1. Purpose

To establish and describe the Office of Sponsor and Regulatory Oversight's (OSRO) Selection of IND or IDE Regulatory Filing Policy.

2. Scope

2.1. OSRO in the Center for Cancer Research (CCR), National Cancer Institute (NCI) shall establish and control the policy.

2.2. Investigators, research team members and other departmental personnel when they are working on studies conducted under a CCR-held Investigational New Drug application (IND,) or Investigational Device Exemption (IDE), Non-Significant Risk Device Study (NSR) or supported by a CCR-held Master File, shall follow the policy.

2.3. Limitations

2.3.1. Personnel are not bound to this policy when working on non-IND/IDE/NSR studies and/or no interdepartmental collaboration with OSRO as Sponsor is required.

2.3.2. Nothing in this policy will supersede NCI, National Institutes of Health (NIH) or Health and Human Services (HHS) requirements.

3. Responsibilities

3.1. CCR Management is committed to providing resources to meet the requirements for implementing a Selection of IND or IDE Regulatory Filing Policy within OSRO and supporting its continual improvement.

3.2. OSRO as the Sponsor is responsible for determining whether an IND or IDE is required.

3.3. OSRO personnel are responsible for understanding the Selection of IND or IDE Regulatory Filing Policy.

3.4. The OSRO Director is responsible for establishing and maintaining the Selection of IND or IDE Regulatory Filing Policy.

4. References

4.1. 21 CRF Part 312 Investigational New Drug Application

4.2. 21 CFR Part 812 Investigational Device Exemptions

4.3. 21 CFR Part 50 Protection of Human Subjects

4.4. 21 CFR Part 56 Institutional Review Boards

4.5. 21 CFR 807 Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices

4.6. 21 CFR Part 809 In Vitro Diagnostic Products for Human Use

4.7. FDA Guidance for Industry: IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer (January 2004)

4.8. FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND (September 2013)

4.9. FDA Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device, Studies – Frequently Asked Questions (June 2010)

4.10. FDA Draft Guidance for Industry: Applications Covered by Section 505(b)(2) (October 1999)

5. Definitions

Refer to the OSRO Lexicon.

6. Policy

6.1. OSRO will determine whether a protocol requires an IND or IDE prior to CCR Scientific Review (SRC) based on the justification presented in the SRC concept and the considerations below.

6.2. The Sponsor shall submit an IND to the Food and Drug Administration (FDA) if the Sponsor intends to support a clinical trial with an investigational new drug or biological product (collectively referred to as "product" in this policy) that is 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.)).

6.3. If all the following apply, as determined by OSRO, the trial is IND exempt and will not receive any additional OSRO services:

6.3.1. The trial is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the product labeling.

6.3.2. The trial is not intended to support a significant change in the advertising for the product.

6.3.3. The trial 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 product.

6.3.4. The trial is conducted in compliance with the requirements for institutional review set forth in 21 CFR 56 (Reference 4.4) and with the requirements for informed consent set forth in 21 CFR 50 (Reference 4.3)).

6.3.5. The trial is conducted in compliance with the requirements of 21 CFR 312.7 (promotion and charging for investigational drugs; Reference 4.1).

6.4. The Sponsor will consider the FDA Guidances and the available scientific information in determination for whether an IND or IDE is required (see also Appendix A).

6.5. The Sponsor will submit an IDE to the FDA if the Sponsor intends to support a clinical trial with an investigational device.

6.6. If one of the following apply, as determined by OSRO, the trial is IDE exempt and will not receive any additional OSRO services:

6.6.1. A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

6.6.2. A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that the FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 (Reference 4.5) in determining substantial equivalence.

6.6.3. A diagnostic device, if the Sponsor complies with applicable requirements in 21 CFR 809.10(c) (Reference 4.6) and if the testing:

6.6.3.1. Is noninvasive

6.6.3.2. Does not require an invasive sampling procedure that presents significant risk

6.6.3.3. Does not by design or intention introduce energy into a subject

6.6.3.4. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure

6.6.4. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

6.6.5. A custom device as defined in 21 CFR 812.3(b) (Reference 4.2), unless the device is being used to determine safety or effectiveness for commercial distribution.

6.7. If a determination is not certain, and at the discretion of the OSRO Director, OSRO will submit a request to the FDA to determine whether the trial requires an IND or IDE. The submission will be presented as if the trial does require an IND or IDE.

6.8. In cases where the Principal Investigator does not agree with the OSRO determination, OSRO will submit a request to the FDA to determine whether the trial requires an IND or IDE. The submission will be presented as if the protocol does require IND or IDE.

7. Change Summary

Revision Number	Effective Date	Description of Change
1	07OCT2019	New Document
2	02DEC2019	Added References 4.6, 4.7, 4.8. Added Appendix A (from Reference 4.6).
3	14JAN2022	Biennial Review Section 4 – added hyperlinks Updated document language as required
4	16MAR2023	Step 6.1 – revised to add "(SRC) based on the justification presented in the SRC concept and the considerations below."

Appendix A: Summary of Guidance for Industry IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer Examples

Protocol Designs that Generally will be Exempted:

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 of 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.

Protocol Designs that Generally will NOT be Exempted:

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. 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.

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)).