

POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

**Emergency Investigational New Drug Application Process
During and After Normal Business Hours**

Table of Contents

PURPOSE.....1
BACKGROUND2
POLICY3
RESPONSIBILITIES AND PROCEDURES4
DEFINITIONS11
EFFECTIVE DATE.....11
 ATTACHMENT 1: Suggested Information to be
 Collected for an EIND12

PURPOSE

- This MAPP describes the policies and procedures established in the Center for Drug Evaluation and Research (CDER) for managing and processing applications for individual patient expanded access for emergency use (henceforth referred to as *emergency investigational new drug applications (EINDs)*) for licensed physicians (i.e., the licensed physician under whose immediate direction an investigational drug is administered or dispensed) seeking access to an investigational drug for treatment use in an individual patient in an emergency situation, both during and after normal business hours.¹
- Although access to an investigational drug for an individual patient in an emergency situation may be requested and authorized through submission of a protocol for such use by an investigational new drug application (IND) holder (e.g., pharmaceutical company) to its existing IND, this situation is not common and is not addressed in this MAPP. Most emergency access is requested and authorized through submission of a protocol under a new IND (EIND). This scenario (emergency access requested and allowed under an EIND) is addressed in this MAPP.

¹ For the purposes of this MAPP, all references to *drugs* include human drugs and therapeutic biological products regulated by CDER.

-
- This MAPP does not describe the policies and procedures for managing and processing submissions for access to an investigational drug for an individual patient in a nonemergency situation.
-

BACKGROUND

- On August 13, 2009, FDA published in the *Federal Register* the final rule “Expanded Access to Investigational Drugs for Treatment Use.” This final rule added subpart I regarding expanded access to investigational new drugs for treatment use into 21 CFR part 312.² “This subpart contains the requirements for the use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient’s disease or condition. The aim of this subpart is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient’s disease or condition.”³
- Subpart I describes the requirements for expanded access to an investigational drug for treatment use (henceforth referred to as *access* or *expanded access*), including access for individual patients in emergencies. Whereas 21 CFR 312.305 describes the requirements for all expanded access uses, 21 CFR 312.310 specifically describes the requirements unique to individual patient access and 21 CFR 312.310(d) describes the procedures for requesting and authorizing access to an investigational new drug for use in an individual patient in an emergency situation.
- As explained in 21 CFR 312.305(c), a patient may obtain access to an investigational drug for treatment use, including in an emergency situation, through a licensed physician. A licensed physician under whose immediate direction an investigational drug is administered or dispensed for an expanded access use is considered an *investigator*. An individual or entity that submits an expanded access IND is considered a *sponsor*. A licensed physician under whose immediate direction an investigational drug is administered or dispensed and who submits an IND for expanded access is a *sponsor-investigator* and must comply with the regulatory requirements for sponsors and investigators.

² 21 CFR 312.300-320

³ 21 CFR 312.300(a)

-
- In June 2016, FDA issued the following guidances for industry:⁴
 - *Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers*. This guidance provides information to industry, researchers, physicians, and patients about the implementation of FDA regulations on expanded access to investigational drugs for treatment use.
 - *Individual Patient Expanded Access Applications: Form FDA 3926*. This guidance describes a streamlined alternative approach for the submission of an IND for individual patient expanded access, including for emergency use, by a physician.
 - FDA cannot compel a pharmaceutical company to provide access, including emergency access, to its investigational drug for treatment use. When a company provides access to its investigational drug for treatment use, it is doing so voluntarily.
-

POLICY

- Because of the urgency of the situation, CDER will review requests for EINDs immediately upon receipt.
- CDER may receive requests for EINDs by telephone, facsimile, or other means of electronic communication, although CDER generally does not monitor (and therefore may not respond promptly to) facsimile transmissions and electronic communications received during nonbusiness hours. During nonbusiness hours, CDER receives requests for EINDs by telephone through FDA's Emergency Call Center, which is operational 24 hours a day/7 days a week.
- The decision to authorize or deny emergency access will be communicated by telephone.
- Staff will obtain verbal agreement from the licensed physician who contacts FDA to request an EIND for treatment use in his or her patient to submit all necessary forms and information within 15 working days of FDA authorizing access.
- As described under 21 CFR 56.104(c), emergency use of an investigational drug is exempt from the requirement of a prospective institutional review board (IRB) review, provided that such emergency use is reported to the IRB within 5 working days of treatment initiation. In general, any subsequent uses of the same

⁴ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

investigational drug at the same institution will require prior IRB review and approval. When, however, prior IRB review and approval is not feasible for a subsequent expanded access emergency use of the same investigational drug at the same institution, FDA will not deny the subsequent request for emergency access because of a lack of prospective IRB review. FDA will advise the sponsor to report the use to his or her IRB within 5 working days of treatment initiation.

- The Office of New Drugs (OND) review staff will accept single copies (instead of the standard three copies) of original IND submissions or subsequent amendments to INDs from physicians who submit individual patient expanded access INDs, including EINDs.
- An EIND will be authorized only when there is an emergency that requires the patient to be treated before a written submission to FDA can be made.
 - Because EINDs are authorized only in emergency situations and some may be authorized after business hours, generally there will not be sufficient time nor, in some cases (i.e., after-hours), sufficient means for FDA to generate written documentation of its authorization of the EIND at the time of such authorization. Therefore, FDA will not generate such written documentation at the time of authorization. Consequently, FDA will not expect EIND sponsors to provide written documentation to the supplier of the investigational drug before the supplier provides the investigational drug to the EIND sponsor.
 - Similarly, FDA will not expect sponsors to provide to FDA any written documentation before FDA's authorization of the EIND. This includes, if applicable, the letter of authorization from the entity developing the investigational drug that permits FDA to reference the developer's IND in support of the EIND. FDA expects the letter of authorization, if applicable, to be included in the written follow-up submission made to FDA within 15 working days of authorization of the EIND.

RESPONSIBILITIES AND PROCEDURES

EIND Requests During Business Hours

For EIND requests initiated during normal business hours (8:00 a.m. to 4:30 p.m., Monday – Friday), FDA's Expanded Access website directs physicians to contact the appropriate OND review division, if known, or the Division of Drug Information (DDI), if not known. If both are unavailable, physicians are directed to contact the CDER Emergency Coordinator (CEC).⁵

⁵ <https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm429610.htm>

The Division of Drug Information will:

- Provide contact information to both the physician and review division as follows:
 - From its list of division contacts, DDI will identify the appropriate OND review division, provide the physician with the review division's telephone number, and instruct the physician to call DDI back if he or she is unable to reach anyone in the review division.
 - DDI will collect contact and other basic information from the physician (e.g., his or her name and telephone number, patient information, investigational drug name) and forward it to the appropriate review division contact with a request for confirmation of receipt and that the physician will be contacted. If no confirmation is received from the review division, DDI will contact the physician to ensure that he or she has heard from the review division.

The CDER Emergency Coordinator will:

- Identify the appropriate OND review division, provide the physician with the review division's telephone number, and forward the physician to the division
- Instruct the physician to call the CEC back if he or she is unable to reach anyone in the review division

Review Division Support Staff will:

- Direct the call to the appropriate individual in the review division, as determined by the division's policy on the management of EIND requests

Review Division Review Staff will:

- Speak to the licensed physician (sponsor-investigator) to collect the necessary patient and treatment information (Attachment 1)
- Inform the physician that the pharmaceutical company will need to agree to provide the investigational drug, if the company has not already done so⁶
- Determine whether an IND should be authorized or denied and inform the sponsor

⁶ Because the existence of and information in an IND are confidential, FDA may not provide or disclose the name of the sponsor of the IND under which an investigational drug is being studied to a third party, such as a physician sponsor. It is the responsibility of the EIND sponsor to identify the entity developing the investigational drug and to request and obtain that entity's permission to access the investigational drug to treat his or her patient before contacting FDA to request an EIND.

-
- If denying the EIND, determine whether treatment may be appropriate under another type of expanded access (e.g., a nonemergency individual patient expanded access IND)
 - If so, direct the physician to resubmit the appropriate type of expanded access IND; document the recommendation and archive the documentation in the file of the new expanded access submission (after receipt, if the submission is a new IND) in CDER’s electronic archive
 - If not, inform the sponsor and provide the reasons behind denying the request and document this discussion
 - Create or have a new IND created in CDER’s electronic archive for the emergency IND request with a status of “deny”
 - File the documentation of the discussion with the sponsor in this file in CDER’s electronic archive

 - If authorizing the EIND
 - Create or have a new IND created in CDER’s electronic archive for the emergency IND request with a status of “active”
 - Provide the physician with his or her IND number and instruct the physician to include this IND number in the designated area on the FDA form that accompanies the EIND submission
 - Remind the physician of his or her obligation to report the emergency use to his or her IRB within 5 working days (21 CFR 56.104(c))
 - Provide instructions to the physician on the location of the EIND paperwork and remind the physician that it is to be completed and submitted to the review division within 15 working days of FDA authorizing access to the investigational drug⁷
 - If applicable (i.e., when there is an IND to reference), remind the physician to include, in the EIND paperwork, the letter of authorization the physician receives or received from the pharmaceutical company that permits the physician to refer to the company’s IND to support the physician’s EIND

⁷ FDA forms and instructions can be found at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343022.htm>.

EIND Requests Outside of Business Hours

EIND requests initiated outside of normal business hours (8 a.m. to 4:30 p.m., Monday – Friday), either directly by a licensed physician or received through the late duty officer in the Office of Emergency Operations, will be managed by the on-call CEC.

For EIND requests for which the CEC has permission from the review division to authorize on the review division’s behalf, the CEC will:

- Speak to the physician to collect the necessary patient and treatment information (Attachment 1).
- Determine whether the pharmaceutical company has agreed to provide the investigational drug to the physician. If the physician has not contacted the company, advise the physician to do so and, after the physician has agreement from the company to provide the investigational drug, contact the CEC again.
- Determine whether the IND meets the authorization criteria established by the review division and should, therefore, be authorized by the CEC on the division’s behalf.
 - If the CEC determines that the request does not meet the authorization criteria, see the next section
 - If the CEC determines that the request meets all the criteria for authorizing the EIND on the division’s behalf, the CEC should:
 - Inform the physician that the EIND is authorized and provide the physician with his or her contact information to serve as a placeholder for the IND number.
 - Instruct the physician to contact the review division the following business day.
 - Document all available information in an email to the review division contact(s), CDER-ER-OPS, and FDA Emergency Operations. Unless otherwise noted by the review division, this email should be sent to the review division’s director, deputy director, and division project management staff.

When contacted by the IND sponsor the following business day, the review division will:

- Provide the physician with his or her IND number and instruct the physician to include this IND number in the designated area on the FDA form that accompanies the EIND submission
- Provide instructions to the physician on the location of the EIND paperwork and remind the physician that it is to be completed and submitted to the review division within 15 working days of FDA authorizing access to the investigational drug
- Remind the physician of his or her obligation to report the emergency use to his or her IRB within 5 working days (21 CFR 56.104(c))
- If applicable (i.e., when there is an IND to reference), remind the physician to include, in the EIND paperwork, the letter of authorization the physician receives or received from the pharmaceutical company that permits the physician to refer to the company's IND to support the physician's EIND

For EIND requests for which the CEC has not received permission from the review division to authorize on the review division's behalf, the CEC will:

- Speak to the physician to collect the necessary patient and treatment information (Attachment 1).
- Determine whether the pharmaceutical company has agreed to provide the investigational drug to the physician. If the physician has not contacted the company, advise the physician to do so and, after the physician has agreement from the company to provide the investigational drug, contact the CEC again.
- Identify the review division with regulatory authority for the requested investigational drug.
- Contact the appropriate on-call after-hours individual in the review division by telephone, using the CDER Emergency Contact List maintained by the Counter-Terrorism and Emergency Coordination Staff (CTECS), and relay all available information regarding the request.
- Document all available information in an email to the review division contact(s), CDER-ER-OPS, and FDA Emergency Operations. Unless otherwise noted by the review division, this email should be sent to the division's director, deputy director, and the division project management staff.

The review division after-hours contact will:

- Call the requesting physician to confirm patient information (Attachment 1)
- Determine whether the IND should be authorized or denied and inform the physician
 - If denying the EIND, determine whether treatment may be appropriate under another type of expanded access (e.g., a nonemergency individual patient expanded access IND)
 - If so, direct the physician accordingly; document the recommendation and archive the documentation in the file of the alternative expanded access submission (after receipt, if the submission is a new IND) in CDER’s electronic archive
 - If not, inform the physician and provide the reasons behind denying the request and document this discussion
 - Create or have a new IND created in CDER’s electronic archive for the emergency IND request with a status of “deny”
 - File the documentation of the discussion with the physician in this file in CDER’s electronic archive
 - If denying the EIND, whether or not treatment may be appropriate under another type of expanded access, notify the CEC and FDA Emergency Operations of the outcome by email
 - If authorizing the EIND:
 - Provide the physician with his or her contact information to serve as a placeholder for the IND number
 - Direct the physician to contact the review division the following business day, and provide the appropriate contact information
 - Notify, via email, the CEC and FDA Emergency Operations of the outcome (that the EIND was authorized)
 - Create or have a new IND created in CDER’s electronic archive for the emergency IND request with a status of “active”

When contacted by the IND sponsor the following business day, the review division will:

- Provide the physician with his or her IND number and instruct the physician to include this IND number in the designated area on the FDA form that accompanies the EIND submission
- Provide instructions to the physician on the location of the EIND paperwork and remind the physician that it is to be submitted to the review division within 15 working days of FDA authorizing access to the investigational drug
- Remind the physician of his or her obligation to report the emergency use to his or her IRB within 5 working days (21 CFR 56.104(c))
- If applicable (i.e., when there is an IND to reference), remind the physician to include, in the EIND paperwork, the letter of authorization the physician receives or received from the pharmaceutical company that permits the physician to refer to the company's IND to support the physician's EIND

For EIND requests for an investigational drug for which the CEC has been informed by the review division that such requests do not meet the criteria for emergency use, but may meet the criteria for another type of expanded access, the CEC will:

- Record the physician's contact information and the investigational drug being sought
- Inform the physician that the criteria for emergency single patient expanded access are not met, but that the criteria for nonemergency single patient expanded access may be met; advise the physician on the process for submitting a request for nonemergency single patient expanded access and recommend that the physician submit such a request to the appropriate review division
- Direct the physician to FDA's online resources regarding nonemergency single patient expanded access
- Forward, via email, the physician's contact information to the appropriate review division, indicating that an emergency IND was denied and that the physician was advised to submit a request to the review division for nonemergency single patient expanded access

Upon receipt of the CEC email notification, the review division staff will:

- Create or have a new IND created in CDER's electronic archive for the emergency IND request with a status of "deny"

- File the communication from the CEC in this file in CDER's electronic archive

After an EIND Is Authorized

Review division project management staff will:

- Create an EIND application in CDER's electronic archive and identify it as an EIND in the archive.
- Send an EIND Acknowledgement letter within 5 working days of authorization of the EIND that includes the official IND number, and complete the entry of data in CDER's electronic archive, as needed.
- If the follow-up EIND paperwork is received by the division instead of the document room, stamp or otherwise identify the receipt date on the paperwork and deliver it to the document room.
- Issue an acknowledge withdrawal letter to the physician in the event an EIND was authorized and the physician subsequently notifies FDA that treatment is completed and requests to withdraw the IND. Upon issuance of this correspondence, the status of the application should be changed in CDER's electronic archive to "withdrawn."
- Issue an IND canceled letter to the physician in the event an EIND was authorized and the physician subsequently notifies FDA that the drug was never administered. Upon issuance of this correspondence, the status of the application should be changed in CDER's electronic archive to "canceled."

DEFINITIONS

CDER Emergency Coordinator — Typically a member of CTECS.

Expanded Access — The use outside of a clinical trial of an investigational drug (i.e., one that has not been approved by FDA).

EFFECTIVE DATE

This MAPP is effective upon date of publication.

ATTACHMENT 1: Suggested Information to be Collected for an EIND

1. The physician's (sponsor's) name, address, contact information, including email address, office and cellular telephone numbers and fax number, and a brief summary of his or her qualifications.
2. The age, sex, weight, allergies, and diagnosis of the patient
3. The patient's initials
4. The indication for which the investigational drug is being requested
5. A brief patient medical history (e.g., a history of the patient's illness, including stage and prior therapy, response to prior therapy, concomitant conditions and/or medications (including previous medications) that may affect dosing)
6. The rationale for the request for treatment with the investigational drug (as opposed to treatment with available therapy) and request for emergency access (as opposed to enrollment in a clinical study or other type of expanded access)
7. The name, dosage form, and manufacturer of the investigational drug being requested
8. The intended dose, dosing regimen, duration of treatment, and route of administration
9. The clinical plan for following patient outcomes (e.g., monitoring procedures, plan for modification to treatment plan in event of toxicity)