POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

INDs: Review of Informed Consent Documents

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PURPOSE

- This MAPP describes: (1) when an informed consent document (ICD) submitted under an investigational new drug application (IND) should be reviewed; (2) when the Center for Drug Evaluation and Research (CDER) should request that an ICD be submitted to an IND; and (3) procedures for reviewing an ICD.

- This MAPP does not address consent for treatment INDs or exception from informed consent. The review of ICDs for those two regulatory scenarios is covered by procedures described in MAPP 6030.6 *INDs: Processing Treatment INDs and Treatment Protocols* and MAPP 6030.8 *INDs: Exception From Informed Consent Requirements for Emergency Research*.

BACKGROUND

- The Federal Food, Drug, and Cosmetic Act (FD&C Act) provides that an IND is conditioned upon the sponsor requiring that the investigator: (1) inform human subjects or their representatives about the investigational purposes for which the drug is being used; and (2) obtain consent of the human subjects or their representatives, except where it is not feasible or is contrary to the human subjects' best interests (section 505(i)(4)).

- Except as described in 21 CFR 50.23 and 50.24, no clinical investigator may involve a human being as a subject in research involving an investigational drug unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative (21 CFR 50.20).

- CDER's review of the ICD does not substitute for the responsibility or authority of the institutional review board (IRB) to review, require modifications, and approve the ICD and consent process as a condition for the clinical investigation to begin (see POLICY). However, CDER retains the authority to review and require changes to the ICD.

- Although the IRB is responsible for reviewing the ICD for all clinical investigations under its jurisdiction, there are situations in which CDER review of an ICD in addition to IRB review is particularly important to determine whether a clinical investigation may safely proceed under 21 CFR part 312 (see POLICY). The IND regulations do not require routine submission of ICDs to CDER; however, CDER can request submission of the ICD for review (in accordance with 21 CFR 312.23(a)(11)) to determine whether it provides adequate information to ensure that human subjects are not exposed to an unreasonable and significant risk of illness or injury (21 CFR 312.42(b)(i)).

POLICY

- If a sponsor does not submit an ICD as part of its IND submission, the review division may request and review the ICD at any time. The request will reference 21 CFR 312.23(a)(11), which states that if requested by the FDA, the sponsor must submit "any other relevant information needed for review of the application." Review is strongly recommended when the proposed investigational use raises a particular concern or concerns such as:

    1. Nonclinical studies that identified an unusual toxicity were submitted in support of the first administration of the study drug in humans

    2. Unusual known clinical toxicity is associated with the study drug, the drug class to which the study drug belongs, or with a different drug with characteristics similar to those of the study drug

    3. The study population is particularly vulnerable[1]

[1] Examples of vulnerable categories of subjects include children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons (see, for example, 21 CFR 56.111(a)(3)). FDA regulations do not specifically define *vulnerable*. As a general matter, subjects may be considered vulnerable when, among other things, they have an increased susceptibility to undue influence or coercion.

4. The study design is unusual for the therapeutic class

5. The clinical investigation has significant potential for serious risk to human subjects

6. The clinical investigation is a postmarketing study or clinical trial required under section 505(o)(3) of the FD&C Act to assess a serious risk related to the use of the drug

7. The clinical investigation involves asking subjects to forego or delay effective treatment that is known to decrease long-term mortality or irreversible morbidity

8. CDER has other confidential or proprietary information not available to an IRB or sponsor that affects the assessment of whether the ICD adequately addresses risks

- CDER will review any ICD that it has requested within the 30-day review clock for a new IND or within 30 days of receipt of the ICD requested for any other study conducted under an established IND.

- CDER review divisions will primarily focus their review of the ICD on the: (1) statement that the study involves research; (2) explanation of the purposes of the research and expected duration of the subject's participation; (3) description of the procedures to be followed and identification of any experimental procedures; (4) description of any reasonably foreseeable risks or discomforts to the subject; (5) description of any benefits to the subject or to others that may be reasonably expected from research; and (6) disclosure of any appropriate alternative procedures or courses of treatment that might be advantageous to the subject (21 CFR 50.25).

- The division will request a consultation from the Office of Scientific Investigations (OSI) and/or an FDA ethicist if there are questions about whether the ICD meets the requirements in the regulations, or if there are ethical concerns about the study.

- After reviewing the consent materials, if CDER reviewers, OSI, and/or an FDA ethicist have advisory comments about the ICD, comments normally will be conveyed to the sponsor in writing and identified as "advisory."

- If CDER reviewers, OSI, and/or an FDA ethicist find an ICD to be misleading, inaccurate, or noncompliant with 21 CFR part 50, comments about required changes will be conveyed to the sponsor in writing as soon as possible.

- If the ICD deficiencies are such that subjects do not have the information necessary to make an informed consent decision, the CDER review division should consider placing the IND on clinical hold under 21 CFR 312.42(b)(i) — human subjects are or would be exposed to an unreasonable and significant risk of illness or injury. Comments about required changes will be conveyed to the sponsor in writing within 30 calendar days of the hold action, identified as required, and noted that a revised ICD is expected for FDA review to determine if the concerns have been adequately addressed. The clinical hold will continue until an acceptable revision of the ICD is received (see MAPP 6030.1 *IND Process and Review Procedures (Including Clinical Holds)* and 21 CFR 312.42, Clinical Holds and Requests for Modification).

  – Placing an IND on clinical hold for ICD deficiencies is expected to be rare because the CDER review division will attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order.

- For multicenter trials with local IRB review of the ICD (i.e., for which the content of the ICD may vary somewhat from site to site), CDER will advise the sponsor to revise the ICD for each site to address CDER comments on safety issues or issues of regulatory noncompliance.

RESPONSIBILITIES AND PROCEDURES

IND Review Team will:

- Request submission of the ICD if it has not been submitted with the IND when one of the circumstances listed in the POLICY section applies or when governed under MAPPs 6030.6 or 6030.8.

- Review the ICD as described in the POLICY section. When indicated, consult OSI and/or an FDA ethicist (see below).

- If requesting a consultation from OSI and/or an FDA ethicist, forward copies of the ICD, the protocol, and other relevant supporting documentation (e.g., investigator's brochure) with the request for consultative review. Requests for consults should include specific questions or concerns the review division has regarding the ICD.

- Forward consult requests to OSI, Human Subject Protection (HSP) Branch, via CDER's electronic archiving system, when CDER has concerns related to the completeness and compliance of the ICD with the requirements of 21 CFR part 50. The IND review team should request a response through the electronic archiving system within 10 calendar days.

- Forward consult requests to an FDA ethicist, when necessary (as discussed in the POLICY section), on form FR-Consult-20 in the electronic archiving system for a specific study population (adults, pediatrics, or both). The IND review team should request a response through the electronic archiving system with a target due date.

- Review the comments provided by OSI and/or an FDA ethicist to determine which comments should be conveyed to the sponsor. A determination not to convey a comment by OSI or an FDA ethicist to the sponsor should be discussed with the consultant. This discussion should take place before a final decision is made not to convey the comment to the sponsor.

- Document ICD reviews in CDER's electronic archiving system.

Human Subject Protection Branch Within the Office of Scientific Investigations, Office of Compliance, will:

- At the request of the review divisions, review the ICD and other study-related documents for concerns about completeness and compliance of the ICD with the requirements of 21 CFR part 50 (see POLICY) and forward written comments on the ICD to the project manager within 10 calendar days of receipt. The HSP Branch will respond via the electronic archiving system.

ETHICS REVIEW

- If the review division requests a consult, it generally involves the following:

  – Upon receipt of an ethics consult, the ethicist reviews the ICD and other study-related documents to evaluate the ethical acceptability of the ICD and its conformance with applicable regulations (e.g., 21 CFR parts 50, 56, and 312) and FDA policies, and to address any questions posed by the consulting review division or that are identified during the ethics review.

  – The ethicist completes a written review addressing the ethics of the ICD and its conformance with applicable regulations, and identifying other concerns

  – The ethicist archives the written review in a timely manner in CDER's regulatory data archiving and tracking system

REFERENCES

MAPPs[2]

- MAPP 6030.1 *IND Process and Review Procedures (Including Clinical Holds)*
- MAPP 6030.6 *INDs: Processing Treatment INDs and Treatment Protocols*
- MAPP 6030.8 *INDs: Exception From Informed Consent Requirements for Emergency Research*

Regulations

- 21 CFR part 50, Protection of Human Subjects (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50)
- 21 CFR 50.25, Elements of informed consent (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25)
- 21 CFR part 56, Institutional Review Boards (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56)
- 21 CFR part 312, Investigational New Drug Application (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312)

DEFINITIONS

- **FDA Ethicist**: An FDA expert in biomedical ethics who addresses and analyzes the moral implications of research in the biomedical sciences and public health and makes recommendations accordingly.
- **Human Subject Protection (HSP) Branch**: The HSP Branch within the OSI, Office of Compliance, is responsible for assigning, participating in (as necessary), and evaluating inspections of IRBs participating in clinical drug studies. The HSP Branch may conduct reviews of ICDs for concerns about completeness and compliance of the ICD with the requirements of 21 CFR part 50.

[2] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm

- **IND Review Team**: The team composed of members of different disciplines (e.g., the medical officer, project manager, chemist, pharmacologist, microbiologist, biopharmaceutist, statistician) who review and make recommendations concerning the IND.

- **Informed Consent**: Informed consent is a process that involves providing a potential subject with adequate information to allow for an informed decision about participation in the clinical investigation, providing adequate opportunity for the potential subject to consider whether or not to participate, obtaining the potential subject's voluntary agreement to participate, and continuing to provide information as the clinical investigation progresses or as the subject or situation requires.

- **Informed Consent Document (ICD)**: The ICD is a written document that provides the study subject with information essential to making an informed decision about participating in a clinical investigation. The signature of the study subject or the subject's legally authorized representative on the ICD indicates the intent of the subject or the subject's legally authorized representative to give informed consent. The term *consent form* is also used to refer to the ICD.

- **Institutional Review Board (IRB)**: Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to ensure the protection of the rights and welfare of the human subjects (21 CFR 56.102(g)).

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
11/13/02	*Initial*	*n/a*
5/2/14	*Rev. 1*	*1. Corrected designation "Office of Scientific Investigation."* *2. Change in Background section.* *3. Change in Policy section clarifying situations when ICDs should be reviewed.* *4. Change in Responsibilities and Procedures section clarifying instructions for requesting OSI and ethics consults.* *5. Added ethics consultation procedures.* *6. Added references.*