Table of Contents

Federal Agency Roles in Investigational New Drug (IND) Activities

Food and Drug Administration (FDA) Overview

FDA is the federal agency responsible for ensuring that:

- foods are safe, wholesome and sanitary;
- dietary supplements are safe;
- human and veterinary drugs, biological products, and medical devices are safe and effective;
- cosmetics are safe; and
- electronic products that emit radiation are safe.

Note: FDA-regulated products account for $.25 of every consumer dollar spent in the U.S.!

FDA is divided into five centers that regulate different types of products.

1. **Center for Drug Evaluation and Research** (CDER) – All drug products
2. **Center for Biologics Evaluation and Research** (CBER) – Biological products such as vaccines, blood, cellular & gene therapy, allergenics, and tissues.
3. **Center for Devices and Radiological Health** (CDHR) – Medical devices, radiation-emitting electronic products.
4. **Center for Veterinary Medicine** (CVM) – Food additives and drugs to be given to animals (pets, companion animals, and animals from which human foods are derived).
5. **Center for Food Safety and Applied Nutrition** (CFSAN) – Foodborne illnesses, nutrition, dietary supplements, all food products except for meat, poultry and some egg products.

National Institutes of Health (NIH), Office of Human Research Protections (OHRP), and the FDA

FDA's role is often confused with that of the Department of Health and Human Services (DHHS) and its branches, especially the NIH and OHRP.

1. **NIH**
   a. Primarily a funding agency, not a regulatory agency.
   b. Many researchers incorrectly assume that because their research is NIH funded or is conducted in an academic center, FDA regulations do not apply.
   c. FDA has responsibility for NIH's clinical investigations of FDA-regulated products, irrespective of:
      i. study funding
      ii. study location in the U.S. (e.g. whether academic or other)
      iii. whether for *scientific knowledge* or for *commercialization/marketing*
2. **OHRP**
   a. A regulatory agency that governs clinical research that is federally funded.
   b. Regulates studies that DO NOT involve FDA-regulated products and are:
      i. Supported by a federal agency (e.g., NIH or NCI)
      ii. Conducted in an institution under a Federal Wide Assurance (e.g., the University of Miami)
3. **FDA**
   a. Regulates research that involves products regulated by the FDA, whether or not there is an IND
   b. Industry-Sponsored studies
   c. Investigator-Initiated ("in house") studies

Note: Both OHRP and FDA regulate federally-funded studies that involve FDA-regulated products.

Examples to Test Your Knowledge

Test your knowledge. For each scenario below, check the box of the regulatory agency to which the study must adhere.

Study Scenario	FDA	OHRP
1. A multi-site industry-sponsored study of a drug for a new indication. UM is one of the sites.		
2. A National Cancer Institute-funded study of a new cancer vaccine.		
3. A survey study of UM students about the effects of sleep deprivation on academic performance.		
4. A study of ultrasound equipment to diagnose auditory canal disturbances. The study was initiated by a UM investigator and supported using departmental funds.		

Answers.

Scenario 1: Both, this study will be primarily regulated by FDA since it is studying an FDA-regulated product. Because it is being conducted at UM, where a Federal Wide Assurance is in place with OHRP, it will also be regulated by OHRP.

Scenario 2: Both, this study will be primarily regulated by FDA since it is studying an FDA-regulated product. Because it is being funded by a federal agency, it will also be regulated by OHRP.

Scenario 3: OHRP, this study does not involve an FDA-regulated product, so it is not regulated by FDA. Because it is being conducted at UM, where a Federal Wide Assurance is in place with OHRP, it will be regulated by OHRP.

Scenario 4: Both, this study will be primarily regulated by FDA since it is studying an FDA-regulated product. Because it is being conducted at UM, where a Federal Wide Assurance is in place with OHRP, it will also be regulated by OHRP.

Reference: Waltz D. (2003). GCP Module: FDA Regulations for Clinical Research. Accessed at: http://www.med.upenn.edu/ohr/por/print/FDA_Regs.pdf. Used by permission from University of Pennsylvania School of Medicine Office of Human Research.

IND Purpose

An IND submission notifies the FDA that a pharmaceutical agent will be used in an experimental way. Information in the IND application should provide the FDA with sufficient information to assure the safety of study participants in studies that involve the administration of unapproved drugs or unapproved uses/delivery of commercially available drugs. Interestingly, the majority of IND submissions are noncommercial (depicted in following chart from FDA's Center for Drug Evaluation and Research (CDER)).[1]

CDER ORIGINAL INDs RECEIVED
CALENDAR YEARS 1986 - 2008

Calendar Year	Commercial	Non-Commercial	Total
1986	332	1286	1618
1987	311	994	1305
1988	371	929	1300
1989	310	1004	1314
1990	382	1123	1505
1991	369	1661	2030
1992	370	2111	2481
1993	384	1848	2232
1994	341	1660	2001
1995	340	1394	1734
1996	389	1194	1583
1997	396	1186	1582
1998	441	1626	2067
1999	425	983	1408
2000	410	974	1384
2001	409	995	1404
2002	417	1338	1755
2003	391	972	1363
2004*	621	1216	1837
2005*	637	1297	1934
2006*	713	1150	1863
2007*	779	1810	2589
2008*	883	1156	2039

* Includes INDs for Therapeutic Biologic Products transferred from CBER to CDER
IND receipt figures exclude INDs meeting the requirements for exemption in accordance with 21 CFR 312.2(b)(4

Studies that Require INDs

In **Appendix A** is a tool that you can use to decide whether you need to file an IND application or not. You should also consult with the Human Subjects Research Office (HSRO). In general, you will need an IND if your study:

1. uses a drug that has not been approved by the FDA
2. uses a drug in a different way or for indications not included in the FDA-approved label (i.e. different indication, dose, population, etc. (please see Item 4 in next paragraph))

Notes: a) The above applies even if the use of the product is simply as a research tool
b) Placebos, in and of themselves, do not require an IND
c) Importantly, an IND may be required even if you, as the investigator, do not intend to submit the results of the study to the FDA, but a *sponsor* does. For example, in an investigator-initiated study being supplied with funds, supplies, or study drug by a pharmaceutical company, if the study contract states that the company has the ability to file the data with the FDA, the study needs to be conducted under an IND.
d) If you are not sure if you need an IND when: a) changing the dose, route, or schedule of administration, or b) trying a new combination of marketed drugs, check the literature. If there are no safety data about the changes you wish to study, you probably need an IND.

In general, INDs are *NOT* required for studies in which *ALL* the following conditions are met[2]:

1. pharmaceutical agent is commercially available in the U.S.
2. approval by the IRB of record is granted,
3. consent procedures established in 21 CFR 50 and 56 are met (*Important note*: an IND is required for all studies that have an "exception" from informed consent—they cannot claim an IND exemption),
4. there is no intention of invoking 21 CFR 50.24 (emergency research),
5. verification that every aspect of the drug's use (in a certain patient population, dose, administration route, dosage, form, new proportions, anything that might affect safety) does not substantially increase associated risk—or reduce the acceptability of the risk,[a]
6. the results are *not* to be used to support a change in product labeling (e.g. a new indication) or a significant change in product advertisements, *and*
7. implementation does not , in effect, serve to commercially distribute or market a new drug, even in instances when clearly defined specifications allow study participants to be charged for the drug (as per 21 CFR 312.7, promotion and charging for investigational drugs).

Notes:

a) Cancer therapeutics, vitro diagnostic biological products, blood grouping serum, reagent red blood cells, and anti-human globulin have different "exception" criteria (detailed in § 312.2(b)(1) (21 CFR 312.2(b)(1))). (Specific details and examples can be found in **Appendix B**, IND Exemptions for Cancer Drugs.)

b) Drugs intended solely for tests *in vitro* or in laboratory research animals are exempt from the requirements of §312.2 if shipped in accordance with §312.160.

Examples to Test Your Knowledge

Test your ability to correctly decide if an IND is required for the following studies. For each scenario below, check whether you need to file an IND application.

Study Scenario	Yes	No
Scenario 1: Your study is investigating the use of a pain reliever that is approved for only oral administration. You intend to administer it rectally. Do you need to file an IND?		
Scenario 2: Your study is investigating the use of sunflower stems to reduce the effects of Rheumatoid Arthritis. If the results of the study are successful, you intend to submit an application to the FDA to market this new indication. Do you need to file an IND?		
Scenario 3: Your study is comparing the use of Prozac and Lexapro to treat depression. You intend to administer both drugs within the FDA-approved use. You do not have a contract with a pharmaceutical company, and do not plan on submitting these results to the FDA for a change in labeling. You hope to publish the results in JAMA. Do you need to file an IND?		

Answers.

Scenario 1: Yes. An IND is needed for this study because: a) it involves the use of a product for the purpose of mitigating the effects of a disease, and b) the results may be used in support of a new indication for labeling and/or marketing.

Scenario 2: Yes. An IND is needed for this study because: a) it involves the use of a product for the purpose of mitigating the effects of a disease, and b) the results may be used in support of a new indication for labeling and/or marketing. (**Note**: Seemingly innocuous substances can have significant effects on humans. For example, digitalis/digoxin is made from the foxglove plant, opium from the poppy plant, and marijuana from the cannabis plant.)

Scenario 3: No. An IND is not needed for this study because: a) the study drugs are being used within the FDA-approved indications, and b) the results will not be used in support of a new indication, or a change in labeling or advertising.

Reference: Waltz D. (2003). GCP Module: FDA Regulations for Clinical Research. Accessed at: http://www.med.upenn.edu/ohr/por/print/FDA_Regs.pdf. Used by permission from University of Pennsylvania School of Medicine Office of Human Research.

[a] Factors that might increase risk or decrease the acceptability of risk include changes in dose or route of administration or chances that study participants might receive a less effective treatment for their condition than the standard of care.

Clarifying the "New" in Investigational New Drug (IND)

The term "IND" can be misleading. Researchers may conclude that if the drug being studied is already approved by the FDA, it is not a "new" drug, and thus, they do not need to file an IND application. ***THIS IS INCORRECT!*** Many factors are taken into consideration in designations of whether a drug being used in a study is "new". FDA approval of a drug includes specifications of the following characteristics (clearly spelled out in the Investigational Brochure or PDR):

- Route of administration
- Dose/duration
- Form (e.g. capsule vs. tablet)
- Intended for specific medical conditions
- With concomitant medications or medical conditions

Generally, an IND is needed if any of the above is changed, even if the drug is not the focus of the investigation and simply being used in the protocol (e.g. research tool).

IND Categories

1. Research IND – For individual sponsor-investigators
2. Commercial IND – When it is clear that the drug will eventually be commercialized or the sponsor is: 1) a corporate entity, 2) the NIH

IND Designations/Types

1. Investigator IND – a Research IND submitted by an investigator who actually conducts the study and supervises use of the study drug.
2. Emergency IND – authorizes use of an experimental drug in 1) emergencies where there is not enough time to file an IND, and 2) patients who do not meet the criteria of an existing study protocol, or 3) if an approved study protocol does not exist.
3. Treatment IND – authorizes use of an experimental drug (that shows promise in clinical testing) in serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.
4. Exploratory IND – allows conducting non-therapeutically-oriented preliminary studies, involving limited human exposure, early in phase I stages of development (e.g. micro-dosing preliminary to safety and tolerance studies).

IND Investigator-Sponsor Responsibilities

1. Responsible for what is required of the investigator as well as the sponsor
2. Meet mandates for protection of human subjects in clinical trials
3. Supply sufficient information about investigational product and its use in the proposed study so the FDA can make an informed judgment about the safety of the research in order to meet their charge to "ensure that subjects will not face undue risk of harm"[3] in a research study that involves use of a drug
4. Register the study in ClinicalTrials.gov (you can do this at http://prsinfo.clinicaltrials.gov/)
5. Keep IRB approvals current
6. Keep IND current, notify FDA of amendments
7. Study monitoring by qualified monitors not associated with the study
8. Drug accountability and tracking
9. Notify FDA of all safety issues
10. Submit annual reports to FDA
11. Study close-out procedures and report to FDA

IND Holder Responsibilities

1. Resources to conduct the study: qualified investigators, facilities, research personnel
2. Human protections: Good Clinical Practice (GCP) and IRB requirements, approvals, and renewals; adverse event reporting and safety updates, medical care of study participants
3. Protocol adherence, study progress, renewal and final reports
4. Quality assurance and quality control: SOPs, ongoing monitoring and follow-up, data validity, handling investigational product, research agreements
5. Keep records: study documentation, records of receipt, shipment, and disposition of investigational product
6. Manage study budgets, research contracts

IND Application Contents

Three forms required in an IND application to the FDA[4]:

1. **FDA Form 1571** – the actual IND Application, describes the proposed study in detail
    a. Cover Sheet (Form FDA 1571)
    b. Table of Contents
    c. Introductory Statement
        i. product description, formulation, route
        ii. broad study objectives
        iii. relevant previous use, foreign experience (please see **Appendix C** for additional information on use of foreign data)
    d. General Investigational Plan
        i. rationale
        ii. indication
        iii. general approach, anticipated studies including number of subjects and possible risks
    e. Investigator Investigator's Brochure
    f. Clinical protocol
    g. Chemistry, Manufacturing and Control (CMC) Information
    h. Pharmacology and Toxicology Information
    i. Previous Human Experience
2. **FDA Form 1572** – describes investigator(s) and study site(s)
3. **FCA Form 3674** – certifies the study is registered in the clinical trials national database (except Phase I studies)

For studies using commercially-available drugs without modification to their approved packaging:

1. Section 6, IND # – leave blank in your initial submission
2. Section 8, Phase of Study – "None"
3. Section 10, Serial number – should be "0000" in the initial application, with subsequent IND amendments numbering increasing by one in order of submission
4. Section 13, Contract Research Organization – "None"
5. Sections 18 and 19, Contact Information for Sponsor Representative – leave blank

Note: several of the items in the 1571 Form will not apply

For studies that involve unapproved administration of a drug

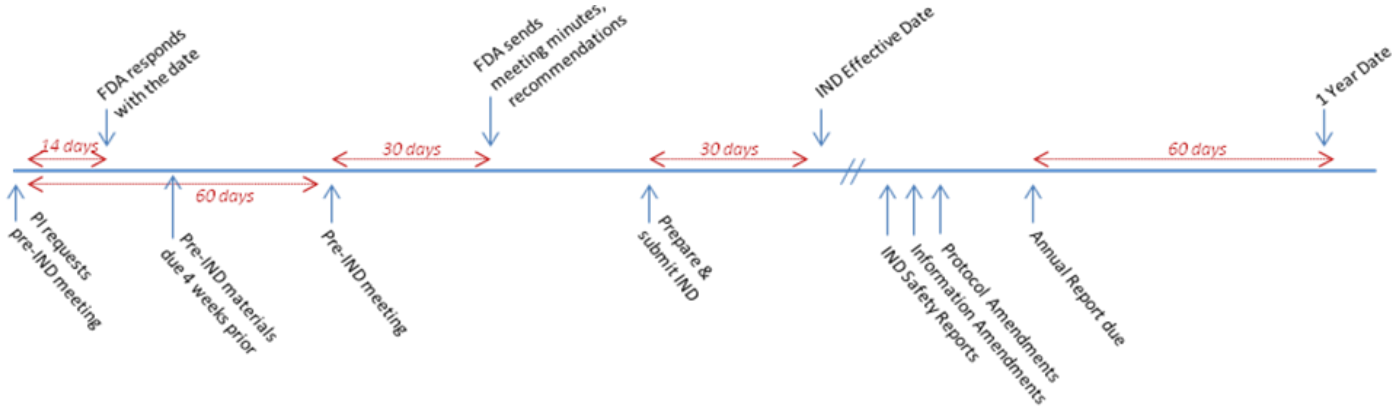
1. Overview – details of the chemistry, mechanism of action, background and rationale for intended clinical use, and the proposed protocol for Phase I human use
2. Manufacturing Information – the composition, manufacturer, stability, and controls used for manufacturing the product. This information has to be complete enough to ensure FDA that the company making the drug can adequately produce and supply consistent batches of the drug and adequate quality control is in place.
3. Preclinical Study Data – you need to supply sufficient preclinical data (data from lab and animal pharmacology and toxicology studies designed to test the mechanisms, safety, and efficacy of an intervention prior to its use in humans) to permit an accurate assessment as to whether the product is reasonably safe for initial testing in humans. You should also include any previous experience with the drug in humans that you may have/know about (often from foreign countries).

4. Clinical Protocols and Investigator Qualifications
    a. Clinical study protocols that are detailed enough for the FDA to be able to assess whether the initial-phase trials that the investigator has planned will expose subjects to unnecessary risks or not.
    b. Clinical investigator qualifications – enough information about the professionals (generally physicians) who are to oversee the administration of the study drug to assure the FDA that all the investigators involved are qualified to fulfill their clinical trial duties.
    c. IRB Review, Study Participant Consent, and Regulatory Compliance – Commits to: a) obtain study IRB approval, b) obtain informed consent from research participants, and c) adhere to IND regulations.

IND Submission and Implementation Procedures

1. Prepare application packet with a cover letter that includes:
    a. Study title
    b. Sponsor-investigator information
    c. A statement that this is an initial IND submission
    d. Serial Number starting with 0000
    e. Complete contact information that EXACTLY matches the contact information on Forms 1571 and 1572
2. Mail in triplicate (one original, two copies) to the FDA:
    a. Center for Drug Evaluation and Research – for a drug
    b. Center for Drug Evaluation & Research Therapeutic Biological Products – for therapeutic biological products

    Note: You can get the correct address from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm#form1571
3. Receive acknowledgment of receipt from the FDA that contains:
    a. Receipt date
    b. IND Number assigned
    c. A description of investigators' obligations under the IND
    d. FDA Project Manager assigned – you should direct all subsequent correspondence to this person
4. Start the study:
    a. The FDA does not approve INDs.
    b. After the acknowledgment letter, you may or may not receive written notification permitting you to proceed with the study.
    c. With IRB approval, an IND goes into effect 30 days after the acknowledgement letter's receipt date *unless* you are notified by FDA that it has placed the study on a clinical hold (see **Appendix E**, FDA Clinical Holds).
    d. The FDA must confirm that all IND deficiencies have been rectified before the study can start.
5. IND activity timeline:



Adapted from Marusina K, Aujla P, Lara PN. (2010). IND Process and General Responsibilities under IND. Retrieved from http://www.ucdmc.ucdavis.edu/ctsc/investigators/IND/2010LectureSeries1.html. 1.14.11

IND Follow-up Reporting Requirements[5]

1. Protocol Amendments (written description of a change or formal clarification to an existing protocol)[6] – cannot be implemented until IRB approval and FDA non-objection has been obtained *unless* a protocol change is

required for patient safety (e.g. an "apparent immediate hazard"). Such changes can be implemented immediately and then submitted to regulatory bodies ASAP.[7]

a. Protocol changes (brief description of clinically significant differences in the existing and proposed protocol)
    i. Phase 1 protocols – any change that significantly affects study participant safety
    ii. Phase 2 or 3 protocols – any change that significantly affects study participant safety, scope of the investigation, or scientific quality of the study (examples: increasing dosage, number of study participants, adding or dropping controls, adding new tests/procedures intended to improve monitoring for, or reduce risk of, side effects/adverse events)
b. New protocol – when the sponsor wishes to conduct a study that is not already part of the IND protocol
c. New investigators –new investigators or changes to investigators (each with a revised FDA Form 1572)

2. IND Information Amendments (advising the FDA of issues not within the scope of protocol amendments, safety reports, or annual reports) (21 CFR 312.31)
    a. Changes to the product's chemistry, manufacturing, controls, or other technical factors (example: changes in manufacturing, quality testing, chemical structure).
    b. Changes to Investigational Brochure
    c. New information about human/animal studies or product toxicology, absorption, distribution, or metabolism
    d. Notice of discontinuance of a clinical study
3. Annual Reports (21 CFR 312.33)
    a. Due annually, starting with the first year's, submitted within 60 days of the anniversary date that the IND went into effect
    b. Study summary
        i. Study title, protocol number, other identifier
        ii. Study purpose
        iii. Patient population, demographics
        iv. Brief summary of the status of studies in progress/completed in the last year
        v. Study participants
            a) total number initially planned,
            b) enrollment to date, tabulated by age group, gender, and race
            c) how many completed participation as planned, number who dropped out for any reason
            d) list of who died during participation, and the cause of death for each
        vi. Adverse event summaries (most frequent and most serious adverse experiences by body system, safety reports, deaths, dropouts)
        vii. Drug action information
        viii. Brief description of any available study results (interim, final)
    c. New information pertinent to understanding the drug's actions (dose response, data from controlled trials, bioavailability, significant manufacturing/microbiological changes etc.)
    d. Study plans going forward
        i. Description of any study modifications/changes in the general investigational plan for the coming year
        ii. Description of any changes in investigator brochure accompanied by a copy of it
    e. Any significant foreign marketing developments (e.g. marketing approvals, withdrawals or suspensions)
4. Safety Reports (21 CFR 312.32)
    a. Safety review – sponsor is required to promptly review all information relevant to safety of the investigational product (from any source)
    b. Notifications to FDA *and* participating investigators
        i. Fatal/life threatening adverse event associated with use of investigational product – required by phone or fax within 7 days
        ii. Serious and unexpected adverse event associated with use of investigational product (including information from non-IND studies) – required in writing within 15 days (to include safety reports previously filed with the IND concerning similar adverse events and an analysis of the significance of the adverse event in light of previous, similar reports)

iii. Laboratory/animal study findings that suggest significant risk for humans – required in writing within 15 days

c. Follow-up of Safety Reports – follow-up information is to be submitted as soon as relevant information is available

Note: The FDA/sponsor may require reporting more frequently than designated in the above according to study-specific risk factors.

IND Study Closeout Requirements

The FDA is not as explicitly demanding about IND study close-out notifications.

1. Final report – the investigator is required to provide the sponsor "with an adequate report shortly after completion of the investigator's participation in the investigation" (§ 312.64(C)).[8]
2. Study medications – must be reconciled and remaining medications should be sent back or destroyed, as per sponsor's instruction.
3. Recordkeeping and retention (§ 312.57)[9]
   a. Study documentation – must be maintained at the site for 2 years *after* drug approval or 2 years after shipment and delivery of investigational drug is discontinued (for studies not resulting in FDA drug approval).
   b. Samples of test article and/or reference standard used in vivo bioequivalence/bioavailability studies – must be retained for 5 years after the application is approved, or, in cases not resulting in FDA drug approval, at least 5 years after the bioavailability study was completed. [10]

A flow diagram of the entire IND process is provided in **Appendix D**.

References/Resources

Engel SI. (2011). De-Risk your IND to avoid a clinical hold. United BioSource Corporation. Accessed at: http://www.unitedbiosource.com/pdfs/webinars/20110421-ind.pdf.

FDA Forms (and their respective contact person): http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

FDA Guidance and Forms. Accessed at: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

FDA's Guidance for Industry for IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer. Accessed at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071717.pdf

FDA's "Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs)": http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm071098.htm

FDA's "Investigational New Drug (IND) Application": http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm

FDA's Pre-IND Submission Consultation Program contacts (individuals who can provide guidance on your IND application before you submit). Accessed at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/UCM166356.pdf

Holbein MEB. (2009). Understanding FDA Regulatory Requirements for Investigational New Drug Applications for Sponsor-Investigators. Journal of Investigative Medicine 57(6):688-694. August.

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University of California at Davis and the CTSA National Consortium IND/IDE Taskforce. Accessed at: http://www.ucdmc.ucdavis.edu/ctsc/investigators/IND/ind_documents/summaryOfINDRegulations.pdf

University of Michigan Human Research Protection Program. IND Decision Tree. Accessed at: http://www.hrpp.umich.edu/policies/IND.pdf.

University of Pennsylvania. IND Decision Tool. Accessed at: http://www.med.upenn.edu/ohr/ind/tool.html

University of Pittsburgh. Required Reports to a FDA-Accepted IND Application. Accessed at: http://www.o3is.pitt.edu/INDSubmissionsMenu.htm.

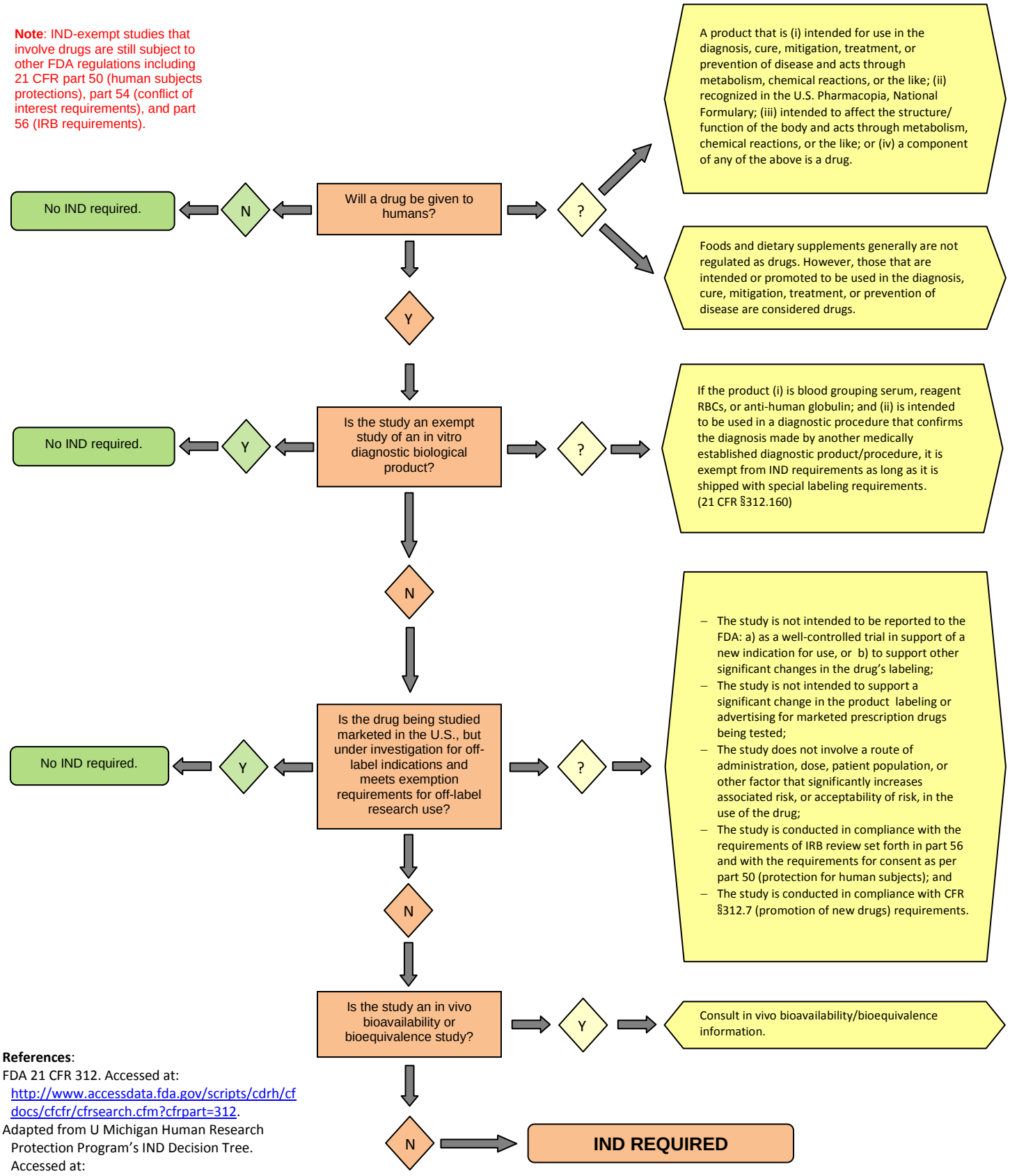
U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research (CDER). (2006). Guidance for Industry, Investigators, and Reviewers Exploratory IND Studies. Accessed at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078933.pdf

Waltz D, GCP Module: FDA Regulations for Clinical Research. University of Pennsylvania Office of Human Research. Accessed at: http://www.med.upenn.edu/ohr/por/print/FDA_Regs.pdf.

Note: Some of the above information was derived from work done by the University of Pennsylvania, the University of Pittsburgh, and the CTSA National Consortium Regulatory Knowledge Key Function Committee. Some of the wording was taken, by permission, directly from their reference documents, accessed at: https://www.ctnbestpractices.org/collaborations/ctsa-regulatory-resources?searchterm=IND%2FIDE, http://www.o3is.pitt.edu/INDSubmissionsMenu.htm, and http://www.med.upenn.edu/ohr/ind/submission.html, respectively.

Appendix A
IND Decision Tree

Note: IND-exempt studies that involve drugs are still subject to other FDA regulations including 21 CFR part 50 (human subjects protections), part 54 (conflict of interest requirements), and part 56 (IRB requirements).



References:

FDA 21 CFR 312. Accessed at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=312.

Adapted from U Michigan Human Research Protection Program's IND Decision Tree. Accessed at: http://www.hrpp.umich.edu/policies/IND.pdf.

Appendix B
IND Exemptions for Cancer Drugs

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) that provide for the exemption of some studies for some cancer drugs from IND regulations. 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 when the studies:

1. are not intended to support FDA approval of a new indication or a significant change in the product labeling,
2. are not intended to support a significant change in the advertising for the product,
3. do not involve an administration route, dose, or use in a patient population or other factor that significantly increases risk (or decreases acceptability of risk) associated with the use of the drug product. (Note: investigators and their IRBs determine, based on the scientific literature and generally known clinical experience, whether there is no significant increase in the risk associated with the use of the drug product.),
4. are conducted in compliance with institutional and IRB guidelines and informed consent regulations in 21 CFR parts 56 and 50, ***and***
5. are conducted in compliance with § 312.7 (promotion and charging for investigational drugs, e.g. the studies will not be used to promote unapproved indications).

(**Note**: Requirements 1, 2, 4, and 5 are not directly related to the specific protocol submitted, and their interpretation is similar for oncologic and non-oncologic 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.)

Examples

Studies that would generally be considered "Exempt"

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 of marketed drugs**: using doses and schedules similar to those already approved to treat a cancer different from what was targeted in the approved label, ***but not when*** standard therapy in the population to be studied is very effective (e.g., is associated with a survival benefit). Use of another regimen may expose patients to the risk of receiving an ineffective therapy, thus, an IND would be necessary.
2. **Phase 1 oncology trials of marketed drugs**: if such therapy is appropriate for the patient population (i.e., if patients have residual cancer) and if there is no effective therapy that the patients have not yet received. The investigator must start at 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. **New combinations of drugs**: if the combinations have been described in the medical literature. 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 in combinations of drugs, if there are no safety data from the literature, the initial study of a new drug combination should ordinarily be performed under an IND. 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. Synergistic toxicity may be anticipated when:
   a. one agent interferes with the metabolism or elimination of the other
   b. both agents target the same metabolic pathway or cellular function
   c. one agent targets signaling pathways that are reasonably expected to modulate sensitivity to the other
4. **New routes or schedules of administration**: if there is sufficient clinical experience described in the literature to document safety (even if not described in the approved label). On the other hand, initial experience with a new route of administration should be based on animal studies and conducted under an IND.
5. **Studies of high-dose therapy in cancer patients**: 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.

Studies that would generally be considered "Not Exempt"

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. **Cytotoxic drugs**: in patients 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. **Adjuvant chemotherapies**: (chemotherapy given after surgery to remove cancer): if
    a. patients studied have a low risk of cancer recurring after surgery (treatment with any toxic therapy may indicate a significantly increased risk)
    b. 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)
    c. properly designed adjuvant trials are able to demonstrate whether the new therapy is safe and effective, and such results may lead to a marketing application (under § 312.2(b)(1), 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. **Substituting standard therapies known to be successful with a new agent of unproven activity**: when standard therapy can already provide a cure or increase in survival (it would be judged unethical to withhold standard therapy known to be successful while testing a new agent)
4. **When safe starting doses/schedules are unknown**:
    a. a marketed drug given by a new route
    b. new drug combinations when safety is not adequately described in the literature (risk of synergistic toxicity)
    c. the schedule of administration is different (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)
    d. chemosensitizers, radiosensitizers, or resistance modulators where the effect of the modulator on toxicity in humans is unknown
5. **Studies intended to support approval of a change**: new indication, significant change in the product labeling, or significant change in advertising (§ 312.2(b)(1)(i), (ii))

Note: *A Manual for Participants in Clinical Trials of Investigational Agents Sponsored by DCTD* [Division of Cancer Treatment and Diagnosis], *NCI* is a good source of information on INDs in cancer treatment. It can be accessed at: http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm.

Appendix C
Use of Foreign Data in IND Applications

Acceptance of foreign data in an IND application is governed by the FDA Code of Federal Regulations 312.120.

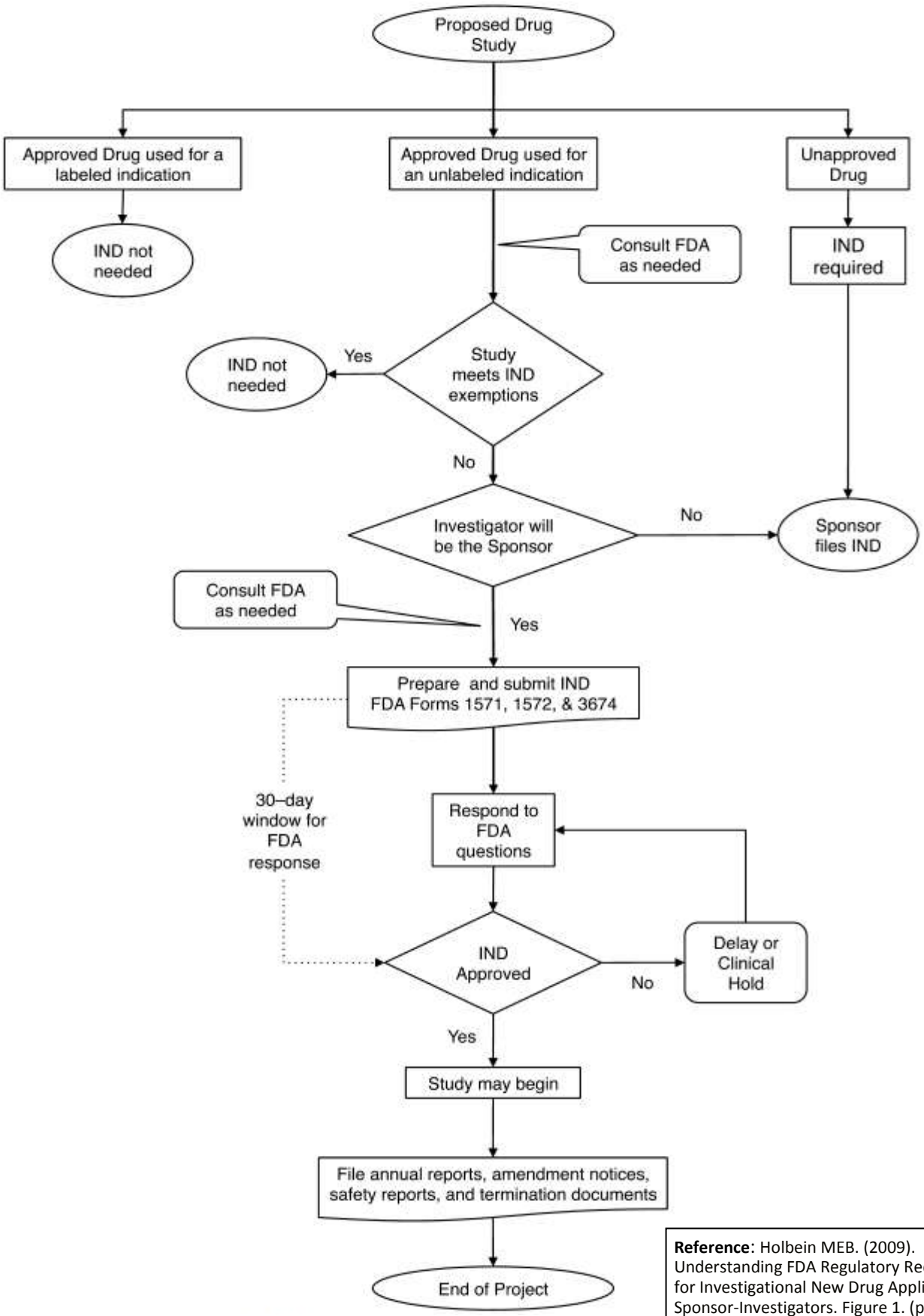
1. Foreign Data Submissions must include:
    a. Investigators' qualifications
    b. Description of research facilities
    c. Protocol summary and study results
    d. Case records/additional information on request
    e. Product information
2. To support efficacy, data must demonstrate that study is adequately designed and well controlled (CFR 314.126)
3. Conformance with ethical principles

For Foreign clinical studies not conducted under an IND (CFR 312.120):

1. The FDA may accept foreign clinical studies, which meet the following criteria, in support of clinical investigations conducted in the U.S. and/or marketing approval:
    a. adequately designed
    b. well controlled
    c. compliant with protocol
    d. performed by qualified investigators
    e. conducted in accordance with ethical principles acceptable to the world community
2. Required data submissions (information requirements listed in Item 1, above) (21 CFR 120(b))

Reference: FDA Code of Federal Regulations (21 CFR 312.23); Perkins V. (2011). CBER/OVRR/DVRPA. IND Overview. Accessed at: http://www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/UCM106624.pdf.

Appendix D
IND Process Flow Diagram



Reference: Holbein MEB. (2009). Understanding FDA Regulatory Requirements for Investigational New Drug Applications for Sponsor-Investigators. Figure 1. (page 689). J of Investigative Med 57(6):688-694. August.

Appendix E
FDA Clinical Holds (21 CFR 312.42)

1. Definitions
   a. Complete Clinical Hold
      i. An FDA order to delay a proposed clinical study or suspend an ongoing one
      ii. The investigational product cannot be administered to study participants
      iii. No new study participants may be recruited to the study and placed on the investigational drug
      iv. Study participants already in the study should be taken off therapy involving the investigational drug unless specifically permitted by the FDA (in the interest of patient safety)
   b. Partial Clinical Hold
      i. Only part of the clinical work in the study is delayed or suspended
      ii. Can be site-specific – the partial hold may involve a particular study or cover all studies conducted at a site
2. Grounds for imposing a clinical hold
   a. Phase I studies (§ 312.42 (b) (1))
      i. Study participants exposed to unreasonable and significant risk
      ii. Investigators not qualified (training, experience) to conduct the study
      iii. Misleading, erroneous, or incomplete study brochure
      iv. IND does not contain sufficient information for the FDA to assess risks in the proposed study
      v. A certain gender is excluded in the proposed study of investigational products that is intended to be used to treat a life-threatening disease/condition (e.g. when the "likelihood of death is high unless the course of the disease is interrupted") that affects both genders
      vi. When men or women with reproductive potential (excluding pregnant women) who have the disease or condition are not eligible because of a risk/potential risk of reproductive or developmental toxicity, *unless* a study that includes the other gender has already been conducted, is being conducted concurrently, or is planned for the short term (e.g. within a reasonable time agreed upon by the agency)
   b. Phase II or III studies (§ 312.42 (b) (2))
      i. Conditions listed in 2.a.
      ii. Proposed study is clearly deficient in design to meet its stated objectives
   c. Expanded access IND or expanded access protocol (§ 312.42 (b) (3))
      i. Pertinent criteria for permitting expanded access use to begin (or to continue, in the case of ongoing use) are not satisfied
      ii. The expanded access IND/protocol does not comply with expanded access submission requirements
   d. Any study, regardless of stage or design, that is not adequately designed or well-controlled, especially ones:
      i. That interfere with other adequately designed and well-controlled studies
      ii. Where insufficient quantities of the investigational drug exist
      iii. Where the drug has already been studied in one or more adequately designed and well-controlled investigations that strongly suggest lack of effectiveness
      iv. Where another available approved or investigational drug for the same indication has demonstrated a better potential benefit/risk balance
      v. For which the Commissioner determines that it would not be in the public interest for the study to be conducted/continued
3. Discussion of deficiency – Unless patients are exposed to immediate and serious risk, the FDA will attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing a clinical hold order.
4. Resumption of studies placed on clinical hold – A study may only resume after FDA has notified the sponsor that the study may proceed after correction of the deficiency has been confirmed.
5. Appeal – If the sponsor disagrees with the reasons cited for a clinical hold, the sponsor may request reconsideration of the decision (§ 312.48).
6. Converting clinical holds to inactive status – If a clinical hold is maintained for a year or more, the FDA may place the IND on inactive status (§ 312.45).

Appendix F
IND Role in Drug Safety

Assessing Pre-Clinical Data

All FDA-approved drugs have undergone some preclinical safety testing. However, the scope of the testing was dependent on the proposed/intended use. For example, a drug approved for short term or single-use administration would not necessarily have undergone any long-term safety or carcinogenicity studies.

To get an idea of what the implications of insufficient preclinical testing, compare your intended use with the FDA-approved uses of the study drug, considering whether the following potential pre-clinical studies may have been conducted:

- Carcinogenicity studies
- Mutagenicity studies
- Teratogenicity studies
- Embryotoxic studies
- Drug Absorption/Distribution/Metabolism studies
- Pharmacokinetic/Pharmacodynamic studies
- Chronic/Long-term safety studies

You may conclude that it would be unsafe to use the study drug as you intended without first conducting pre-clinical safety studies.

Examples to consider

If a drug was indicated exclusively for use in men over the age of 65, would embryotoxicity and teratogenicity studies be important?

Yes. For example, Propecia®, which was originally developed as a treatment for benign prostatic hypertrophy and therefore only intended for men, was found to distribute in many body fluids, including semen. The drug was also found to be highly teratogenic (caused malformations in external genitalia of male offpsring in rats). Had these preclinical studies NOT be done, pregnancies of female sexual partners of treated males may have been put at risk. This risk is so high that the drug labeling includes warning against women coming in contact with crushed or broken tablets.

Tylenol®, originally developed as an oral tablet, can be taken rectally. Since the rectal mucosa has markedly different absorptive properties than the gastrointestinal tract, it was important to study pharmacokinetic properties in animals prior to introducing this route of administration to humans. It was found that a markedly different formulation of Tylenol® was necessary to achieve the same pharmacokinetic and therapeutic profile as the oral formulation.

Properties of the Study Drug

Another factor to consider when determining the need for an IND is how the study drug will be physically modified for the purposes of the study. This may actually place the subject in a situation of unanticipated risks. Consider if the following issues:

Changing the Form 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.

Example: Coumadin® is very unstable in high humidity, which is why the pills are coated. Crushing these caplets can change them chemically and result in unanticipated safety risks and a lack of efficacy.

Example: Niaspan® pills are specially formulated to control absorption rate to reduce side effects and maintain consistent drug delivery over a 24-hour period. Crushing the Niaspan® pill (such as one might do to put a drug in a gelatin capsule for study blinding) would cause the drug to be absorbed much more rapidly. This would lead to significant side effects, a markedly shortened duration of drug delivery, and wide variations in peak drug concentration.

Manufacturing Issues

Good Manufacturing Processes (GMP) dictate that proper controls are in place to ensure the product is safe, the stability

is known, and that the product's storage or delivery system is effective. These regulations are just as important as regulations on clinical drug development in the protection of human patients/subjects.

Example: A cytotoxin used in a psoriasis study would not only have potentially unacceptable toxicities in that setting but it might also expose the research team, who is not familiar with the safe handling of cytotoxins, to be at increased risk.

Example: The packaging of some drugs is very important to preserve its chemical composition. Some drugs are in blister packs, for example, because they decompose when they come in contact with air. Other drugs must be maintained in a dark brown glass bottle, as they are photosensitive.

How the Data Will Be Used

Another consideration when determining whether or not an IND is needed has to do with the way that the data collected from the study will be used. This is important, because the results of your study may be used to **change the labeling or marketing of a drug**.

Also, if your intention (or someone supplying funds) is to **influence prescribing habits**, there is a possibility that an IND may be required. In both cases, a larger population of patients could be placed at risk.

Interestingly, even if the on-site investigator is not intending to submit the results of the study to the FDA, the **sponsor may have intentions** on doing so. If this is the case, an IND may still be required. For example, an investigator-initiated study is being supplied with funds and/or supplies of the study drug by a pharmaceutical company. If the contract with the company states that they have the ability to file the data with the FDA, then that study needs to be conducted under an IND.

Reference: Used by permission from the University of Pennsylvania School of Medicine Office of Human Research. Accessed at: http://www.med.upenn.edu/ohr/ind/preclinical.html

Appendix G
CFR Part 312 Highlights of Mandated Responsibilities in IND Studies

21 CFR 312.6 – Labeling investigational products
21 CFR 312.7 – Promoting and distributing investigational products
21 CFR 312.23 – Format and documents required for an IND application to FDA
21 CFR 312.32 – Safety reports to FDA (including adverse experiences and information from animal studies that would indicate significant risk to humans)
21 CFR 312.33 – Annual reports to FDA
21 CFR 312.42 – Clinical holds
21 CFR 312.44 – IND Termination by FDA
21 CFR 312.50 – General responsibilities of sponsors

- Ensuring the study is conducted in accordance with the protocol
- Maintaining an effective IND with respect to the investigation
- Ensuring proper monitoring of the study
- Ensuring the FDA is promptly informed of significant adverse effects/risks associated with the drug

21 CFR 312.53

- Selecting, training, and documenting appropriately qualified investigators based on training, experience
- Shipping investigational drugs only to investigators participating in the study
- Obtaining FDA Form 1572 from investigators
- Obtaining a written statement that investigators will conduct the study as outlined in the protocol
- Obtaining relevant financial information from investigators
- Selecting, training, and documenting appropriately qualified monitors (training and experience) to monitor the study

21 CFR 312.54 – FDA regulations regarding emergency use
21 CFR 312.55 – Keeping investigator(s) informed of protocol, safety and effectiveness of investigational product (investigators' brochure, new observations of adverse effects and safe use)
21 CFR 312.56 – Review of ongoing investigations

- Assuring appropriate monitoring of all studies be conducted under the IND
- Submitting annual reports to the FDA
- Reviewing and evaluating investigational product safety and effectiveness data
- Submitting safety reports to FDA
- Discontinuing the study if the investigational product presents an unreasonable and significant risk to study participants
- Securing unused drug
- Ending participation of non-complying investigators (making sure investigators comply with the signed agreement (Form 1572), the study protocol, and IND regulations) and notifying FDA of such actions
- Notifying the FDA, IRB, and participating investigators if the study is discontinued

21 CFR 312.57 – Recordkeeping and record retention (with timeframes)

- Maintaining complete and accurate records to confirm stewardship of investigational product (including receipt, shipment, or other disposition)
- Full documentation of investigators' financial interests relating to the study (including payments made to investigators)
- Retaining reserve samples of test articles

21 CFR 312.58 – Inspecting records and reports

- FDA access to records and reports of IND clinical trials
- DEA/Department of Justice access to records/reports of IND studies involving controlled substances

21 CFR 312.59 – Disposition/return of unused investigational products (including documentation requirements)

21 CFR 312.60 – General responsibilities of investigators

- Ensuring study is conducted according to signed agreement, investigational plan/study protocol, and applicable regulations.
- Protecting study participants' rights, safety, and welfare
- Controlling investigational product under study
- Obtaining consent from study participants

21 CFR 312.61 – Maintaining control of investigational product, administering it under investigator supervision

21 CFR 312.62 – Requiring investigator(s) to maintain adequate records

- Drug disposition
- Case histories on every individual in the trial (recording observations/pertinent data on study participants administered the investigational drug as well as those who served as controls)

21 CFR 312.64 – Reports required from investigators

- Progress/annual reports
- Safety reports (adverse events, side effects)
- Final reports
- Financial disclosures

21 CFR 312.66 – Assuring IRB review and oversight

- IRB to be responsible for initial and continuing review and approval of the clinical study
- Requiring investigator(s) to meet local IRB requirements
- Requiring prompt reporting to the IRB of all research activity changes and unanticipated problems involving risk to study participants
- Prohibiting changes in the research without IRB approval, except where necessary to eliminate hazards to study participants

21 CFR 312.68 – Authorizes FDA to access, copy, and verify investigator's records and reports

21 CFR 312.69 – Handling of controlled substances

21 CFR 312.70 – Disqualification of a clinical investigator

21 CFR 312.120 – Foreign Data

21 CFR 312.552 – Responsibilities relating to transferring obligations to a contract research organization

21 CFR 314.106 – Foreign Data

Appendix H
Glossary of Clinical Research Terms Used in IND Activities

Adverse Event (AE) – any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Associated with Use of a Drug – there is a reasonable possibility that the experience may have been caused by the drug.

Audit – a systematic review, inspection, or verification, typically conducted by an independent individual or group.

Case Report Form (CRF) – a printed, optical, or electronic (eCRF) document designed to capture all protocol-required information for a study.

Coordinating Center (CC) – a group organized to coordinate the planning and operational aspects of a multi-center clinical trial. CCs may also be referred to as Data Coordinating Centers (DCCs) or Data Management Centers (DMCs).

Clinical Research or Study Coordinator (CRC) – an individual who handles the administrative and day-to-day responsibilities of a clinical trial and acts as a liaison for the clinical site. This person may collect the data or review it before it is entered into a study database.

Clinical Research – NIH defines clinical research as: *(1)* Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies. *(2)* Epidemiologic and behavioral studies. *(3)* Outcomes research and health.

Clinical Trial –NIH defines a clinical trial as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, nutritional supplements, surgical intervention, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective. Behavioral clinical trials involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fit this definition of a clinical trial.

Conflict of Interest – when individuals involved with the conduct, reporting, oversight, or review of research also have financial or other interests, from which they can benefit, depending on the results of the research.

Consent Form – a document that describes the rights of a study participant and provides details about the study, such as its purpose, duration, required procedures, and key contacts. Risks and potential benefits are explained in the consent document.

Current Good Tissue Practice (cGTP) – minimum requirements for methods to be used in, and the facilities or controls to be used for, the manufacture of human cell, tissue, and cellular and tissue-based products (HCT/P); recordkeeping; and the establishment of a quality program.

Data Management – the processes of handling data collected during a clinical trial from development of the study forms/CRFs through the database locking process and transmission to statistician for final analysis.

Data Management Plan (DMP) – a plan that documents the processes for handling the flow of data from collection through analysis. Software and hardware systems along with quality control and validation of these systems, as relevant are described.

Data and Safety Monitoring Board (DSMB) – a group of individuals independent of the study that is appointed to monitor participant safety, data quality and to assess clinical trial progress.

Disability – A substantial disruption of a person's ability to conduct normal life functions.

Efficacy – Indication that the therapeutic effect of a clinical trial intervention is acceptable; that is, at least as good as the control intervention or standard of care to which it is compared.

Eligibility Criteria – criteria guiding enrollment of participants into a study. The criteria describe both inclusionary and exclusionary factors, (e.g. inclusion criterion - participants must be between 55 and 85 years old; exclusion criterion – must not take drug X three month prior to the study).

Food and Drug Administration (FDA) – an agency within the U.S. Department of Health and Human Services (DHHS) responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, nation's food supply, cosmetics, and products that emit radiation.

FDA Acknowledgment Letter – a letter that typically comes 1-2 weeks after the FDA receives an IND submission. It includes the IND number assigned, date of FDA receipt of the IND application, and a description of investigators' obligations under the IND. ***This letter is NOT an approval to begin the study.***

Good Clinical Practice – a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.

Good Manufacturing Practices (cGMP) – minimum requirements for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug or biologic. Adherence to cGMP assures that the drug or biologic:

a) meets requirements of the Food, Drug, and Cosmetic Act in regard to safety,
b) is what (identity and strength) it is purported to be, and
c) meets the quality and purity characteristics that it is represented to possess.

Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule – the first comprehensive Federal protection for the privacy of personal health information. The Privacy Rule regulates the way certain health care groups, organizations, or businesses, called covered entities under the Rule, handle the individually identifiable health information known as protected health information (PHI).

Human Subject – a patient or healthy individual who is or becomes a participant in research, either as a recipient of the intervention or as a control.

Informed Consent – a process by which a participant or legal guardian voluntarily confirms his/her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to take part. Informed consent is usually documented by means of a written, signed, and dated consent form that has been approved by an IRB.

Institutional Review Board (IRB) – an independent body constituted of medical, scientific, and nonscientific members whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, protocols and amendments, and of the methods and material to be used to obtaining and documenting informed consent of the trial participant.

Intervention – a procedure (e.g. venipuncture), drug, nutritional supplement, gene transfer, vaccine, behavior- or device-modification that is performed for clinical research purposes (45 CFR 46.102(f)).

Investigational Agent – a pharmaceutical form of an active ingredient/placebo being tested /used as a reference in a clinical trial. This includes products with marketing authorization when they are formulated, packaged, or administered in a way different from the approved form, products used for off-label use, or products used to gain further information about an approved use (such as an unapproved population).

Investigational Drug/Biologic – a new drug/biological drug that is used in a clinical investigation. This also includes a biological product that is used *in vitro* for diagnostic purposes. Investigational drugs/biologics may include either products that are not generally recognized by the FDA as being safe and effective or products already approved by the FDA as safe and effective for specific indications that are being studied for new indications, doses, strengths, dosing frequency, or in new populations. (This latter description is known as off-label use.)

Investigational New Drug Application (IND) – a request for authorization from the FDA to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application (21 CFR 312).

Investigator – the individual who actually conducts the clinical investigation/study; the one under whose immediate direction the drug is administered or dispensed to a study participant (CFR 21 Part 312).

Life-threatening Adverse Event – Adverse event that places a study participant at immediate risk of death from the event as it actually occurred (this does not include a reaction that, had it occurred in a more severe form, might have caused death).

Manual of Procedures (MOP) – a set of procedures describing study conduct. A MOP is developed to facilitate consistency in protocol implementation and data collection across study participants and clinical sites.

New Drug Application (NDA) – an application submitted by the manufacturer of a drug to the FDA, after the clinical trial has been completed, for a license to market the drug for a specified indication.

Office for Human Research Protection (OHRP) – the federal government agency within the Department of Health and Human Services (DHHS) charged with the protection of human subjects participating in government funded research. It issues assurances and oversees compliance of regulatory guidelines by research institutions.

Phase I clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects). It can include healthy participants or patients.

Phase II clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety. It is conducted in participants with the condition or disease under study and will determine common short-term side effects and risks.

Phase III studies investigate the efficacy of a biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

Phase IV studies conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

NIH-Defined Phase III – a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, to a) evaluate an experimental intervention in comparison with a standard or controlled intervention or b) compare two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Placebo – an inactive pill, liquid, powder, or other intervention that has no treatment value. In clinical trials, experimental treatments are often compared with placebos to assess the treatment's effectiveness.

Placebo Controlled Study – a method of investigation in which an inactive substance/treatment (the placebo) is given to one group of participants, while the test article is given to another group. The results obtained in the two groups are then compared to see if the investigational treatment is more effective in treating the condition.

Protocol – a description of the objective(s), design, methods, statistical consideration, and organization of a trial.

Protocol Amendment – a written description of a change(s) to or formal clarification of a protocol.

Protocol Deviation – failure to conduct a study as described in the protocol. The failure may be accidental or due to negligence and in either case, the protocol deviation should be documented. This also includes failure to comply with federal laws and regulations, the institution's commitments and policies, and standards of professional conduct and practice. Examples of noncompliance include:

- failure to obtain/maintain approval for research,
- failure to obtain informed consent when required,
- failure to file adverse event reports,
- performance of an unapproved study procedure,
- performance of research at an unapproved site,
- failure to file protocol modifications and
- failure to adhere to an approved protocol.

Protocol Deviation Report – internal document created as part of the ongoing quality control process summarizing compliance with the protocol and listing protocol deviations and/or violations.

Quality Assurance (QA) – systematic approach to ensure that the data are generated, documented (recorded), and reported in compliance with the protocol and good clinical practice (GCP) standards.

Quality Control (QC) – the internal operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of trial related activities have been fulfilled (e.g., data and form checks, monitoring by study staff, routine reports, correction actions, etc.).

Quality Improvement – an ongoing process implemented to develop/enhance a procedure and institutionalize it.

Randomization – the process of assigning clinical trial participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Recruitment Plan – outlines how participants will be recruited and how recruitment goals for the study will be reached.

Retention Plan – details the methods in which the study will use in order to retain study participation in the clinical trial.

Safety Monitoring Plan – outlines the oversight of a clinical trial.

Screening Log – an essential document that records all individuals who entered the screening process for the study. The screening log demonstrates the investigator's attempt to enroll a representative sample of participants.

Screening Process – a process designed to determine individual's eligibility for participation in a clinical research study.

Serious Adverse Event (SAE) – any adverse event that:

- results in death
- is life threatening, or places the participant at immediate risk of death from the event as it occurred
- requires or prolongs hospitalization
- causes persistent or significant disability or incapacity
- results in congenital anomalies or birth defects
- is another condition which investigators judge to represent significant hazards

Site Signature Log/Delegation of Authority – a list of individuals authorized to execute specific functions in a study. Authority to execute these functions is granted to the study staff by the principal investigator and documented through signatures and initials in the log.

Source Document – original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participant diaries, recorded data from automated instruments, x-rays, etc.) that are used in a clinical trial.

Sponsor – the individual, commercial company (e.g. pharmaceutical company), organization (e.g. a university), or governmental agency that takes responsibility for the conduct of the study described in the IND.

Sponsor-investigator – the investigator who initiates and conduct the clinical study *and* who is directly accountable for administering or dispensing the investigational drug. Requirements applicable to a sponsor-investigator include those applicable to an investigator ***and*** a sponsor.

Standard Operating Procedure (SOPs) – detailed written instructions to achieve uniformity of the performance of a specific function across studies and patients at an individual site.

Stopping Rules – established safety criteria that would either pause or halt a study because of futility or risk(s) to study participants.

Stratification – separation of a study cohort into subgroups or strata according to specific characteristics such as age, gender, etc., so that factors which might affect the outcome of the study, can be taken into account.

Unexpected Adverse Event – adverse event, the specificity/severity of which is not consistent with the current investigator brochure or risk information described in the general investigational plan/study protocol

Unmasking/Unblinding – a procedure in which one or more parties to the trial are made aware of the treatment assignment(s).

Waiver – a request to FDA to waive applicable requirements under 21 CFR 312 – Investigational New Drug Application.

Endnotes

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