

PROCEDURES

OFFICE OF NEW DRUGS

INDs: Processing Treatment INDs and Treatment Protocols

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PURPOSE

This MAPP describes the procedures for processing submissions that propose widespread expanded access to an investigational drug for treatment use through: (1) a treatment investigational new drug application (treatment IND); or (2) a treatment protocol submitted to an existing IND in the Center for Drug Evaluation and Research (CDER).

This MAPP does not address the procedures for processing submissions that propose other types of expanded access to an investigational drug for treatment use (i.e., single-patient INDs and protocols or intermediate-size patient population access INDs or protocols).

BACKGROUND

On August 13, 2009, the Food and Drug Administration (FDA) published in the *Federal Register* the final rule “Expanded Access to Investigational Drugs for Treatment Use,” which created 21 CFR part 312, subpart I. The final rule describes the requirements for the use of investigational new drugs (and approved drugs where availability is limited by a risk evaluation and mitigation strategy) when the primary purpose is to diagnose, monitor, or treat a patient’s disease or condition. The rule applies to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat a patient’s disease or condition.

Under the final rule, expanded access to investigational drugs for treatment use is available to: (1) individual patients, including in emergencies (single-patient INDs/protocols and emergency INDs/protocols); (2) intermediate-size patient populations (intermediate-size patient population access INDs/protocols); and (3) larger populations under a treatment protocol or treatment IND (treatment INDs/protocols).¹ The final rule details the criteria, submission requirements, and safeguards for these three types of expanded access for treatment use of an investigational drug. This MAPP addresses the third type of expanded access program, the treatment IND or treatment protocol.

Because of the potential for exposing thousands of patients to an investigational drug under a treatment IND or protocol, the authority to impose a clinical hold on a treatment IND or protocol or to allow it to proceed has been assigned to the directors of the Offices of Drug Evaluation (ODEs) I through IV, the Office of Hematology and Oncology Products, and the Office of Antimicrobial Products in the Office of New Drugs (OND) in CDER. The authority to impose a clinical hold on all other INDs or to allow them to proceed is assigned to the OND division directors, as described in MAPP 6030.1.

RESPONSIBILITIES AND PROCEDURES

- **Processing the Application or Protocol**

Recommended response times are in reference to the submission receipt (stamp) date (Day 0).

Document Room Staff will:

1. Upon receipt, log in the treatment IND or protocol according to standard document room procedures.
2. Process and deliver the submission to the appropriate OND review division staff on or before Day 2.

OND Regulatory Project Manager will:

1. Review the submission, in consultation with other division staff (if necessary), to determine if it qualifies as a treatment IND or protocol.
 - a. If the IND or protocol does not qualify as a treatment IND or protocol (e.g., a sponsor-investigator specifies on Form FDA 1571 that the submission is a treatment IND, but intends to treat only one patient), the

¹ When an access protocol that provides for widespread access to an investigational drug is submitted to an existing IND, the submission is referred to as a treatment protocol. When such a protocol is submitted in an original IND and is the only protocol under that IND, the submission is referred to as a treatment IND.

regulatory project manager (RPM) will notify the sponsor and the document room staff that the submission does not qualify as a treatment IND or protocol. The RPM will inform the document room staff of the appropriate supporting document category for the submission.

- b. If the submission qualifies as a treatment IND or protocol, the RPM will ensure that an acknowledgment letter for a treatment IND or protocol is prepared and issued to the sponsor.
2. Confirm that the submission will be, or has been, forwarded to the appropriate review staff.
 3. On or before Day 3, notify staff involved in the treatment IND or protocol review of the receipt of the IND or protocol submission and provide the following information: IND/amendment number, drug name, treatment use indication, 30-day due date, and review timeline (see the template timetable in Attachment A). The following staff should be notified, as appropriate:
 - a. Primary Reviewers in OND or other offices
 - b. Supervisors, Team Leaders, or Laboratory Chiefs in OND or other offices
 - c. In the Office of Pharmaceutical Science:
 - i. Product Quality RPM, Chemistry, Manufacturing, and Controls (CMC) Lead, Biopharmaceutics Lead, Branch Chief, and Division Director in the Office of New Drug Quality Assessment (ONDQA)
 - or
 - ii. Director, Division of Therapeutic Proteins, or Deputy Director, Division of Monoclonal Antibodies in the Office of Biotechnology Products (OBP)
 - d. Chief, Project Management Staff
 - e. Director, OND Review Division
 - f. Director, Office of Scientific Investigations (OSI), Office of Compliance (OC)

- g. In the Office of Compliance:
 - i. Chief, Biotech Manufacturing Assessment Branch, Office of Manufacturing and Product Quality (OMPQ), Division of Good Manufacturing Practice Assessment (DGMPA) (note: use CDER EESQUESTIONS email address)
 - ii. Chief, New Drug Manufacturing Assessment Branch, OMPQ/DGMPA (note: use CDER EESQUESTIONS email address)
 - h. Associate Director for Regulatory Affairs of the appropriate ODE
 - i. Director, appropriate ODE
 - j. Division of Business Analysis and Reporting Staff (note: use CDER BARS email address), Office of Business Informatics, in the Office of Planning and Informatics
4. On or before Day 4, consult OSI if the OND review division has specific concerns about whether the protocol's informed consent document (ICD) complies with 21 CFR part 50. In the consult request, include copies of the ICD, the protocol, the investigator's brochure (if any), a summary of the review division's specific concerns, and other relevant supporting documentation. If the sponsor has not submitted the ICD, the RPM should request that the sponsor submit it as soon as possible. Refer to MAPP 6030.2 *INDs: Review of Informed Consent Documents*.
5. Consult the Office of Medical Policy's Office of Prescription Drug Promotion (OPDP) if materials such as patient brochures or an announcement of the study are submitted. Include these materials, along with the protocol, in the consult to OPDP for review.
6. If a public communication about the treatment IND/protocol (provided it is allowed to proceed) is warranted, request that CDER's Executive Operations Staff arrange a communications planning meeting that includes the appropriate press office member.

Clinical Reviewer will:

On or before Day 4, discuss with the CMC/product quality reviewer any issues that might warrant an inspection of the facilities, such as an anticipated extent of exposure (i.e., size and nature of the population exposed to the investigational drug) that substantially exceeds what would normally be expected for a drug development program for the treatment of the disease or condition in question.

CMC/Product Quality Reviewer will:

On or before Day 4, discuss with the clinical reviewer any issues that might warrant an inspection of the facilities, as described above. Subsequently:

1. For drug products:

On or before Day 5 (i.e., within 2 days of notification of receipt of the IND), request an establishment evaluation by entering (or by having the ONDQA RPM enter) the relevant information about the facilities where the drug substance and final dosage form for the treatment IND or protocol studies will be manufactured into the Establishment Evaluation System (EES).

- a. Identify the entry as a “Treatment IND or Protocol” in the product section of the EES. After creating the Establishment Evaluation Request (EER), select the product tab and check the box titled: “9. Treatment IND, Request for Charge IND.” Specify any concerns about the facility or process in the comment section of the entry. If it is anticipated that the extent of exposure will substantially exceed what would normally be expected for a drug development program for the treatment of the disease or condition in question, include this information in the EES comment section as well.
- b. In addition, if the review division wants a facility inspected, note this in the EES comment section and provide the rationale behind the inspection request. Also, send a follow-up email to the Chief, New Drug Manufacturing Assessment Branch of OMPQ’s DGMPA (using the CDER EESQUESTIONS email address) reiterating the request for an inspection and the rationale behind the request. In the subject line of the email, note that the request is for an inspection of a treatment IND or protocol facility (in capital letters), to highlight the time-sensitive nature of the request.

2. For biologic products:

On or before Day 5 (i.e., within 2 days of notification of receipt of the IND), submit to OMPQ a Therapeutic Biologic Establishment Evaluation Request (TB EER) for each manufacturing facility referenced in the treatment IND/protocol submission.

- a. Send this request by email to the Chief, Biotech Manufacturing Assessment Branch of DGMPA, using the CDER-TB-EER email address. If it is anticipated that the extent of exposure will substantially exceed what would normally be expected for a drug development program for the

treatment of the disease or condition in question, include this information in the TB EER.

- b. If the review division wants a facility inspected, note this in the TB EER and provide the rationale behind the inspection request. In the subject line of the email, note that the request is for an inspection of a treatment IND or protocol facility (in capital letters), to highlight the time-sensitive nature of the request.

Office of Compliance, Office of Manufacturing and Product Quality will:

On or before Day 8, respond to the CMC/product quality reviewer on the current good manufacturing practice (CGMP) status of the establishment (i.e., *acceptable*, *withhold*, or *evaluation ongoing*).

1. On or before Day 14, based on all information available, DGMPA will enter an overall recommendation into EES or, for biologic products, will provide a recommendation by email to OBP.
2. Ordinarily, CDER will not inspect manufacturing facilities for a treatment IND or protocol. However, an inspection of the manufacturing facilities may be necessary to ensure the quality and consistency of the drug to be used in the proposed study. If DGMPA determines that a site inspection is necessary, it will request an inspection on a priority basis. DGMPA may recommend placing the study on clinical hold based on significant nonconformance with CGMPs. When determining CGMP status, DGMPA may request information from the CMC/product quality reviewer on product-specific quality requirements.

Office of Scientific Investigations will:

If asked to review the ICD, respond to the request within 7 days of receipt of the request.

• **Evaluating the Application or Protocol, and Routing the Clearance Package**

During the review, the ODE director should be notified of any potential concerns as soon as they are identified. If appropriate, the RPM should schedule a meeting with the ODE director and the division as soon as possible to discuss these concerns.

Primary Reviewers in OND or other offices will:

On or before Day 19, file their completed review in CDER's electronic archive and forward the completed review to their discipline team leader for electronic review and sign-off. The reviewers will use the appropriate treatment

IND/protocol review template² and include a recommendation as to whether the protocol may proceed or should be placed on hold and the reasons for their recommendation.

Secondary Reviewers will:

1. On or before Day 21, sign the primary review in the electronic archive, noting concurrence or nonconcurrence with the primary reviewer's recommendation, along with a brief explanation for their concurrence/nonconcurrence. If the secondary reviewer does not concur with the primary reviewer's recommendation, he or she will file a separate review that more fully explains the rationale behind such nonconcurrence.
2. Forward the review and accompanying documentation, if any, to the OND RPM. Any difference of opinion should be discussed with the division director (and ODE director, if necessary) as soon as possible.

OND Regulatory Project Manager will:

1. On or before Day 22, complete, in consultation with other division staff (as necessary), the Treatment IND/Protocol Executive Summary Review and file it in CDER's electronic archive for signature by the division director and ODE director.³
2. Draft a clinical hold letter, if applicable, for the ODE director's signature. The letter should describe the reasons for the clinical hold and the information needed to resolve the deficiencies, as described in MAPP 6030.1.
3. Prepare a package that consists of copies of the following documents, as applicable: Treatment IND/Protocol Executive Summary Review, review timeline, all reviews, EER printout or TB EER email, protocol, investigator's brochure, ICD, OSI review, any additional relevant information from the treatment IND/protocol submission, draft press release, and the draft clinical hold letter, if applicable.
4. On or before Day 22, circulate the treatment IND/protocol package (the package) within the division.

² Review templates are located in the CDER Standard Templates eRoom.

³ The Treatment IND/Protocol Executive Summary Review template is located in the CDER Standard Templates eRoom.

5. On or before Day 23, forward the package to the OND review division director.

OND Review Division Director will:

1. Review the package and meet with the review team, if necessary. The package documents may be revised, if necessary.
2. On or before Day 26, sign the Treatment IND/Protocol Executive Summary Review in CDER's electronic archive, initial the draft hold letter (if applicable), and forward the package to the ODE director.

ODE Director will:

On or before Day 30, review the package (discussing it with the review team if necessary) and make the final decision on whether the treatment IND or protocol may proceed or will be placed on clinical hold. If the ODE director's decision is consistent with the review division's recommendation, the ODE director will indicate concurrence when signing the Treatment IND/Protocol Executive Summary Review in CDER's electronic archive. If the ODE director's decision is not consistent with the review division's recommendation, the ODE director will indicate nonconcurrence when signing the Treatment IND/Protocol Executive Summary Review in CDER's electronic archive and document the reasons for his or her nonconcurrence in a separate written review to be filed in CDER's electronic archive by Day 30. If the final decision is to issue a clinical hold, the ODE director should make any necessary changes to the draft hold letter and forward the package and draft letter to the RPM.

• Managing the Treatment IND/Protocol Decision

1. If a public announcement about the treatment IND/protocol is planned, the RPM will inform the sponsor of this plan.
2. If the treatment IND/protocol is to be placed on clinical hold:

OND Regulatory Project Manager will:

- a. Ensure that the sponsor is notified by telephone of the clinical hold decision by Day 30, and document the notification as described in MAPP 6030.1 (see the following OND Review Division Director section).
- b. Ensure, when the ODE director returns the draft hold letter, that the letter is revised (if necessary), filed in CDER's electronic archive, and signed by

the ODE director within 30 calendar days of the sponsor's notification that the treatment IND/protocol was placed on clinical hold.

OND Review Division Director will:

Notify the sponsor of a commercial IND, by telephone, of the hold decision if the protocol is placed on clinical hold (as described in MAPP 6030.1).

ODE Director will:

If applicable, sign (in CDER's electronic archive) the final hold letter within 30 calendar days of the sponsor's notification that the protocol was placed on clinical hold, although earlier filing and signing of the letter is encouraged.

- **Follow-Up Procedures for Applications on Clinical Hold**

A complete response to a clinical hold letter for a treatment IND or protocol should be processed in the same manner as the original treatment IND/protocol (i.e., 30-day time frame applies and the ODE director makes the final decision).

REFERENCES

1. MAPP 6030.1 *IND Process and Review Procedures (Including Clinical Holds)* (<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/default.htm>)
2. MAPP 6030.2 *INDs: Review of Informed Consent Documents* (<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/default.htm>)
3. Final rule "Expanded Access to Investigational Drugs for Treatment Use" (74 FR 40900, August 13, 2009) (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm172492.htm>)

EFFECTIVE DATE

This MAPP is effective upon date of publication.

ATTACHMENT A:

TREATMENT IND/PROTOCOL REVIEW TIMETABLE

IND #
Drug Name

Day*	Action	Date
Day 0	Receipt in document room	
Day 2	Document room staff forwards IND/protocol to division staff	
Day 4	RPM forwards ICD to OSI (optional)	
Day 5	Product quality discipline enters establishment in EES or sends TB-EER email	
Day 8	DGMPA responds to EER/Compliance check request	
Day 11**	OSI responds to ICD consult	
Day 14	DGMPA provides final response to CMC/product quality reviewer	
Day 19	Primary reviewers forward their reviews to secondary reviewers	
Day 21	Secondary reviewers file and/or sign reviews in electronic archive and forward the reviews to the OND RPM	
Day 22	RPM circulates package in division	
Day 23	RPM forwards package to OND review division director	
Day 26	Division forwards package to office	
Day 30	ODE director signs Treatment IND/Protocol Executive Summary Review	
Day 30	If a hold is imposed, sponsor is notified of hold decision***	

* Because the timetable reflects calendar days, the review team should evaluate the due dates carefully to take weekends and holidays into consideration.

** Around Day 11, depending on when OSI received the consult from the OND review division.

*** Hold letter is to be signed within 30 calendar days of sponsor's notification of the decision (i.e., that the treatment IND/protocol was placed on clinical hold).