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# Nonclinical Testing of Orally Inhaled Nicotine- Containing Drug Products Guidance for Industry

## *DRAFT GUIDANCE*

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For questions regarding this draft document, contact Alina Salvatore at 240-402-0379.

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

**August 2018  
Pharmacology/Toxicology**

# **Nonclinical Testing of Orally Inhaled Nicotine- Containing Drug Products Guidance for Industry**

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# Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products Guidance for Industry<sup>1</sup>

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

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

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<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> The term *drug* is defined in section 201(g)(1) the Federal Food, Drug, and Cosmetic Act.

<sup>4</sup> 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.

<sup>5</sup> 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.

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

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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.<sup>7,8,9,10</sup>

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*.<sup>11</sup>

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.

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<sup>7</sup> 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.

<sup>8</sup> 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.

<sup>9</sup> 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.

<sup>10</sup> 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.

<sup>11</sup> 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>.

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### 54 **II. NONCLINICAL DEVELOPMENT**

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#### 56 **A. Key Considerations**

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

60

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

63

64 – For smoking cessation, the sponsor can consider if the nicotine exposure is within the  
65 range of exposure expected from lawfully marketed cigarettes, based on local and  
66 systemic exposures relevant to the proposed orally inhaled nicotine-containing drug  
67 product.

68

69 – The sponsor can rely on the exposure to nicotine in an approved drug to inform the  
70 nonclinical toxicity evaluation for this purpose. If the sponsor references a relevant  
71 approved drug, that drug should provide equal or higher exposure than the exposure  
72 anticipated from the proposed orally inhaled nicotine-containing drug product,  
73 considering the conditions of use proposed in labeling. For example, a relevant  
74 approved drug is one that has similar conditions of use to the proposed orally inhaled  
75 nicotine-containing drug product, including the dose, duration, route of  
76 administration, and the indicated population.

77

78 • The sponsor should submit toxicity information for all components of the drug product  
79 formulation, heat-generated products, and impurities to support clinical use.

80

81 – In many cases, use of the delivery system will generate novel chemicals (e.g., heat-  
82 generated products).

83

84 • FDA will consider existing information that supports the use of novel chemicals, to the  
85 extent that such data reflect current scientific standards and sponsors have the right to  
86 rely on the data. In this case, such data should adequately provide the toxicity  
87 information that the FDA-recommended studies (see section II. B., Recommendations for  
88 Nonclinical Development) are designed to provide.

89

90 • The risks from orally inhaled nicotine-containing drug products need to be properly  
91 characterized by the sponsor. Orally inhaled nicotine-containing drug products result in  
92 local and systemic exposure to nicotine and other chemicals, including heat-generated  
93 chemicals, via the inhalation, buccal, and oral routes of administration. Some chemicals  
94 may be novel, not found in relevant, previously approved drug products, or may not have  
95 adequate toxicity information available. Local and systemic exposure should be  
96 addressed in the toxicity assessment.

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- All drugs have risks. FDA weighs the benefits and risks with respect to the proposed indication and patient population.<sup>12</sup> 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**

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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<sup>13</sup> (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.<sup>14</sup>

#### *1. General Principles*

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

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- 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

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<sup>12</sup> 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>.

<sup>13</sup> See the ICH guidance for industry *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*.

<sup>14</sup> 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.

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134 being administered to animals. For example, the dose is measured at the site of  
135 administration (e.g., the nose for rats) in nonclinical inhalation studies. The resulting  
136 systemic exposure is determined based on toxicokinetic data.

- 137
- 138 • In general, FDA recommends inhalation studies to support use of novel chemicals  
139 because systemic toxicity studies by other routes do not sufficiently model drug  
140 deposition in the lung (i.e., bronchi, bronchioles, and alveoli) that occurs following oral  
141 inhalation exposure.
  - 142
  - 143 • Toxicokinetic measurements are usually obtained during ongoing nonclinical toxicity  
144 studies, rather than through separate studies.
  - 145
  - 146 • FDA recognizes that metabolism may affect toxicity, and so sponsors should characterize  
147 metabolism as recommended in ICH M3(R2).
  - 148
  - 149 • Sponsors should follow available guidance on assessment of drug substance and drug  
150 product impurities<sup>15</sup> and consider if the nicotine derived from plant-based products may  
151 be associated with genotoxic impurities. Nicotine-specific impurities that are present at  
152 higher levels than in approved drug products, considering the route of administration,  
153 population, dose, and duration, are a concern if the drug products also exceed relevant  
154 ICH-recommended limits. FDA will assess such impurities on a case-by-case basis.
  - 155
  - 156 • To support marketing approval, the sponsor should submit a toxicological assessment of  
157 extractables and leachables of the delivery system and any container/closure system.  
158 Sponsors should consider the level of these impurities under different conditions,  
159 including when overheating occurs to produce a dry puff.

### 160 2. *General Toxicology Studies*

161 The following are FDA recommendations for a general toxicology assessment:

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- 163 • For general toxicology studies to address novel chemicals, FDA recommends studies in  
164 rodent and nonrodent species (see Appendix A), consistent with international standards  
165 for pharmaceutical development.<sup>16</sup> It is strongly preferred that both species be dosed by  
166 the inhalation route of administration provided that this route of administration results in  
167 systemic exposure in at least one species sufficient to assess toxicity compared to the  
168 anticipated clinical systemic exposure. Inhalation studies should include a full panel of  
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<sup>15</sup> 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*.

<sup>16</sup> See *ICH M3(R2)*.



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

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

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176     ▪ The rodent species be dosed by a noninhalation route to allow for systemic  
177 toxicity assessment.

178

179     ▪ The nonrodent species be dosed by the inhalation route of exposure, using a  
180 method (e.g., a face mask) that allows for oral and nasal inhalation of chemicals,  
181 resulting in buccal and oral exposure to the drug, to model oral inhalation in  
182 humans. Rodents are primarily nose breathers and may not receive adequate  
183 buccal and oral exposure to the drug relevant to clinical use of orally inhaled  
184 nicotine-containing drug products.

185

186     ▪ The relevant mucosa be evaluated macroscopically and microscopically.

187

### 188 3. *Developmental and Reproductive Toxicology*

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190 FDA recommends developmental and reproductive toxicology studies<sup>17</sup> for novel chemicals for  
191 which adequate toxicity data are not available. The sponsor should conduct these studies using a  
192 route of administration that results in systemic exposure and exposure to the reproductive organs.  
193 The following are FDA recommendations for a developmental and reproductive toxicology  
194 assessment:

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196     • Sponsors should consider FDA’s general recommendations (see Appendix A) and refer to  
197 ICH M3(R2) for more specific recommendations on the timing of reproductive and  
198 developmental toxicology studies.

199

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

203

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

207

### 208 4. *Carcinogenicity*

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210 The following are FDA recommendations for a carcinogenicity assessment:

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

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<sup>17</sup> 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*.

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

222  
223 – Carcinogenicity studies by the oral route in two different rodent species (e.g., mouse  
224 and rat) can be sufficient (i.e., no inhalation carcinogenicity study) for novel  
225 chemicals when proliferative or preneoplastic changes in the respiratory tract are not  
226 observed in chronic inhalation toxicity studies and when adequate local buccal and  
227 airway exposure by the oral route is demonstrated.<sup>21</sup>

### 228 229 5. *Genetic Toxicology*

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231 The following are FDA recommendations for a genetic toxicology assessment:

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- 233 • FDA’s recommendation for genetic toxicology studies of novel chemicals depends on the  
234 tobacco use and smoking status of subjects in the proposed clinical trials because of the  
235 differential cancer risks in these populations.  
236
    - 237 – FDA recommends genetic toxicology studies, as described in ICH M3(R2), to assess  
238 the toxicity of novel chemicals if clinical trials are conducted in subjects who are not  
239 current smokers.
    - 240 – In general, FDA does not recommend genetic toxicology studies to support clinical  
241 trials in current smokers because this population is already at risk for cancer, and  
242 genetic toxicology studies do not provide organ-specific risk assessment for cancer  
243 relevant to current smokers.  
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<sup>18</sup> See the ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals*.

<sup>19</sup> See the ICH guidance for industry *S1B Testing for Carcinogenicity of Pharmaceuticals*.

<sup>20</sup> 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*.

<sup>21</sup> 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*.

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**APPENDIX A**

**Table 1: Milestones and Pivotal Toxicity Studies Recommended for Novel Components and Chemicals<sup>1</sup>**

Milestones and toxicity studies	Drug product development phase			
	Phase 1	Phase 2	Phase 3	Phase 4
<b>Clinical Characteristics</b>	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
<b>General toxicity</b>	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
<b>Developmental and reproductive toxicity</b>	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)
<b>Carcinogenicity</b>	Not necessary	Not necessary	Not necessary	Carcinogenicity assessment (e.g., carcinogenicity studies in two rodent species)

*continued*

<sup>1</sup> 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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254 *Table 1, continued*

<b>Genetic toxicity</b>	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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