timing of metabolite characterization follows recommendations in ICH M3(R2).

Table 1, continued

Milestones and toxicity studies	Drug product development phase			
	Phase 1	**Phase 2**	**Phase 3**	**Phase 4**
Carcinogenicity	Not necessary	Not necessary	Not necessary	Carcinogenicity assessment (e.g., carcinogenicity studies in two rodent species)
Genetic toxicity	Depends on tobacco use/smoking status of clinical trial subjects	Depends on tobacco use/smoking status of clinical trial subjects	Depends on tobacco use/smoking status of clinical trial subjects	Addressed earlier in development, if recommended