
Guidance for Industry

IND Exemptions for Studies of Lawfully Marketed Cancer Drug or Biological Products

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DRAFT GUIDANCE

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Center for Biologics Evaluation and Research (CBER)

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40 the Agency.² However, these regulations also provide for the exemption of some
41 studies from the requirement to submit an IND if they meet certain criteria. Each year,
42 many IND applications for cancer drugs are submitted that contain studies that the
43 Agency determines are exempt. This guidance should help applicants identify which
44 studies may be exempt.

45
46 **A. Regulations**

47
48 Regulations at 21 CFR 312.2(b)(1) provide for the exemption of some studies for some
49 drugs from IND regulations if the studies meet the following five criteria:

- 50
- 51 1. The study is not intended to support FDA approval of a new indication or a
52 significant change in the product labeling.
 - 53
 - 54 2. The study is not intended to support a significant change in advertising for the
55 product.
 - 56
 - 57 3. The investigation does not involve a route of administration or dosage level or use
58 in a patient population or other factor that *significantly increases the risks* (or
59 decreases the acceptability of the risks) associated with the use of the drug
60 product.
 - 61
 - 62 4. The study is conducted in compliance with IRB and informed consent regulations
63 set forth in 21 CFR parts 56 and 50.
 - 64
 - 65 5. The study is conducted in compliance with 21 CFR 312.7 (promotion and charging
66 for investigational drugs).

67
68 Requirements 1, 2, 4, and 5 are not directly related to the specific protocol submitted,
69 and their interpretation is similar for oncologic and nononcologic therapies. Requirement
70 3 is protocol related and has special meaning in the oncology therapy setting, particularly
71 with respect to doses above the labeled dose, use with other treatments, and use in
72 different populations.

73
74 In the preamble to the IND regulations, which published in the *Federal Register* on March
75 19, 1987, the Agency explained that the exemption was not necessarily intended to tie
76 the investigator to the doses and routes of administration and patient population
77 described in the approved labeling, but to permit deviations from the approved labeling to
78 the extent that such changes are supported by the scientific literature and generally
79 known clinical experience. The Agency recognizes that a considerable amount of
80 professional judgment is exercised in determining whether the conditions significantly

² 21 CFR 312 applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)).

81 increase the risk associated with the use of the drug. FDA maintains that “because the
82 assessment of risks involved in a therapeutic procedure is an everyday part of the
83 practice of medicine, the individual investigator should usually be able to determine the
84 applicability of the exemption.”³

85
86 **B. 1996 Agency Cancer Initiative**

87
88 In 1996, as part of the President's National Performance Review, the Agency launched
89 its *Reinventing the Regulation of Cancer Drugs* initiative with the goal of accelerating the
90 approval of and expanding patient access to cancer drugs.⁴ As part of this initiative, the
91 Agency explained that many physician-investigators were submitting INDs for exploratory
92 studies for so-called off-label indications for two reasons: (1) IRBs incorrectly believe an
93 IND is required, or (2) the pharmaceutical manufacturer agrees to provide a drug free of
94 charge, but mistakenly concludes that the FDA will view this as promotional activity. With
95 the intent of clarifying the Agency's policy and decreasing the burden to investigators, the
96 Agency emphasized that it would no longer accept INDs considered exempt under 21
97 CFR 312.2(b)(1). Furthermore, FDA stated that providing a drug for study would not, in
98 and of itself, be viewed as a promotional activity if the manufacturer or distributor
99 provides the product for a physician-initiated, bona fide clinical investigation. The Agency
100 explained that it is the responsibility of the investigator to determine whether or not an
101 IND is necessary.

102
103 Despite the Agency's attempts to clarify its policy on IND exemptions, many cancer drug
104 IND applications that the Agency determines are exempt from IND regulation are still
105 being submitted. From 1997 to 1999, a majority of investigator IND submissions for
106 marketed cancer drugs were considered exempt (204, 205, and 140 applications in
107 1997, 1998, and 1999, respectively).

108
109
110 **III. RISK/BENEFIT ANALYSIS IN THE PRACTICE OF ONCOLOGY**

111
112 As noted above, a critical question in determining whether a study is exempt involves
113 criterion 3 in the exemption regulations (§ 312.2(b)(1)(iii)): The investigation may not
114 *significantly increase the risk* associated with use of a drug product. Ordinarily, the
115 question of increased risk would be related to the use as labeled and uses much above
116 the recommended dose would be a concern, but in oncology, modifications of labeled
117 dosing recommendations are common and occur as part of ordinary use. As outlined
118 below, oncologists are unusually familiar with evaluating the risk of new dosing regimens.
119

³ *Federal Register*, March 19, 1987, Vol. 52, Nr. 53, p. 8802.

⁴ *Reinventing the Regulation of Cancer Drugs -Accelerating Approval and Expanding Access* (March 1996), CBER, Office of Communication, Training, and Manufacturer Assistance FAX Information System, 1-888-CBER-FAX; document FAX ID number 0281.

- 120 • Treatment with cancer drugs, even when used according to the instructions in the
121 approved labeling, may be associated with significant risk from known toxicity.
122 Because effectiveness is believed to be related to dose, a dose close to the
123 *maximal tolerated dose* is often selected for studies of cancer drugs. This same
124 dose usually becomes the recommended dose in labeling when the new cancer
125 drug is approved with the expectation that the dose will be reduced if it is not
126 tolerated by a patient. Because it is not generally possible to have maximal
127 efficacy in a population without inducing toxicity in some patients, it is not
128 uncommon to observe severe or even lethal side effects from cancer drugs in
129 some patients, even when they are used according to the approved labeling. In
130 general, these circumstances mean that the toxicity, even potentially lethal toxicity,
131 of cancer drugs is described in approved labeling.
132
- 133 • Off-label therapy with cancer drugs is common in practice. When there is no
134 established therapy for a cancer, or stage of cancer, it is common to try different
135 regimens or combinations of established drugs. A 1996 GAO report (*Prescription
136 Drugs, Implications of Drug Labeling and Off-Label Use*) showed that there was
137 substantial off-label use in situations where satisfactory treatment was not
138 available, and lower rates of off-label use when there was an effective therapy. In
139 their daily practice, many oncologists treat cancer patients with regimens that
140 include off-label use of drugs. They evaluate the published data to assess the risk
141 of such treatments, and they keep patients aware of these risks through informed
142 consent. Such treatment of individual patients with approved drugs does not
143 require an IND (21 CFR 312.2(d)). In many cases, as discussed in the examples
144 in Section V below, treatment of patients with similar regimens in the context of a
145 small study would seem to involve no increased risk to patients, and an
146 investigator could conclude that such a study would not *significantly increase the
147 risk* associated with the use of a drug product and the study could be conducted
148 without an IND. Oversight by an IRB and informed consent in compliance with 21
149 CFR parts 56 and 50, respectively, would be required as usual (21 CFR
150 312.2(b)(iv)).
151

152 153 **IV. DETERMINING APPLICATION STATUS**

154 155 **A. Agency Determination**

156
157 As explained in FDA's 1996 cancer initiative, FDA does not intend to accept applications
158 for clinical studies that it determines to be exempt from the requirement for an IND.
159 Although 21 CFR 312.2(b)(1) does not require a submission for a determination of
160 exempt status, whenever an IND application is submitted, FDA staff perform an initial
161 limited review of the application to determine whether the study is exempt. The protocol-
162 related criterion FDA considers in assessing exemption is: The investigation may not
163 involve a route of administration or dosage level or use in a patient population or other

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164 factor that significantly increases the risks (or decreases the acceptability of the risks)
165 associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)). Thus, when
166 determining if the risk is significantly increased, FDA staff examine the parts of the
167 protocol that concern dose, schedule, route of administration, and patient population. If
168 the Agency's initial limited review determines that a study protocol is exempt from the
169 requirement for an IND, the Agency performs no further review of the application. A
170 letter is sent to the sponsor giving notice of the exemption.

171
172 **B. Investigator Determination**

173
174 When determining if an IND should be submitted to study marketed drugs for treating
175 cancer, investigators also should apply the exemption criteria listed in § 312.2(b)(1)(i-v)
176 in light of the discussion in this guidance. Planned studies may be considered exempt
177 from the requirements of an IND if the studies involve a new use, dosage, schedule,
178 route of administration, or new combination of marketed cancer products in a patient
179 population with cancer and the following conditions apply:

- 180
- 181 • The studies are not intended to support FDA approval of a new indication or a
182 significant change in the product labeling.
 - 183
 - 184 • The studies are not intended to support a significant change in advertising for the
185 product.
 - 186
 - 187 • Investigators and their IRBs determine that based on the scientific literature and
188 generally known clinical experience, there is no *significant increase in the risk*
189 *associated with the use of the drug product*.
 - 190
 - 191 • The studies are to be conducted in compliance with IRB and informed consent
192 regulations, pursuant to 21 CFR parts 50 and 56.
 - 193
 - 194 • The studies will not be used to promote unapproved indications, in compliance with 21
195 CFR 312.7.
- 196

197
198 **V. EXAMPLES OF STUDIES**

199
200 The following examples of studies are being provided to illustrate the types of studies
201 that the Agency considers to be exempt, or not, from IND regulation.

202
203 **A. Studies That Generally Are Exempt**

- 204
- 205 1. Single-arm, phase 2 trials using marketed drugs to treat a cancer different
206 from that indicated in the approved labeling and using doses and schedules
207 similar to those in the marketed drug labeling are usually exempt. An

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- 208 exception may exist when standard therapy in the population to be studied is
209 very effective (e.g., is associated with a survival benefit); in that case, use of
210 another regimen may expose patients to the risk of receiving an ineffective
211 therapy.
212
- 213 2. Phase 1 oncology trials of marketed drugs may be considered exempt if such
214 therapy is appropriate for the patient population (i.e., if patients have residual
215 cancer) and if there is no effective therapy that the patients have not yet
216 received (i.e., therapy producing cure or a documented increase in survival). It
217 remains the investigator's responsibility to use starting doses that appear safe
218 based on approved labeling or detailed literature reports, use incremental
219 changes in dose or schedule, and carefully evaluate toxicity prior to dose
220 escalation.
221
- 222 3. The study of new combinations of drugs would not ordinarily constitute a
223 significant risk if these combinations have been described in the literature.
224 Even when the regimen described in the literature does not use exactly the
225 doses planned for study, incremental differences in doses from those
226 described in the literature would not normally pose a significant risk and would
227 not require an IND.
228
- 229 Because of the danger of synergistic toxicity occurring with a new drug
230 combination, if there are no data from the literature on its safety, the initial
231 study of a new drug combination should ordinarily be performed under an IND.
232 Synergistic toxicity may be anticipated when one agent interferes with the
233 metabolism or elimination of the other agent; when both agents target the
234 same metabolic pathway or cellular function; or when one agent targets
235 signaling pathways that are reasonably expected to modulate sensitivity to the
236 other agent. If it is determined that synergistic toxicity is likely, animal studies
237 should be considered for determining a safe starting dose for the drug
238 combination in humans.
239
- 240 4. Studies of new routes or schedules of administration not described in the
241 approved labeling are generally exempt if there is sufficient clinical experience
242 described in the literature to determine that treatment is safe. Initial
243 experience with a new route of administration should be based on studies in
244 animals and an IND should be submitted.
245
- 246 5. Many studies of high-dose therapy in patients with cancer are exempt.
247 Studies involving adequately evaluated regimens that appear to have an
248 acceptable therapeutic ratio for the population being studied may be
249 considered exempt. Similarly, phase 1 studies involving incremental changes
250 from such well-described regimens are generally exempt.
251

252 **B. Studies That Generally Are Not Exempt**

253
254 As noted above, of the five criteria in § 312.2(b)(1), four are not protocol related
255 and one is protocol related. The following are examples of general categories of
256 studies of marketed cancer drugs that would likely *not* be exempt from IND
257 regulation because of protocol-related issues.

- 258
- 259 1. Studies of cytotoxic drugs are normally not exempt in patients for whom
260 cytotoxic therapy would not be considered standard therapy and would require
261 special justification. Any use of cytotoxic agents in non-malignant disease
262 (e.g., rheumatoid arthritis, multiple sclerosis) would, most likely, be considered
263 to alter the acceptability of the risk of the agent.
264
 - 265 2. Studies of adjuvant chemotherapy (chemotherapy given after surgery to
266 remove cancer) are likely not exempt for the following reasons:
267
 - 268 • If the population studied has a low risk of cancer recurring after surgery,
269 treatment with any toxic therapy may indicate a significantly increased risk.
 - 270
 - 271 • If standard adjuvant therapy is available and produces a survival benefit,
272 substitution of new therapy for standard therapy poses a significant risk
273 that the new therapy will not produce the same survival benefit.
274
 - 275 • If adjuvant trials are properly designed, they usually will be able to
276 demonstrate whether the new therapy is safe and effective, and such
277 results may lead to a marketing application. As discussed earlier, under
278 regulations at 21 CFR 312.2(b)(1), all investigations intended to support
279 marketing of a new product indication, significant change in product
280 labeling, or a significant change in the advertising for a product require an
281 IND. During FDA review of INDs intended to support marketing
282 applications, the Agency will provide feedback about the acceptability of
283 trial design for this purpose.
284
 - 285 3. Studies involving substitution of a new agent of unproven activity are generally
286 not exempt in settings where standard therapy provides cure or increase in
287 survival. For instance, in the first-line treatment of testicular cancer, ovarian
288 cancer, breast cancer, leukemia, and lymphoma, studies of new agents
289 without proven efficacy would likely not be exempt. In this case, the critical
290 judgment is whether it is ethical to withhold standard therapy while testing a
291 new agent.
292
 - 293 4. Studies are generally not exempt in settings where animal studies should be
294 conducted to determine a safe starting dose or schedule.
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For example:

- Initial studies of a marketed drug given by a new route of administration are likely not exempt.
 - Unless adequately described in the literature, initial studies of new drug combinations should usually be performed under an IND because of the possible occurrence of synergistic toxicity. As noted earlier, synergistic toxicity may be anticipated when one agent interferes with the metabolism or elimination of the other agent; when both agents target the same metabolic pathway or cellular function; or when one agent targets signaling pathways that are reasonably expected to modulate sensitivity to the other agent.
 - Initial studies in humans of changes in schedule of drug administration should generally be submitted in an IND. Some drugs have demonstrated significantly greater toxicity when given by an alternative schedule (e.g., methotrexate demonstrates much more hematologic toxicity when given by prolonged administration compared to intermittent administration).
 - Initial studies of drugs intended to be chemosensitizers, radiosensitizers, or resistance modulators should generally be submitted in an IND. Animal studies should be used to estimate the effect of the modulator on toxicity and to allow estimation of a safe starting dose in humans.
5. Studies intended to support approval of a new indication, a significant change in the product labeling, or a significant change in advertising are not exempt (21 CFR 312.2(b)(1)(i), (ii)). FDA believes that most randomized studies of a size that could support a labeling supplement would fall in this category.