
Guidance for Industry

Nonclinical Studies for

Development of

Pharmaceutical Excipients

DRAFT GUIDANCE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)
Center for Biologics Evaluation and Research (CBER)
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Nonclinical Studies for Development of Pharmaceutical Excipients

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This document provides guidance concerning development of safety profiles to support use of new excipients as components of drug or biological products. It is intended for use by reviewers within both the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) and by interested individuals in industry. This guidance is intended to foster and expedite the development of new excipients, communicate to industry current CDER and CBER thoughts pertaining to the safety data that should be generated to support excipient development, and to increase uniformity within CDER and CBER as to expectations for the nonclinical development of excipients.

II. BACKGROUND

In this guidance, the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration. Examples of ingredients include fillers, extenders, diluents, wetting agents, solvents, emulsifiers, preservatives, flavors, absorption enhancers, sustained-release matrices, and coloring agents. Within the context of this guidance, the term excipient does not apply to macromolecular compounds like albumin, or compounds like amino acids and sugars that are used in biological products, nor does it apply to process or

¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

42 product-related impurities (e.g. degradation products, leachates, residual solvents), or extraneous
43 contaminants.

44
45 Excipients are potential toxicants. It is important to perform risk-benefit assessments on
46 proposed new excipients in drug products and to establish permissible and safe limits for these
47 compounds. Safety data should be submitted to support use of new excipients. As a result, there
48 is a perception that development of new excipients is resource intensive. With proper planning,
49 however, it is often possible to assess the toxicology of an excipient in a relatively efficient
50 manner. For example, sponsors may be able to develop new excipients concurrently with
51 development of new therapeutic substances by adding groups of animals that receive the
52 excipient to studies that would have been conducted anyway to develop a drug substance. We
53 recognize that existing human data for some excipients can substitute for nonclinical safety data,
54 and an excipient with documented prior human exposure under circumstances relevant to the
55 proposed use may not require evaluation in the full battery of toxicology studies outlined below.
56 For example, we will continue to consider factors such as use in previously approved products or
57 GRAS status as a food additive. Under some circumstances (e.g., similar route of
58 administration, level of exposure, patient population, and duration of exposure) other factors can
59 adequately qualify an excipient, although it may be important for the safety database associated
60 with that excipient to be brought up to current standards (e.g., submission of additional genetic
61 toxicology data). The applicable information that supported the prior use will be considered in
62 light of any proposed new use.

63
64 For products marketed under OTC drug monographs, 21 CFR 330.1(e) sets the criteria for
65 inactive ingredients: "The product contains only suitable inactive ingredients which are safe in
66 the amounts administered and do not interfere with the effectiveness of the preparation or with
67 suitable tests or assays to determine if the product meets its professed standards of identity,
68 strength, quality, and purity. Color additives may be used only in accordance with section 721 of
69 the act and subchapter A of this chapter." It is the manufacturer's responsibility to meet these
70 criteria and to have appropriate supporting data in its files. The provisions of section 330.1(e) do
71 not apply to OTC products marketed under new drug applications (NDAs) or abbreviated new
72 drug applications (ANDAs).

73
74 Requirements for submitting safety information on inactive ingredients in ANDAs for generic
75 products are stated in 21 CFR 314.94 (a)(9). Under this regulation, drug products intended for
76 parenteral, ophthalmic, or otic use should contain the same inactive ingredients in the same
77 concentrations as the reference listed drug product, with the exception of buffers, antioxidants,
78 and preservatives, provided that the applicant identifies and characterizes the differences and
79 provides information demonstrating that the differences do not affect the safety of the proposed
80 drug product. For other routes of administration (e.g., topical dermal, oral), there is no
81 requirement that the inactive ingredients in the final formulations be the same as those in the
82 reference listed drug product. However, the applicant is required to identify and characterize the
83 differences in inactive ingredients and provide information demonstrating that the differences do
84 not affect the safety of the proposed drug product. Consideration should be given to the prior
85 indication and patient population for which use of the excipient was previously deemed safe.
86 Alternatively, new or additional information to support the proposed new use should be
87 referenced.

88
89 A new or inadequately qualified inactive ingredient proposed for use in any product to be
90 marketed pursuant to an NDA, BLA, or ANDA should be supported by adequate data, which
91 may be placed in the application directly or in a drug master file (DMF). This guidance
92 describes what nonclinical data should be submitted to verify that a proposed excipient is safe in
93 the amounts administered if relevant prior human use cannot be adequately documented.

94
95 We may request additional safety data if we determine that the proposed conditions of use are
96 not fully supported by the available data. A pharmacokinetic profile could be requested for
97 excipients that are extensively absorbed or biotransformed. Where applicable, drug-excipient
98 interaction studies might also be requested. The proposed conditions of use of a new excipient
99 (e.g., use in pediatric patients) may affect the need for toxicology data.

100
101 We recognize that every compound is unique and that scientifically valid reasons may exist for
102 modifying and deleting certain of the studies listed below for a given combination of excipient
103 and proposed use. For example, it may be justifiable for the development of excipients deemed
104 necessary for the delivery of life saving therapies to be abbreviated (relative to development of
105 excipients for use in products for low morbidity indications) or completed postapproval. As
106 another example, excipients that are large polymers that differ from previously characterized
107 compounds only in molecular weight (chain length) may be adequate using less safety data,
108 provided that the new compound and the previously studied compound are sufficiently similar
109 with regard to physical state, pharmacokinetics, and levels of unreacted monomers and other
110 impurities. We will consider such excipients on a case-by-case basis. All pivotal toxicology
111 studies should be performed in accordance with state-of-the-art protocols and good laboratory
112 practice regulations. The recommendations given below are primarily intended for compounds
113 for which adequate prior human exposure has not been documented.

114
115

116 **III. RECOMMENDED DEVELOPMENT STRATEGIES TO SUPPORT** 117 **MARKETING OF NEW EXCIPIENTS IN DRUG PRODUCTS**

118 119 **A. Safety Pharmacology**

120
121 It is recommended that all potential new excipients be appropriately evaluated for
122 pharmacological activity using a battery of standard tests (see ICH S7 guidance). These
123 evaluations may be performed during the course of toxicology studies or as independent
124 *safety pharmacology* studies. It is useful for these data to be obtained at an early point
125 during the development of an excipient, since, if the excipient is found to be
126 pharmacologically active, this information may influence subsequent development.

127 128 **B. Potential Excipients Intended for a Maximum Duration of Clinical Use of 14** 129 **Consecutive Days or Less.**

130
131 It is recommended that the safety development of potential new excipients that are
132 intended for use in products that are limited by labeling to clinical use of 14 or fewer

133 consecutive days per treatment episode and are infrequently used include at least the
134 following:

- 136 1. Acute toxicology studies should be performed in both a rodent species and a
137 mammalian nonrodent species by the route(s) of administration intended for
138 clinical use (see CDER guidance for industry, *Single Dose Acute Toxicity*
139 *Testing for Pharmaceuticals*). It is not necessary to determine the LD₅₀ of an
140 excipient.² It may be appropriate to omit acute toxicology studies from the
141 development of a new excipient under certain circumstances. For example, if
142 repeat-dose toxicology studies are performed in which the *high* dose is the
143 maximum feasible dose (MFD,³ e.g., 5 g/kg or 5% of the diet) and little or no
144 toxicity is observed at the MFD, it can be assumed that the acute toxicity has
145 been adequately evaluated.
- 146 2. It is highly recommended that the absorption, distribution, metabolism, and
147 excretion of the excipient be studied following administration by the clinically
148 relevant route(s) to the same species that are used in the nonclinical safety
149 studies (see the ICH S3A and S3B guidances). These data may be obtained in
150 separate (pharmacokinetic) studies or as toxicokinetic analyses associated
151 with toxicology studies.
- 152 3. Excipients should be evaluated in the standard battery of genetic toxicology
153 studies discussed in the ICH S2B guidance.
- 154 4. One-month repeat dose toxicology studies should be performed in both a
155 rodent species and a mammalian nonrodent species by the route(s) of
156 administration intended for clinical use. The studies should use state-of-the-
157 art protocols and include complete clinical pathology, histopathology, and
158 toxicokinetic analysis.
- 159 5. The reproductive toxicology of the excipient should be evaluated as discussed
160 in the ICH S5A and S5B guidances, including: (1) assessment of potential to
161 affect fertility or early embryonic development to implantation, (2) teratology
162 in both a rodent species and a mammalian nonrodent species, and (3) effects
163 on prenatal and postnatal development, including maternal function. It is
164 suggested that the most efficient way to address these different developmental
165 landmarks is use of a *single-study* rodent assay (as defined in the ICH S5A
166 guidance) to assess all phases of reproductive toxicity, in conjunction with a
167 teratology study in a nonrodent species provided that the available data predict
168 the excipient has minimal toxicity.

174 **C. Potential Excipients Intended for a Maximum Duration of Clinical Use of**
175 **More than 14 days but Less than or Equal to 90 Consecutive Days.**
176

² 53 FR 39650 (October 11, 1988)

³ Maximum feasible dose

177 It is recommended that the nonclinical development of potential new excipients that are
178 intended for use in drug products that are labeled for clinical use of more than 14 days
179 but less than or equal to 90 consecutive days per treatment episode include at least the
180 following:

- 181
182 1. All studies from sections A and B in this guidance, with the exception of the
183 1-month toxicology studies. Note: If toxicity or significant biological activity
184 is observed in short-term studies, one-month toxicology studies may be useful
185 for establishing dosages to be used in 3-month studies.
- 186
187 2. Three-month repeat dose toxicology studies should be performed in both a
188 rodent species and a mammalian nonrodent species by the appropriate route(s)
189 of administration. The studies should use state-of-the-art protocols and
190 include complete clinical pathology, histopathology, and toxicokinetic
191 analysis.
- 192
193 3. Other studies may be called for (e.g., studies involving parenteral
194 administration). Whether more data should be gathered is usually driven by
195 questions raised in the already completed studies.

196
197 **D. Potential Excipients Intended for a Maximum Duration of Clinical Use of**
198 **More Than 3 Months.**

199
200 It is recommended that the safety development of potential new excipients that are
201 intended for use in drug products labeled for clinical use of more than 3 months in a
202 given patient (either as a single treatment episode or as a result of multiple courses of
203 therapy to treat a chronic or recurrent condition) include at least the following:

- 204
205 1. All studies from sections A, B, and C of this guidance. Note that 28-day and
206 90-day toxicology studies are not essential, but may provide useful dosage
207 selection data.
- 208
209 2. A 6-month repeat-dose toxicology study should be performed in a rodent
210 species by the appropriate route(s). The study should use state-of-the-art
211 protocols and include complete clinical pathology, histopathology, and
212 toxicokinetic analysis. Studies involving excipients of low toxicity should, in
213 general, use the MFD as the upper limit for testing.
- 214
215 3. A chronic toxicology study should be performed in a mammalian nonrodent
216 species by the appropriate route(s). If toxicity and pharmacologic effect were
217 absent in state-of-the-art subchronic studies, a 6-month study may be
218 sufficient. When toxicity is detected in shorter duration studies, or in rodents,
219 the chronic study in nonrodents should be extended to 1 year.⁴

⁴ A 9 month study may be adequate in cases in which substantial human experience exists with closely related excipients or when long-term clinical testing will provide a substantial portion of the safety database.

- 221 4. If appropriate (see ICH S1A guidance), one of the following approaches
222 should be used to evaluate carcinogenic potential:
223
224 a. Two-year carcinogenicity bioassays in two appropriate species by the
225 relevant route(s).⁵
226
227 b. A two-year carcinogenicity study in one rodent species plus an
228 *alternative* study (e.g., appropriate use of neonatal or transgenic
229 animals) in a different rodent species. The usual choice for that
230 alternative, absent evidence of genotoxicity, should be a model
231 sensitive to nongenotoxic carcinogenic events.
232
233 c. Submission of documentation providing scientific justification that
234 carcinogenicity data are not necessary. For example, based on
235 negative genetic toxicology data (see ICH S2B guidance for
236 recommended assays), limited systemic exposure, absence of
237 accumulation based on nonclinical and clinical pharmacokinetic data,
238 negative histopathology data from chronic toxicology studies
239 performed at the MFD (absence of preneoplastic lesions and other
240 toxicologic effects), and knowledge of other compounds in the same
241 class, it may be reasonable to forego carcinogenicity testing.
242 Decisions concerning the adequacy of this approach would be made on
243 a case-by-case basis, using a weight-of-evidence approach. In other
244 cases, adequately performed cell transformation assays or one 2-year
245 bioassay in the rat or one transgenic assay, if negative, may be
246 sufficient to contribute to the weight of evidence assessment to address
247 the carcinogenic potential of the excipient. It is strongly encouraged
248 that application of the above approach be undertaken in consultation
249 with appropriate CDER or CBER staff.
250

251 **E. Potential excipients for use in pulmonary or topical products.**
252

253 It is recommended that the safety development of potential new excipients that are
254 intended for use in topical (dermal, intranasal, intraoral, ophthalmic, rectal, or vaginal) or
255 pulmonary drug products include the following⁶:
256

- 257 1. All studies from sections A, B, C, or D, as appropriate, using the appropriate
258 route of administration. Studies that include the to-be-marketed formulation of

⁵ When possible, it may be most cost-effective for excipients to be evaluated for carcinogenicity through inclusion in bioassays that are conducted in support of active ingredients. In such cases, it may be appropriate for the carcinogenicity assessment of an excipient to be limited to administration of a single dosage of the excipient per species (addition of a single *arm* to each bioassay), provided that the dosage was either the maximum tolerated dose (MTD) or the MFD.

⁶ For cases in which a new excipient is being developed in relation to a specific product, sponsors are encouraged to consult with the appropriate division to determine if additional guidance is available.

- 259 the drug product are preferred, if this information is available at the time of
260 excipient development.
261
- 262 2. Sensitization study (e.g., guinea pig maximization study or murine local
263 lymph node assay).
264
 - 265 3. Excipients intended for topical use may require support from toxicology
266 studies by both the intended clinical route and by the oral or parenteral route if
267 clinical pharmacokinetic studies conducted under conditions of maximum
268 exposure show patients would experience systemic exposure to the excipient
269 or its metabolite, particularly if limited systemic exposure were observed in
270 nonclinical studies conducted by the clinical route of administration. The
271 developer of a potential new excipient is invited to contact the appropriate
272 center to discuss whether or not this is appropriate for a specific compound.
273
 - 274 4. For topical dermal products and ophthalmic products, it may be appropriate to
275 conduct an ocular irritation study.
276

277 **F. Photosafety data.**
278

279 It is recommended that excipients be evaluated for photosafety as described in the CDER
280 guidance for industry entitled *Photosafety Testing*.
281

282
283 **IV. SUMMARY**
284

285 In summary, acknowledging the need to develop new excipients, CDER and CBER have
286 proposed a flexible approach that attempts to consider both the type of use the excipient will
287 have in approved products and the biological activity and physical properties of the molecular
288 entity. It is recognized that during the course of data evaluation, the reasons for additional data
289 or the potential to eliminate some studies may become apparent. In such cases, consultation with
290 appropriate center staff is recommended to avoid development delays
291