Guidance for Industry

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

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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Clinical Medical

Revision 1

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Contains Nonbinding Recommendations

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This guidance represents 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. You can use an alternative approach if that approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist sponsors in deciding whether a study of marketed drugs or biological products for treating cancer falls within the exemption under § 312.2(b)(1) (21 CFR 312.2(b)(1)) from the general requirement to submit an investigational new drug application (IND). The guidance discusses the Agency's current thinking on when studies of marketed cancer products are exempt from IND regulation based on a risk assessment. The Agency hopes that clarifying its policy will help sponsors identify which studies are exempt, thus saving them from submitting unnecessary IND applications.

This guidance revises the guidance of the same title published in September 2003. In the September 2003 version, the Agency's final statement was that it believed that most randomized studies of a size that could support a labeling supplement would likely ***not*** be exempt from IND regulation under § 312.2(b)(1)(i), (ii). This is because they would be intended to support approval of a new indication, a significant change in the product labeling, or a significant change in advertising. Experience has shown that this interpretation was formulated too broadly and inappropriately referred to size alone. The Agency has decided to revise this guidance by removing that statement (the last sentence in section V.B). Whether a study could support a change in labeling is a complex determination, based on study design, size, and other factors.

FDA's guidance documents, including this guidance, 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

[1] This guidance has been prepared by the Division of Oncology Drug Products in the Center for Drug Evaluation and Research (CDER) and by the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Generally, regulations in part 312 (21 CFR part 312) require sponsors who wish to study a drug or biological product in humans to submit an IND to the Agency.[2] However, these regulations also provide for the exemption of some studies from the requirement to submit an IND if they meet certain criteria. Each year, many INDs for cancer drugs are submitted that contain studies that the Agency determines are exempt. This guidance is intended to help applicants identify which studies may be exempt.

A. Regulations

Regulations in § 312.2(b)(1) provide for the exemption of some studies for some drugs from IND regulations if the studies meet the following five criteria:

1. The study is not intended to support FDA approval of a new indication or a significant change in the product labeling.

2. The study is not intended to support a significant change in the advertising for the product.

3. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that *significantly increases the risks* (or decreases the acceptability of the risks) associated with the use of the drug product.

4. The study is conducted in compliance with institutional review board (IRB) and informed consent regulations set forth in parts 56 and 50 (21 CFR parts 56 and 50).

5. The study is conducted in compliance with § 312.7 (promotion and charging for investigational drugs).

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

In the preamble to the IND regulations, which published in the *Federal Register* on March 19, 1987, the Agency explained that the exemption was not necessarily intended to tie the investigator to the doses and routes of administration and patient population described in the

[2] Part 312 applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)).

approved labeling, but to permit deviations from the approved labeling to the extent that such changes are supported by the scientific literature and generally known clinical experience. The Agency recognizes that a considerable amount of professional judgment is exercised in determining whether the planned investigation significantly increases the risk associated with the use of the drug. FDA maintains that "because the assessment of risks involved in a therapeutic procedure is an everyday part of the practice of medicine, the individual investigator should usually be able to determine the applicability of the exemption."[3]

B. 1996 Agency Cancer Initiative

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

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

III. RISK/BENEFIT ANALYSIS IN THE PRACTICE OF ONCOLOGY

As noted above, a critical question in determining whether a study is exempt involves criterion 3 in the exemption regulations (§ 312.2(b)(1)(iii)): The investigation may not *significantly increase the risk* associated with use of a drug product. The question of increased risk is determined by assessing the deviation in the planned investigation from the use described in the approved label. In oncology, modifications of labeled dosing recommendations are common and

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[3] New Drug, Antibiotic, and Biologic Drug Product Regulations, *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, Voice Information System at 1-800-835-4709 or 301-827-1800, document ID number 0281. Available on the Internet at http://www.fda.gov/cber/genadmin/reincanc.htm

occur as part of oncologists' clinical practice. As outlined below, oncologists are familiar with evaluating the risk of off-label dosing regimens for cancer drug and biological products.

- Treatment with cancer drugs may be associated with significant risk from known toxicity. Because effectiveness is often related to dose, a dose close to the *maximal tolerated dose* is often selected for studies of cancer drugs. This same dose usually becomes the recommended dose in labeling when the new cancer drug is approved with the knowledge that the dose may be altered if it is not tolerated by a patient. Because it is not generally possible to have maximal efficacy in a population without inducing toxicity in some patients, it is not uncommon to observe severe or even lethal side effects from cancer drugs in some patients. In general, these circumstances mean that the toxicity, even potentially lethal toxicity, of cancer drugs is described in approved labeling.

- Off-label therapy with cancer drugs is common in practice. When there is no established therapy for a cancer, or stage of cancer, it is common for oncologists to try different regimens or combinations of established drugs. A 1996 GAO report (*Prescription Drugs, Implications of Drug Labeling and Off-Label Use*) showed that there was substantial off-label use in situations where satisfactory treatment was not available, and lower rates of off-label use when there was an effective therapy. In their daily practice, many oncologists treat cancer patients with regimens that include off-label use of drugs. They evaluate the published data and past clinical experience to assess the risk of such treatments. Such treatment of individual patients with approved drugs within their clinical practice does not require an IND (§ 312.2(d)).

- In many cases, as discussed in the examples in section V below, drug administration to patients with similar off-label regimens in the context of an investigation seems to involve no increased risk to patients, and an investigator could conclude that such a study would not *significantly increase the risk* associated with the labeled use of a drug product and the study could be conducted without an IND. Oversight by an IRB and informed consent in compliance with parts 56 and 50, respectively, would be required as usual (§ 312.2(b)(1)(iv)). On request, FDA will advise on the applicability of the IND exemption to a planned clinical investigation (§ 312.2(e)).

IV. DETERMINING APPLICATION STATUS

A. Agency Determination

As explained in FDA's 1996 cancer initiative and the IND exemption regulation, FDA will not accept applications for clinical studies that it determines to be exempt from the requirement for an IND (§ 312.2(b)(4)). Although § 312.2(b)(1) does not require a submission for a determination of exempt status, whenever an IND application is submitted, FDA staff perform an initial limited review of the application to determine whether the study is exempt. The protocol-related criterion FDA considers in assessing exemption is: The investigation may not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the

use of the drug product (§ 312.2(b)(1)(iii)). Thus, when determining if the risk is significantly increased, FDA staff examine the parts of the protocol that concern dose, schedule, route of administration, and patient population. If the Agency's initial limited review determines that a study protocol is exempt from the requirement for an IND, the Agency performs no further review of the application. A letter is sent to the sponsor giving notice of the exemption.

B. Investigator Determination

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

- The studies are not intended to support FDA approval of a new indication or a significant change in the product labeling.
- The studies are not intended to support a significant change in the advertising for the product.
- Investigators and their IRBs determine that based on the scientific literature and generally known clinical experience, there is no *significant increase in the risk associated with the use of the drug product.*
- The studies are to be conducted in compliance with IRB and informed consent regulations, pursuant to parts 50 and 56.
- The studies will not be used to promote unapproved indications, in compliance with § 312.7.

V. EXAMPLES OF STUDIES

The following examples of studies are being provided to illustrate the Agency's current thinking on the types of studies that the Agency considers to be exempt from IND regulation based on a risk assessment.

A. Studies That Generally Are Exempt

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

1. Single-arm, phase 2 trials using marketed drugs to treat a cancer different from that indicated in the approved labeling and using doses and schedules similar to those in

the marketed drug labeling are usually exempt. An exception may exist when standard therapy in the population to be studied is very effective (e.g., is associated with a survival benefit); in that case, use of another regimen may expose patients to the risk of receiving an ineffective therapy and an IND would be necessary.

2. Phase 1 oncology trials of marketed drugs may be considered exempt if such therapy is appropriate for the patient population (i.e., if patients have residual cancer) and if there is no effective therapy (i.e., therapy producing cure or a documented increase in survival) that the patients have not yet received. It remains the investigator's responsibility to use starting doses that appear safe based on approved labeling or detailed literature reports, use incremental changes in dose or schedule, and carefully evaluate toxicity prior to dose escalation.

3. The study of new combinations of drugs would not ordinarily constitute a significant risk if these combinations have been described in the professional medical literature. Even when the regimen described in the literature does not use exactly the doses planned for study, incremental differences in doses from those described in the literature would not normally pose a significant risk and would not require an IND.

   Because of the danger of synergistic toxicity (i.e., enhanced effects from the combination) occurring with a new drug combination, if there are no data from the literature on its safety, the initial study of a new drug combination should ordinarily be performed under an IND. 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. If it is determined that synergistic toxicity is likely, animal studies should be considered for determining a safe starting dose for the drug combination in humans.

4. Studies of new routes or schedules of administration not described in the approved labeling are generally exempt if there is sufficient clinical experience described in the literature documenting safety to determine that treatment is safe. On the other hand, initial experience with a new route of administration should be based on studies in animals, and an IND should be submitted.

5. Studies of high-dose therapy in cancer patients are likely to be considered exempt if the studies use adequately evaluated regimens that appear to have an acceptable therapeutic ratio for the population being studied. Similarly, phase 1 studies involving incremental changes from such well-described regimens are generally exempt.

B. Studies That Generally Are Not Exempt

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

1. Studies of cytotoxic drugs are normally not exempt in patients for whom cytotoxic therapy would not be considered standard therapy and would require special justification. Any use of cytotoxic agents in nonmalignant disease (e.g., rheumatoid arthritis, multiple sclerosis) would, most likely, be considered to alter the acceptability of the risk of the agent.

2. Studies of adjuvant chemotherapy (chemotherapy given after surgery to remove cancer) are likely not exempt for the following reasons:

   - If the population studied has a low risk of cancer recurring after surgery, treatment with any toxic therapy may indicate a significantly increased risk.

   - If standard adjuvant therapy is available and produces a survival benefit, substitution of new therapy for standard therapy poses a significant risk that the new therapy will not produce the same survival benefit.

   - If adjuvant trials are properly designed, they usually will be able to demonstrate whether the new therapy is safe and effective, and such results may lead to a marketing application. As discussed earlier, under regulations at § 312.2(b)(1), all investigations intended to support marketing of a new product indication, significant change in product labeling, or a significant change in the advertising for a product require an IND. During FDA review of INDs intended to support marketing applications, the Agency will provide feedback about the acceptability of trial design for this purpose.

3. Studies involving substitution of a new agent of unproven activity are generally not exempt in settings where standard therapy provides a cure or increase in survival. For instance, in the first-line treatment of testicular cancer, ovarian cancer, breast cancer, leukemia, and lymphoma, studies of new agents without proven efficacy would likely not be exempt. In this case, the critical judgment is whether it is ethical to withhold standard therapy while testing a new agent.

4. Studies are generally not exempt in settings where animal studies should be conducted to determine a safe starting dose or schedule.

   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 the 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 (§ 312.2(b)(1)(i), (ii)).