Regulations in 21CFR312 require sponsors who wish to study a drug or biological therapeutic in humans to submit an Investigational New Drug application to the FDA. However, 21CFR2(b)(1) provides for the exemption for some studies from the requirement to submit an IND prior to initiation of the clinical study. Many studies involving cancer drugs or post-approval evaluation of drugs (Phase IV studies) are exempt.

Regulations in 21CFR312.2(b)(1) provide exemptions for studies which 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 increase the risks (or decreases the acceptability of 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 (21CFR parts 56 and 50).
5. The study is conducted in compliance with 21CFR312.7 (promotion and charging for investigational drugs).

Requirements 1, 2, 4, and 5 are not directly related to the specific protocol submitted, and apply to both cancer and Phase IV clinical trials. Requirement 3 is protocol related and has specific meaning in the oncology therapy setting.
particularly with respect to doses above the labeled dose, use with other treatments, and use in different patient populations.

**FDA Determination of Exemption:**

Although 21CFR312.2(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 used to assess exemption is: The investigation must 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 risks) associated with the use of the drug product. If the FDA's initial limited review determines that a study protocol is exempt from the requirement for an IND, no further review of the study is performed. A letter is sent to the sponsor giving notice of the exemption.

**Cancer Clinical Trials:**

The FDA provides examples of studies which it generally considers IND exempt in the Guidance for Industry: IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer, 2004 ([http://www.fda.gov/cder/guidance/6036fnl.pdf](http://www.fda.gov/cder/guidance/6036fnl.pdf)).

- Generally Exempt

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.
• Generally Not Exempt

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)).

**Phase IV Studies:**

The investigational use of approved, marketed drugs differs from “Off-label” use by physicians whose intent is “practice of medicine.” “Investigational use” suggests the use of an approved drug in a clinical trial (Phase IV). Because Phase IV studies initiated by a drug manufacturer are often designed for commercial purposes and are likely to affect the product’s labeling or advertising (by supporting approval for new indications and new patient populations), the FDA has stated that IND submission exemptions for Phase IV studies will apply primarily to researchers in academia or other research institutions.

FDA contact information to aid in the determination of a potential IND exemption for a clinical trial involving Off-label use of an approved drug is contained in the FDA Information Sheet: “Off-Label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices