MICHR MICHIGAN INSTITUTE FOR CLINICAL & HEALTH RESEARCH UNIVERSITY OF MICHIGAN

IND DECISION WORKSHEET- Reference Document
For Investigator-Initiated Clinical Investigations

The purpose of this document is to assist investigators with assessing the need for an IND and with completing the MICHR IND DECISION WORKSHEET.

One of the FDA's primary mechanisms for ensuring the safety of research subjects is through **Investigational New Drug (IND)** filing requirements. An academic researcher may be required to submit an IND application to the FDA to study a marketed medical product in a new (i.e., unapproved) clinical indication, a different route of administration or in a different patient population. For a study involving an un-marketed or unapproved medical product an IND is required. **In both cases**, the products are considered "investigational" by the FDA.

This document is intended to help UM investigators determine if an IND may be required prior to initiating a new clinical study and assist with completing the MICHR IND DECISION WORKSHEET. This WORKSHEET will need to be provided to the IRB in support of an eResearch application prior to initiating an Investigator-Initiated Clinical Trial. Further information about determining if an IND is required can be found in the following FDA Guidance Documents:

- Determining Whether Human Research Studies Can be Conducted Without an IND
- IND Exemptions for Studies for the Treatment of Cancer

The **MICHR IND/IDE Investigator Assistance Program (MIAP)** Team will be happy to meet with any UM investigators to discuss the issues outlined in this document. MIAP can provide advice regarding the IND exemption status, IND process and support, FDA filing strategies, and protocol review and recommendations. If you are conducting a multi-site study, it is particularly important to contact MIAP to discuss FDA filing strategies.

If you have questions or need assistance, please contact MIAP at MICHRMIAP@med.umich.edu.

The questions and answer below will guide you through completing the MICHR IND DECISION WORKSHEET.

Does the product utilized in my study meet the FDA definition of a DRUG?

Definitions:

DRUG

A **DRUG** is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals or an article (other than food) intended to affect the structure or any function of the body of man or other animals.

BIOLOGIC

A **BIOLOGIC** is any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, applicable to the prevention, treatment or cure of diseases or injuries to humans. **A biologic is, therefore, also a subset of a DRUG.** Biologics differ from chemically synthesized drugs in that biologics are derived from living sources such as humans, animals, plants, and microorganisms.

> **Exemption:**
> If the product is a blood grouping serum, reagent, red blood cells, or anti-human globulin, AND is it intended to be used in a diagnostic procedure that confirms the diagnosis made by another medically established, diagnostic product or procedure **it is exempt from IND requirements as long as it is shipped with special labeling requirements (**21 CFR 312.160)**.**

DIETARY SUPPLEMENT

A **DIETARY SUPPLEMENT** is a product (other than tobacco) that is intended to supplement the diet and that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb, herbal product, or other botanical, an amino acid, a dietary substance for use by man to supplement the diet. This includes complementary or alternative medicines that were derived from organic materials from a botanical source.

If the product is being used or promoted to be used in the diagnosis, cure, mitigation, treatment, or prevention of diseases **it is considered a DRUG for research purposes.**

FOOD

A **FOOD** is considered to be a drug if it is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease," except that a food may bear an authorized health claim about reducing the risk of a disease without becoming a drug (see section VI.D.3 in this Guidance document).
Therefore, a clinical investigation intended to evaluate the effect of a food on a disease would require an IND under part 312. For example, a clinical investigation intended to evaluate the effect of a food on the signs and symptoms of Crohn's disease would require an IND.

A clinical study intended to evaluate the safety of a food ingredient generally does not require an IND, even if the ingredient is known to have an effect on the structure and function of the body . For example, a study of the safety of a flavor ingredient that has been found to bind to a receptor outside of the target location in the mouth would not require an IND if the intent of the study is to evaluate the safety of the ingredient when ingested as food.

If the product is being used or promoted to be used in the diagnosis, cure, mitigation, treatment, or prevention of diseases **it is considered a DRUG for research purposes.**

COSMETIC
A **COSMETIC** is any article intended: to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance.
Information on cosmetic-related regulations can be found here:
Is It a Cosmetic, a Drug, or Both? (Or Is It Soap?)
INCI Database Directory
Cosmetic Ingredients

If the product is being used or promoted to be used in the diagnosis, cure, mitigation, treatment, or prevention of diseases **it is considered a DRUG for research purposes.**

Is the product utilized in my study currently LAWFULLY MARKETED as a drug in the United States? (WORKSHEET introduction and criterion 3)

To accurately assess the status of the product, answer the following questions:

a. Have you **modified the formulation** from the FDA approved formulation?
b. Are you **utilizing a compounded** product?
   Some investigators or research pharmacies compound their own versions of lawfully marketed drug products for use in clinical studies, and these are NOT considered lawfully marketed.
c. Have you **changed the formulation** of the drug?
   Some drugs have an encapsulation or coating that can be a protectant or can have special properties that determine the location and rate at which the drug is absorbed. If you have changed the form of the drug, it is no longer considered the lawfully marketed drug product.
d. Is the product a DIETARY SUPPLMENT, FOOD or COSMETIC? NOTE: Dietary supplements, food or cosmetics are **not** lawfully marketed drugs.
e. If a drug company is providing the drug/product, do they provide **an investigational product** (also called research supply or clinical supply)?
   NOTE: if you purchase the drug from the University of Michigan Department of Pharmacy Services using study funds, the product is the **lawfully marketed drug**.

- If you answered YES to any of the questions (a-e) the product is **NOT** currently **LAWFULLY MARKETED** in the United States. **You will need to submit an IND to the FDA.** Contact MIAP for assistance with an IND submission.

- If you answered **NO** to all the questions (a-e), your study **may be exempted** from an IND. Proceed to answering the rest of the questions on the WORKSHEET.

How will the data be used (WORKSHEET criteria 1-3)?

To determine if criteria 1, 2, and 3 listed on the WORKSHEET are TRUE or FALSE, you will need to assess how the data generated by your study will be used.

- Even if the on-site investigator is not intending to submit the results of the study to the FDA, the study drug manufacturer may have intentions of doing so.
- Check if there is a contract or will there be a contract with any company that allows submission to the FDA.

If your intention (or someone supplying the drug or the funds for your study) is to support a new indication, change in the labeling, or advertising of the DRUG, the answer to one or more of these criteria is **FALSE.**

Is the use of the DRUG in the study different from the FDA-approved use (WORKSHEET criteria 4-6)?

To determine if criteria 4, 5, and 6 listed on the WORKSHEET are TRUE or FALSE, you will need to check the latest approved drug label (prescribing information) for the drug and evaluate the risk of the off-label use.

The approved drug label will list the approved indication, patient population, dose level, dosing regimen, and concomitant medications. To make sure that are using the most up-to-date FDA-approved label, check both DailyMeds and Drugs@FDA.

Please note **that Standard of care** does not necessarily equate approved use.

Some examples that can significantly increase the risk are:

- A drug marketed for oral administration that will be administered as intravenous, intrathecal, or inhalation
- An increase in the dose, frequency, or duration of administration from the on-label dose
- Use in a pediatric population if only approved for adults.

Is the investigation involving ANY OTHER FACTOR that significantly increases the risks (or decreases the risk/benefit ratio) associated with the use of the drug product (WORKSHEET criterion 7)?

Examples for other factors are combination treatments or interacting drugs. Assess the following, if applicable:

a. Does the investigation involve administering the product in **combination with other treatments** (other drugs, radiation therapy, surgery) that are not part of the approved indication on the FDA product label?
b. Does the investigation involve administering the product in combination with other interacting drugs (e.g., cytochrome P450 inducers or inhibitors) that are not excluded in the study selection criteria?
NOTE: you can revise the protocol to address interacting drugs in the selection criteria or concomitant drug sections.

If you answered YES to a and or b, then mark **FALSE** for item 7.

There could be other factors to consider regarding increased risk or decreased risk/benefit ratio. Additional examples of factors that may increase the risk can be found in the FDA Guidance Documents listed on the first page of this document. The cancer treatment guidance is also a useful reference for clinical studies of marketed drugs in other therapeutic areas, as the risk-benefit scenarios may be relevant to non-oncologic settings.

What are that Institution Review Board (IRB) and Human Subject Protection Regulations that are considered in IND exemption (WORKSHEET criterion 8)?

Since you are submitting this study to the IRB for review, the answer to Criterion 8 is likely going to be **TRUE**. Here are the links to the Code of Federal Regulation sections mentioned in this criterion:

a. Institutional Review Board (IRB) 21 CFR part 56.
b. Protection of human subjects 21 CFR Part 50.

What are the regulations that address promotion of DRUGs? (WORKSHEET criterion 9)?

To mark this criterion as **TRUE** you will have to agree not to promote the investigational product being studied as safe and effective (in compliance with 21 CFR Part 312.7)

Can a study that requests an exception of Informed Consent be exempted from an IND (WORKSHEET criterion 10)?

To mark this criterion as **TRUE** you cannot request an exception of Informed Consent.

> Investigations using an investigational drug that request an emergency exemption from informed consent or other IRB waiver of informed consent must be conducted under an IND 21 CFR Part 50.24.

Conclusion:

If you have marked all criteria on the WORKSHEET as TRUE, your study may meet the criteria for IND exemption as set forth in 21 CFR Part 312.2. The IRB will make the final determination.

Final NOTE:

Studies involving drugs that are exempt from IND requirements are still subject to other FDA regulations including 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (IRBs), and 42 CFR Part 11 (Clinical Trials Registration and results information submission).