Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products

Guidance for Industry

DRAFT GUIDANCE

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

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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[2] necessary to support development and approval of orally inhaled nicotine-containing drug products,[3] including electronic nicotine delivery systems intended for smoking cessation and other chronic uses.[4]

This guidance focuses on novel components of the drug product formulation;[5] novel chemicals generated from any component of the drug product formulation by the delivery system[6] (e.g., heat-generated chemicals); and novel impurities from the drug product formulation and delivery system.

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

[2] This guidance does not address nonclinical studies that may be requested by the Center for Devices and Radiological Health to support use of the delivery system (e.g., biocompatibility studies).

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

[4] 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.

[5] In this guidance, the phrase *novel components of the 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.

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

An adequate nonclinical 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.[7,8,9,10]

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. The recommendations for nonclinical toxicity evaluation in this guidance are intended to support the indication of smoking cessation and other chronic uses, in an adult population, for either prescription or nonprescription use.

These recommendations for nonclinical testing of orally inhaled nicotine-containing drug products rely 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 evaluation 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 (ICH M3(R2))* and the guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*.[11]

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.

[7] 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):e65-67.

[8] 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.

[9] 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.

[10] 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.

[11] 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/RegulatoryInformation/Guidances/default.htm.

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, the sponsor can consider if the nicotine exposure is within the range of exposure expected from lawfully marketed cigarettes, based on local and systemic exposures relevant to the proposed orally inhaled nicotine-containing drug product.
  - The sponsor can rely on the exposure to nicotine in an approved drug to inform the nonclinical toxicity evaluation for this purpose. If the sponsor references a relevant approved drug, that drug should provide equal or higher exposure 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 similar conditions of use to the proposed orally inhaled nicotine-containing drug product, including the dose, duration, route of administration, and the indicated population.
- The sponsor should submit toxicity information for all components of the drug product formulation, heat-generated products, and impurities to support clinical use.
  - In many cases, use of the delivery system will generate novel chemicals (e.g., heat-generated products).
- FDA will consider existing information that supports the use of novel chemicals, to the extent that such data reflect current scientific standards and sponsors have the right to rely on 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.
- The risks from orally inhaled nicotine-containing drug products need to be properly characterized by the sponsor. 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 toxicity assessment.

- All drugs have risks. FDA weighs the benefits and risks with respect to the proposed indication and patient population.[12] For example, FDA has considered the risk of cancer from cigarette smoking when recommending carcinogenicity assessments for novel chemicals intended for smoking cessation or other chronic uses. Carcinogenicity assessments determine the carcinogenic potential in all organs (not just the organs that are known targets for tobacco).

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[13] (see Appendix A). Whether genetic toxicology 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 studies.[14]

1. General Principles

The following are FDA recommendations for general principles that apply to development of orally inhaled nicotine-containing drug products:

- We recommend a full analytical characterization of the aerosol, including heat-generated chemicals, using the proposed delivery system.

- FDA does not recommend pharmacology studies to address the mechanism of action if nicotine is the only active ingredient.

- To inform the benefit-risk assessment, toxicity studies can benefit from the inclusion of a testing group(s) exposed to aerosol from the proposed formulation(s) heated in a relevant delivery system, compared to a reference testing group exposed to cigarette smoke.

- Heat-generated chemicals should be evaluated as a mixture in toxicology studies. Novel chemicals (e.g., heat-generated products) that result in the highest level of exposure and chemicals that are a safety concern should be identified by quantitative dosing analysis and measurement of exposure (e.g., toxicokinetics) in toxicology studies. Quantitative dosing analysis in toxicology studies should measure the level of chemicals as they are

[12] For information on benefit-risk assessment, see the guidance for industry *Premarketing Risk Assessment* See also the FDA Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making available at https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM602885.pdf.

[13] See the ICH guidance for industry *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*.

[14] We support the principles of the 3Rs (replace/reduce/refine) 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 to determine if it is adequate to meet a nonclinical regulatory need.

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 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.

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

- FDA recognizes that metabolism may affect toxicity, and so sponsors should characterize metabolism as recommended in ICH M3(R2).

- Sponsors should follow available guidance on assessment of drug substance and drug product impurities[15] 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 drug products also exceed relevant ICH-recommended limits. FDA will assess such impurities on a case-by-case basis.

- To support marketing approval, the sponsor should submit a toxicological 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 Toxicology Studies

The following are FDA recommendations for a general toxicology assessment:

- For general toxicology studies to address novel chemicals, FDA recommends studies in rodent and nonrodent species (see Appendix A), consistent with international standards for pharmaceutical development.[16] It is strongly preferred 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 to the anticipated clinical systemic exposure. Inhalation studies should include a full panel of

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

[16] See *ICH M3(R2).*

tissues, not only tissues of the respiratory tract, to address route-dependent systemic toxicity.

- 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.
  - The nonrodent species 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. Rodents are primarily nose breathers and may not receive adequate buccal and oral exposure to the drug relevant to clinical use of orally inhaled nicotine-containing drug products.
  - The relevant mucosa be evaluated macroscopically and microscopically.

3. Developmental and Reproductive Toxicology

FDA recommends developmental and reproductive toxicology studies[17] for novel chemicals for which adequate toxicity data are not available. The sponsor should conduct these studies using a route of administration that results in systemic exposure and exposure to the reproductive organs. The following are FDA recommendations for a developmental and reproductive toxicology 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 reproductive and developmental toxicology studies.
- Timing of developmental and reproductive toxicology 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 toxicology 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

The following are FDA recommendations for a carcinogenicity assessment:

- FDA recommends that the sponsor conduct carcinogenicity studies in two rodent species for novel chemicals for which adequate toxicity data are not available, consistent with

[17] See the ICH guidances for industry *S5A Detection of Toxicity to Reproduction for Medicinal Products* and *S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility*.

international standards for pharmaceutical development[18]. In general, the sponsor should conduct a carcinogenicity study that involves administration of novel chemicals by the inhalation route to mice or rats for 2 years. The sponsor should also conduct a second carcinogenicity study by a route that produces adequate systemic exposure. This study can be a 2-year study or a shorter (usually 6 months) alternative carcinogenicity model, but either study should be conducted in a species different from that used in the inhalation carcinogenicity study.[19] Regardless of the route of administration, all carcinogenicity studies should address a full panel of tissues.[20]

- 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.[21]

5. Genetic Toxicology

The following are FDA recommendations for a genetic toxicology assessment:

- FDA's recommendation for genetic toxicology 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 toxicology 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 toxicology studies to support clinical trials in current smokers because this population is already at risk for cancer, and genetic toxicology studies do not provide organ-specific risk assessment for cancer relevant to current smokers.

[18] See the ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals.*

[19] See the ICH guidance for industry *S1B Testing for Carcinogenicity of Pharmaceuticals.*

[20] FDA recommends submitting the carcinogenicity study protocol(s) 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*.

[21] 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*.

APPENDIX A

Table 1: Milestones and Pivotal Toxicity Studies Recommended for Novel Components and Chemicals[1]

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 two species (adequate dose/duration studies in rodent and nonrodent species)	Maximum 6-month rodent, 9-month non-rodent studies (adequate dose/duration studies in two species)	Chronic studies in two species (6-month rodent, 9-month nonrodent studies)	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)
Carcinogenicity	Not necessary	Not necessary	Not necessary	Carcinogenicity assessment (e.g., carcinogenicity studies in two rodent species)

continued

[1] Section II. B. in the draft guidance for industry *Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products* provides additional recommendations regarding the assessment of impurities, including assessment of extractables and leachables of the delivery system of any container/closure system. 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/RegulatoryInformation/Guidances/default.htm.

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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

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