
Guidance for Industry, Investigators, and Reviewers

Exploratory IND Studies

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) David Jacobson-Kram 301-443-5346.

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

**April 2005
Pharmacology/Toxicology**

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry, Investigators, and Reviewers

Exploratory IND Studies

*Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
<http://www.fda.gov/cder/guidance/index.htm>*

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Guidance for Industry and Reviewers¹

Exploratory IND Studies

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. Alternative approaches can be used if the approach satisfies the requirements of the applicable statutes and regulations. Discussions of an alternative approaches can be scheduled by contacting the FDA staff responsible for implementing this guidance. If the appropriate FDA staff cannot be located, contact can be made using the telephone number listed on the title page of this guidance.

I. INTRODUCTION

This guidance clarifies what preclinical and clinical approaches (including chemistry, manufacturing, and controls) should be considered when planning exploratory IND studies in humans, including studies of closely related drugs or therapeutic biological products, under an investigational new drug (IND) application (21 CFR 312). Existing regulations allow a great deal of flexibility in terms of the amount of data that need to be submitted with an IND application, depending on the goals of an investigation, the specific human testing being proposed, and the expected risks. The Agency believes that sponsors have not taken full advantage of that flexibility and often provide more supporting information in their INDs than is required by regulations. This guidance is intended to clarify what approaches (preclinical and clinical) can be considered when planning limited, early exploratory IND studies in humans.

For the purposes of this guidance the phrase *exploratory IND study* is intended to describe a clinical trial that occurs very early in phase 1, involves very limited human exposure, and has no therapeutic intent (e.g., screening studies, microdose studies). Such exploratory IND studies are conducted prior to the traditional dose escalation, safety, and tolerance studies that ordinarily initiate a clinical drug development program. The duration of dosing in an exploratory IND study is expected to be limited (e.g., 7 days). This guidance applies to early phase 1 clinical

¹ This guidance was developed by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

This draft guidance contains information collection provisions that are subject to review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collection of information in this guidance has been approved under OMB Control No. 0910-0014.

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38 studies involving investigational new drug and biological products that assess feasibility for
39 further development of a drug or biological product.²

40
41 FDA's guidance documents, including this guidance, do not establish legally enforceable
42 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
43 be viewed only as recommendations, unless specific regulatory or statutory requirements are
44 cited. The use of the word *should* in Agency guidances means that something is suggested or
45 recommended, but not required.

46
47

II. BACKGROUND

48

49
50 In its March 2004 *Critical Path Report*,³ the Agency explained that to reduce the time and
51 resources expended during early drug development on candidates that are unlikely to succeed,⁴
52 tools are needed to distinguish earlier in the process those candidates that hold promise from
53 those that do not. This guidance describes some early phase 1 exploratory approaches that are
54 consistent with regulatory requirements, but that will enable sponsors to move ahead more
55 efficiently with the development of promising candidate products while maintaining needed
56 human subject protections.

57

A. Traditional Phase 1 Approach

58

59
60 Typically, during pharmaceutical development, large numbers of molecules are generated in very
61 small quantities with the goal of identifying the most promising candidates for further
62 development. These molecules are generally related in some way, either as a single active
63 ingredient with multiple salts or esters, or closely related active moieties. Promising candidates
64 are often selected using in vitro testing models that examine binding to receptors, effects on
65 enzyme activities, toxic effects, or other in vitro pharmacological parameters. Candidates that
66 are not rejected during these early tests are prepared in greater quantities for in vivo animal
67 testing for efficacy and safety. Commonly, a single candidate is selected for an IND application
68 and introduction into human subjects, often healthy volunteers.

69

70 Before the human studies can begin, an IND must be submitted to the Agency containing, among
71 other things, information on any risks anticipated based on the results of pharmacological and
72 toxicological data collected during studies of the drug in animals (21 CFR 312.23(a)(8)). These
73 basic safety tests are most often performed in rats and dogs. The studies are designed to permit
74 the selection of a safe starting dose for humans, to gain an understanding of which organs may be

² Specifically, this guidance is limited to drug and certain well-characterized therapeutic biological products (e.g., recombinant therapeutic proteins and monoclonal antibodies) regulated by CDER. The guidance does not apply to human cell or tissue products, blood and blood proteins, vaccines, or to products regulated as devices.

³ *Innovation or Stagnation, Challenge and Opportunity on the critical Path to New Medical Products* (March 2004).

⁴ "A new medical compound entering phase 1 testing, often representing the culmination of upwards of a decade of preclinical screening and evaluation, is estimated to have only an 8 percent chance of reaching the market," *Critical Path Report*, March 2004.

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75 the targets of toxicity, to estimate the margin of safety between a clinical and a toxic dose, and to
76 predict pharmacokinetic and pharmacodynamic parameters. These early tests are usually
77 resource intensive, requiring significant investment in product synthesis, animal use, laboratory
78 analyses, and time. Many resources are invested in, and thus wasted on, drug candidates that
79 subsequently are found to have unacceptable profiles when evaluated in humans. Fewer than 10
80 percent of INDs for new molecular entities (NME) progress beyond the investigational stage. In
81 addition, animal testing does not always predict performance in humans, and potentially effective
82 candidates may not be developed because of resource constraints.

83
84 Existing regulations allow a great deal of flexibility in terms of the amount of data that need to
85 be submitted with any IND application, depending on the goals of an investigation, the specific
86 human testing being proposed, and the expected risks. The Agency believes that sponsors have
87 not taken full advantage of that flexibility. As a result, limited, early phase 1 studies, such as
88 those described in this guidance, are often supported by a more extensive preclinical database
89 than is required by regulations. This guidance is intended to clarify what preclinical and clinical
90 approaches (including chemistry, manufacturing, and controls) should be considered when
91 planning exploratory IND studies in humans, including studies of closely related drugs or
92 therapeutic biological products, under an investigational new drug (IND) application (21 CFR
93 312).

94

B. Exploratory IND Approach

96

97 Exploratory IND studies, which usually involve very limited human exposure and have no
98 therapeutic intent, can serve a number of useful goals. For example, an exploratory IND study
99 can help sponsors

100

101 • Gain an understanding of the relationship between a specific mechanism of action and the
102 treatment of a disease

103 • Provide important information on pharmacokinetics, including, for example,
104 biodistribution of a candidate drug

105 • Select the most promising lead product from a group of candidates⁵ designed to interact
106 with a particular therapeutic target in humans

107 • Explore a product's biodistribution characteristics using various imaging technologies.

108

⁵ For the purposes of this guidance, the term *candidate*, or *candidate product*, is used to describe a drug or biologic that is being testing in early exploratory studies under an IND. In contrast to other Agency guidances, this guidance does not distinguish between a *drug product* and a *drug substance*.

A *drug product* is usually used to refer to a finished dosage form (e.g., tablet, capsule, solution) that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo. A *drug substance* is usually used to refer to any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body.

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109 Whatever the goal of the study, exploratory IND studies can help identify, early in the process,
110 promising candidates for continued development, and eliminate those lacking promise. As a
111 result, exploratory IND studies may help reduce the number of human subjects and resources,
112 including the amount of candidate product, needed to select promising drugs.

113
114 The studies discussed in this guidance involve dosing a limited number of subjects with a limited
115 dose range for a limited period of time. Under an exploratory IND, depending on the study, the
116 preclinical testing programs for exploratory IND studies can be more flexible than for traditional
117 IND studies. However, sponsors submitting the kinds of studies described in this guidance have
118 not always taken full advantage of that flexibility. They often provide more supporting
119 information in their INDs than is required by the regulations. Because exploratory IND studies
120 involve administering either sub-therapeutic doses of a product, or doses expected to produce a
121 pharmacological, but not a toxic, effect, the potential risk to human subjects is less than for a
122 traditional phase 1 study that, for example, seeks to establish a maximally tolerated dose.

123 ***Therefore, limited exploratory IND investigations in humans can be initiated with less, or***
124 ***different, preclinical support than is required for traditional IND studies because exploratory***
125 ***IND studies present fewer potential risks than do traditional phase 1 studies that look for dose-***
126 ***limiting toxicities.***⁶

127
128 The Agency expects that this early phase 1, exploratory IND approach will apply to a number of
129 different study paradigms. This guidance explores several potential applications; however, many
130 others can be proposed. The Agency believes that, consistent with its Critical Path Initiative,
131 clarifying Agency thinking about how much and what kind of testing is needed to support early
132 studies in humans will facilitate the entry of new products into clinical testing and speed product
133 development.

134
135 Although exploratory IND studies may be used during development of products intended for any
136 indication, it is particularly important for manufacturers to consider this approach when
137 developing products to treat serious diseases. Because the approach can help identify promising
138 candidates more quickly and precisely, exploratory IND studies could become an important part
139 of the armamentarium when developing drug and biological products to treat serious or life-
140 threatening illness. The Agency has previously articulated its commitment to ensuring that
141 appropriate flexibility is applied when patients with a serious disease and no satisfactory
142 alternative therapies are enrolled in a trial with therapeutic intent.⁷

143

144

III. CONTENT OF IND SUBMISSIONS

145

146
147 To begin any kind of testing in humans, applicants must submit an IND application to the
148 Agency with certain types of information (see 21 CFR 312.23 IND Content and Format). The

⁶ Generally, these types of studies would not be carried out in pediatric patients or in pregnant or lactating women.

⁷ Subpart H Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. See also FDA guidance for industry *Fast Track Drug Development Programs — Designation, Development, and Application Review*.

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149 primary purpose of the IND submission is to ensure that subjects will not face undue risk of
150 harm. The major information that must be submitted includes:

151

- 152 • Information on a clinical development plan
- 153 • Chemistry, manufacturing, and controls information
- 154 • Pharmacology and toxicology information
- 155 • Previous human experience with the investigational candidate or related compounds,
156 if there is any

157

158 The following sections discuss the first three in more detail. Because the exploratory IND
159 studies addressed by this guidance will be first in human studies, previous human experience is
160 not pertinent and will not be discussed. The common theme throughout is that, depending on the
161 study, the information requirements for exploratory IND studies are more flexible than for
162 traditional IND studies.

163

A. Clinical Information

165

1. Introductory statement and general investigational plan

167

168 A traditional IND application describes the rationale for the proposed clinical trial program and
169 discusses the potential outcome of the clinical investigation. The exploratory IND studies
170 discussed here focus on a circumscribed study or group of studies, and plans for further
171 development cannot be formulated without the results of these studies. Therefore, we
172 recommend that an exploratory IND application articulate the rationale for selecting a compound
173 (or compounds) and for studying them in a single trial or related trials as this represents what is
174 known about the overall development plan at this stage. This section should also describe the
175 plan to withdraw the exploratory IND application⁸ after completing the outlined study or studies,
176 or the intent to supplement the exploratory IND with the appropriate complement of preclinical
177 data to permit expanded clinical testing.

178

2. Types of studies

180

181 Potentially useful study designs include both single- and multiple-dose studies. In single-dose
182 studies, a sub-pharmacologic⁹ or pharmacologic dose is administered to a limited number of
183 subjects. For example, microdose studies usually involve the single administration of a small
184 dose with the goal of collecting pharmacokinetic information or performing imaging studies, or
185 both.

186

⁸ The withdrawn, or inactive, IND can be referenced in the traditional IND.

⁹ A radiolabeled candidate compound can be administered at doses that are known to have no pharmacologic effect in humans without an IND application in basic research studies, following the initial publication in the medical literature of a first in human experience with that radiolabeled compound. These basic research investigations are conducted under the oversight of an institutional review board (IRB) and a radioactive drug research committee (21 CFR 361.1).

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187 Repeat dose clinical studies can be designed with pharmacological or pharmacodynamic
188 endpoints. In exploratory IND studies, the duration of dosing should be limited (e.g., 7 days).
189 For escalating dose studies done under an exploratory IND, dosing should be designed to
190 investigate a pharmacodynamic endpoint, not to determine the limits of tolerability.

191

B. Chemistry, Manufacturing, and Controls Information

192

193
194 The regulations at 21 CFR 312.23(a)(7)(i) emphasize the graded nature of chemistry,
195 manufacturing, and controls (CMC) information needed as development under an IND
196 application progresses. Although, in each phase of a clinical investigational program, sufficient
197 information should be submitted to ensure the proper identification, strength, quality, purity, and
198 potency of the investigational candidate, the amount of information that will provide that
199 assurance will vary with the phase of the investigation, the proposed duration of the
200 investigation, the dosage form, and the amount of information otherwise available. For the
201 purpose of an exploratory IND application, the CMC information indicated below can be
202 provided in a summary report to enable the Agency to make the necessary safety assessment.

203

204 The sponsor must state in the beginning of the exploratory IND application whether it believes
205 the chemistry of the candidate product presents any signals of potential human risk (e.g., specific
206 findings in preclinical studies associated with known risks of related compounds) (§ 312.23). If
207 so, these signals should be discussed, and the steps proposed to monitor for such risks should be
208 described, or the reasons why the signals are not relevant to safety should be discussed.

209

210 The Agency is in the process of developing guidance explaining the stepwise approach to
211 meeting current good manufacturing practice (CGMP) regulations. Once finalized, that guidance
212 will be useful to persons seeking to manufacture, or prepare, products intended for use in an
213 exploratory IND study.

214

1. General information for the candidate product

215

216
217 Except as noted below, the extent and type of chemistry and manufacturing information to be
218 submitted in an exploratory IND application is similar to that described in current guidance for
219 use of investigational products.¹⁰ Information on the candidate product (i.e., the active
220 ingredient) can be submitted in a summary report containing the following items.

221

- 222 • Description of the candidate product, including physical, chemical, and/or biological
223 characteristics, as well as its source (e.g., synthetic, animal source, plant extract, or
224 biotechnology-derived) and therapeutic class (e.g., radiopharmaceutic,
225 immunosuppressant, agonist, antagonist) (see sections below for exceptions).
- 226 • For oral administration, sponsors can consider using suspensions or solutions in addition
227 to pills, powders, and capsules. For products intended for ophthalmic, inhalational, or
228 parenteral administration, sterility must be ensured. Any formulation or routes of

¹⁰ See guidance for industry *Content and Format of Investigational New Drug Applications for Phase I Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products*.

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229 administration intended to be used in the human trial should be described in the
230 submission. All excipients should be generally recognized as safe¹¹ or approved in
231 another product by the same route of administration and amount.¹²

232 • The grade and quality (e.g., USP, NF, ACS) of excipients used in the manufacture of the
233 investigational candidate product, including both those components intended to appear in
234 the product and those that may not appear, but that are used in the manufacturing process

235 • Name and address of the manufacturer(s) (if different from the sponsor)
236

237 • The method of preparation of the candidate product lots used in preclinical studies and
238 intended for the proposed human study, including a brief description of the method of
239 manufacture and packaging including a description of the container and closure system.
240 For the active substance include a list of the starting materials, reagents, solvents,
241 catalysts used, and purification steps employed to prepare the candidate product. For
242 sterile products, describe the sterilization process and controls for ensuring sterility. For
243 biotechnology-derived products, also identify the source material (e.g., Master Cell
244 Bank), describe the expression system (e.g., fermentation methods) and harvest methods,
245 as well as methods for removal/inactivation of potential viral contaminants. We
246 recommend the use of a detailed flow diagram as the usual, most effective, presentation
247 of this information.
248

249 • Quantitative composition of the product
250

251 • A brief description of adequate test methods used to ensure the identity, strength, quality,
252 purity, and potency accompanied by the test results, or a certificate of analysis, of the
253 candidate product lots used in toxicological studies and intended for the proposed human
254 study. For biotechnology products produced in mammalian cells or animals, this will
255 include tests and studies to ensure the removal and/or inactivation of potential viral
256 contaminants.

257 • Information that demonstrates the stability of the product during toxicology studies and
258 an explanation of how stability will be evaluated during the clinical studies

259 • For ophthalmic, inhalational, or parenteral dosage forms, results from sterility and
260 pyrogenicity tests
261

262 2. *Analytical characterization of candidate product* 263

264 There are two scenarios under which CMC information can be provided to an IND application.
265 In the first scenario, the **same batch** of candidate product is used in both the toxicology studies

¹¹ Excipients considered to be generally recognized as safe (GRAS) are included in a list that is maintained on the Internet at <http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>. See also 21 CFR 330.1, which explains the GRAS concept.

¹² Novel excipients should be appropriately qualified for their intended use. FDA has issued draft guidance on *Nonclinical Studies for Development of Pharmaceutical Excipients*. Once finalized, it will represent the Agency's thinking on this issue.

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266 and clinical trials. This material will be qualified for human use based on the CMC information
267 (see III.B.1, above) and results of the toxicology studies described elsewhere in this guidance.
268 We recommend establishing the impurity profile to the extent possible for future reference
269 and/or comparison. However, all impurities of the candidate product may not need
270 characterization at this stage of product development. If an issue arises during the toxicology
271 qualification of the product, the appropriate parameters can be studied further, on an as-needed
272 basis. Impurities should be characterized in accordance with recommendations in Agency
273 guidance,¹³ if and when, the sponsor files a traditional IND for further clinical investigation.
274

275 In the second scenario, the batch of candidate drug product to be used in the clinical studies may
276 not be the same as that used in the nonclinical toxicology studies. In such a case, the sponsor
277 should demonstrate by analytical testing that the batch to be used is **representative** of batches
278 used in the nonclinical toxicology studies. To achieve this, relevant analytical quality test
279 results should be sufficient to enable comparison of different batches of the product. Tests to
280 accomplish this include:

- 281
- 282 • Identity
 - 283 • Structure (e.g., optical rotation (for chiral compounds), reducing/non-reducing
284 electrophoresis (for proteins))
 - 285 • Assay for purity
 - 286 • Impurity profile (e.g., product- and process-related impurities, residual solvents,
287 heavy metals)
 - 288 • Assay for potency (biologic)
 - 289 • Physical characteristics (as appropriate)
- 290

C. Safety Program Designs — Examples

291
292
293 Pharmacology and toxicology information is derived from preclinical safety testing performed in
294 animals and in vitro. The toxicology evaluation recommended for an exploratory IND
295 application is more limited than for a traditional IND application.¹⁴ The basis for the reduced
296 preclinical package lies in the reduced scope of an exploratory IND study. Although exploratory
297 IND studies in some cases are expected to induce pharmacological effects, they are not designed
298 specifically to establish maximally tolerated doses. Furthermore, the duration of drug exposure
299 in exploratory IND studies is limited. The level of preclinical testing performed to ensure safety
300 will depend on the scope and intended goals of the clinical trials.
301

302 There are a number of study objectives for which the preclinical safety programs may be tailored
303 to the study design. Examples include: confirming mechanism of action; evaluating binding
304 affinity or metabolites across species; establishing the novelty of a potential therapeutic target in
305 comparison to other therapies; and validating a clinical model in healthy volunteers. Three
306 examples are discussed in detail in the following paragraphs.

¹³ See footnote 10 and guidance for industry, *INDs for Phase 2 and Phase 3 Studies, Chemistry, Manufacturing, and Controls Information*.

¹⁴ Guidance for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* describes what is expected for a traditional IND.

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1. Clinical studies of pharmacokinetics or imaging

A microdose is defined as less than 1/100th of the dose calculated to yield a pharmacological effect of a test substance and a maximum dose of ≤ 100 micrograms.¹⁵ Microdose studies are designed to evaluate pharmacokinetics or imaging of specific targets and are designed not to induce pharmacological effects. Because of this, the potential risk to human subjects is very limited and information adequate to support the initiation of such limited human studies can be derived from limited nonclinical safety studies.

FDA's current policy accepts the use of extended, single-dose toxicity studies in animals to support single-dose studies in humans. For microdose studies, a single mammalian species can be used if justified by in vitro metabolism data and by comparative data on in vitro pharmacodynamic effects. The route of exposure in animals should be the intended clinical route. In these studies, animals should be observed for 14 days postdosing with an interim sacrifice, typically on day 2, and endpoints evaluated should include body weights, clinical signs, clinical chemistries, hematology, and histopathology. The study should be designed to establish a dose inducing a minimal toxic effect, or alternatively, establishing a margin of safety. To establish a margin of safety, the sponsor should demonstrate that a large multiple (e.g., 100X) of the proposed human dose does not induce adverse effects in the experimental animals. Scaling from animals to humans based on body surface area can be used to select the dose for use in the clinical trial.

Because microdose studies involve only single exposures to microgram quantities of test materials and because such exposures are comparable to routine environmental exposures, routine genetic toxicology testing is not needed.

2. Clinical trials to study pharmacological effects

A second example involves clinical trials designed to study pharmacological effects of candidate products. More extensive preclinical safety data would be needed to support the safety of such studies. However, since the goal would not include defining a maximally tolerated dose, the evaluation can still be less extensive than typically needed to support a traditional IND application. See the flow chart in the Attachment to this document.

Repeat dose clinical trials lasting up to 7 days can be supported by a 2-week repeat dose toxicology study in a sensitive species accompanied by toxicokinetic evaluations. The goal of such a study would be to select safe starting and maximum doses for the clinical trial. The rat is the usual species chosen for this purpose, but other species might be selected. If a rodent species is used, additional studies in nonrodents, most often dogs, can be used to confirm that the rodent is an appropriately sensitive species. This confirmation can be approached in a number of ways. A lack of gender difference in the rodent study can serve as a basis for testing only a single sex in the second species if only a single sex will be studied in the clinical trial. The numbers of

¹⁵ See European Medicines Agency (EMA), Evaluation of Medicines for Human Use, "Position Paper on Non-Clinical Safety Studies to Support Clinical Trials with a Single Microdose," CPMP/SWP/2599/02Rev 1, 23 June 2004.

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350 animals used in the confirmatory study can be fewer than normally used to attain statistically
351 meaningful comparisons, but of sufficient number to meaningfully identify a toxic response. The
352 confirmatory study could be a dedicated study involving repeat administrations of a single dose
353 level approximating the rat NOAEL¹⁶ calculated on the basis of body surface area.

354
355 Alternatively, the test in the second species could be incorporated as part of an exploratory, dose
356 escalating study culminating in repeated doses equivalent to the rat NOAEL. The number of
357 repeat administrations at the rat NOAEL should, at a minimum, be equal to the number of
358 administrations, given with the same schedule, intended clinically. The route of administration
359 should be the same as the expected clinical route, and toxicokinetic measurements should be
360 used to assess exposure. The same endpoints assessed in the rodent study should be evaluated in
361 the second species. If the data from the confirmatory study suggest that the rodent is not the
362 more sensitive species, a 2-week repeated dose toxicity study should be performed in the second
363 species to select doses for human trials. This study should include measurements of body
364 weight, clinical signs, clinical chemistries, hematology, and histopathology.

365
366 If an exploratory IND study is designed to elicit pharmacological effects, each candidate product
367 to be tested should be evaluated for safety pharmacology.¹⁷ Evaluation of the central nervous and
368 respiratory systems can be performed as part the rodent toxicology studies while safety
369 pharmacology for the cardiovascular system can be assessed in the nonrodent species, generally
370 the dog.

371
372 In general, each product in this type of exploratory IND should be tested for potential
373 genotoxicity unless such testing is not appropriate for the population to be studied. The genetic
374 toxicology tests should include a bacterial mutation assay using all strains and exposure
375 conditions¹⁸ as well as a test for chromosomal aberrations either in vitro or in vivo. The in vivo
376 test can be performed in conjunction with the repeated dose toxicity study in the rodent species.
377 The high dose in this case should be a maximally tolerated dose.

378
379 The results from the preclinical program may be used to select starting and maximum doses for
380 the clinical trials. The starting dose is anticipated to be no greater than 1/50 of the NOAEL from
381 the 2-week toxicology study in the sensitive species on an mg/m² basis. The maximum clinical
382 dose would be the lowest of the following: (1) ¼ of the 2-week NOAEL; (2) ½ of the AUC at the
383 NOAEL in the 2-week rodent study, or the AUC in the dog at the rat NOAEL, whichever is
384 lower; or (3) the dose that produces a pharmacological response or at which target modulation is
385 observed in the clinical trial. Escalation from the proposed stopping dose should only be
386 performed after consultation with and concurrence of the FDA.
387

¹⁶ No-observed-adverse-effect level (NOAEL).

¹⁷ For details see the guidance for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals*.

¹⁸ For details see guidance for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals*.

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3. *Clinical studies of MOAs related to efficacy*

A third example involves clinical studies intended to evaluate mechanisms of action (MOAs). To support this approach, the FDA will accept alternative, or modified, pharmacological and toxicological studies to select clinical starting doses and dose escalation schemes. For example, short-term, modified toxicity or safety studies in two animal species based on a dosing strategy to achieve a clinical pharmacodynamic endpoint can in some instances serve as the basis for selecting the safe clinical starting dose for a new candidate drug. These animal studies would incorporate endpoints that are mechanistically based on the pharmacology of the new chemical entity and thought to be important to clinical effectiveness. For example, if the degree of saturation of a receptor or the inhibition of an enzyme were considered possibly related to effectiveness, this parameter would be characterized and determined in the animal study and then used as an endpoint in a subsequent clinical investigation. The dose and dosing regimen determined in the animal study would be extrapolated for use in the clinical investigation. In some cases, a single species could be used if it is established as the most relevant species based on scientific evidence using the specific candidate intended for the clinical investigation. Although the production of frank toxicity is not the primary intended goal of the nonclinical study, many informative endpoints (e.g., hematology and histopathology) typically incorporated into toxicity studies should be investigated at all doses.

For example, an antibody that binds with a high degree of selectivity to a tumor-associated antigen could be studied in accordance with this third category. The mechanism of action of antibody-based products is generally associated with their binding properties and the effect on functions associated with immunoglobulins. Pharmacology and toxicology studies provide information about the selection of doses used in clinical studies through evidence of both a safe upper and potentially efficacious lower limit of exposure. These doses might be consistent with target plasma levels of the drug based on animal models of disease. The upper safe levels could be established in animal studies that show a lack of toxicity at these levels.

It is expected that all preclinical safety studies supporting the safety of an exploratory IND application will be performed in a manner consistent with good laboratory practices (GLP) (21 CFR Part 58). The GLP provisions apply to a broad variety of studies, test articles, and test systems. Nonetheless, the Agency realizes that not all GLP provisions apply to all studies and, indeed, for some special studies, certain of the GLP provisions may compromise proper science. For this reason, sponsors should provide a factual basis for exemptions from conformity with GLP provisions (21 CFR 312.23(a)(8)(iii)). Sponsors are encouraged to discuss the necessity of exemptions from GLP provisions with the FDA prior to conducting safety related studies.

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426 **IV. CONCLUSION**

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428 Existing regulations allow a great deal of flexibility in terms of the amount of data that need to
429 be submitted with any IND application, depending on the goals of an investigation, the specific
430 human testing being proposed, and the expected risks. Sponsors have not taken full advantage of
431 that flexibility and limited, early phase 1 studies, such as those described in this guidance, are
432 often supported by a more extensive preclinical database than is needed for those studies alone.
433

434 The common theme throughout this guidance is that, depending on the study, the preclinical
435 testing programs for exploratory IND studies can be less detailed and more flexible than for
436 traditional IND studies. This is because for the approaches discussed in this guidance, which
437 involve administering sub-therapeutic doses of a candidate product or products, the potential
438 risks to human subjects are less than for a traditional phase 1 study.
439

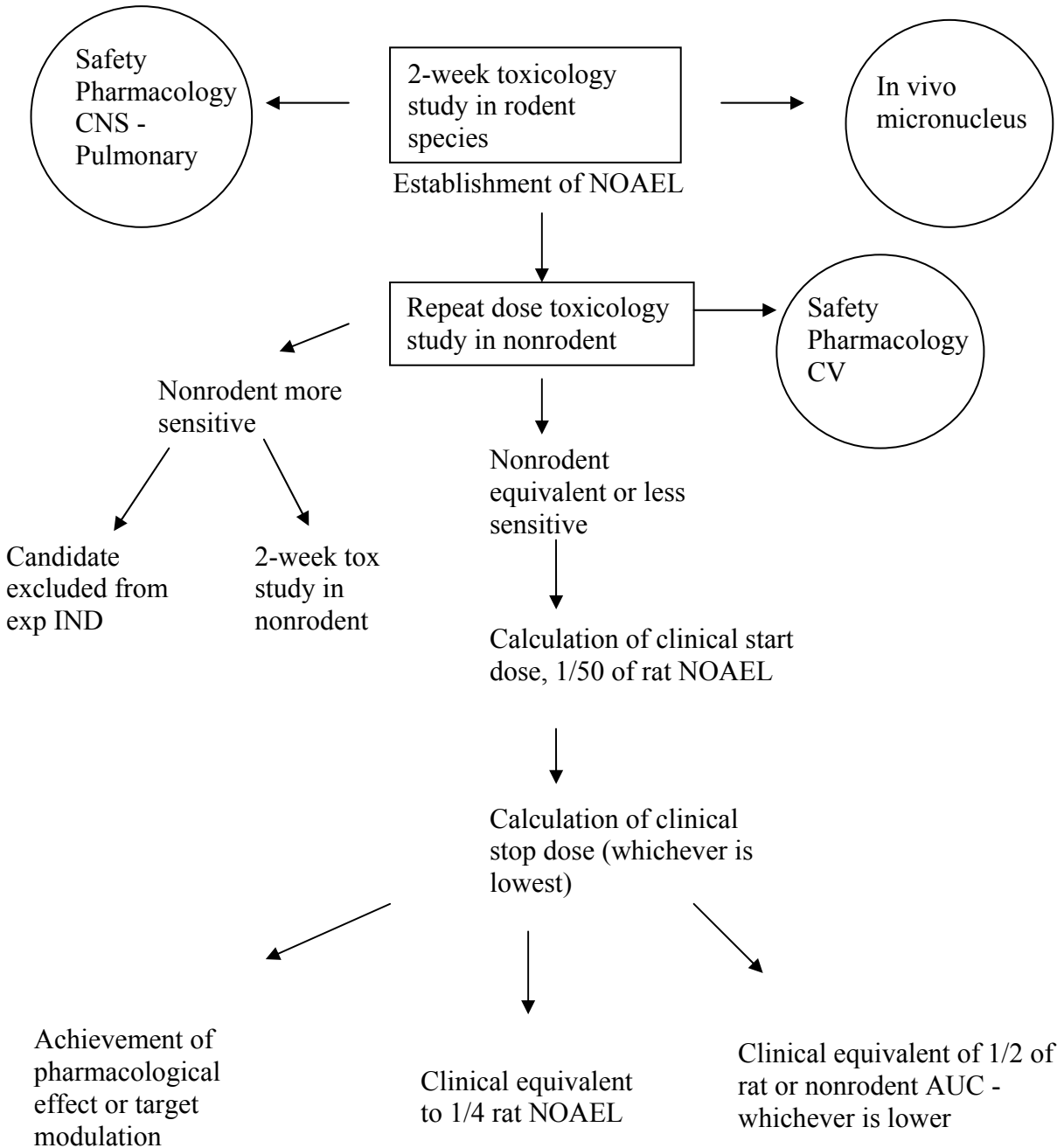
440 The Agency is undertaking a number of efforts to reduce the time spent in early drug
441 development on products that are unlikely to succeed. This guidance describes some exploratory
442 approaches that are consistent with regulatory requirements, but that will enable sponsors to
443 move ahead more efficiently with the development of promising candidate products while
444 maintaining needed human subject protections.

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ATTACHMENT

A Preclinical Toxicology Testing Strategy For Exploratory INDs Designed To Administer Pharmacologically Active Doses



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