Expanded Access to Investigational Drugs for Treatment Use

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Learning Objectives

- Understand FDA's regulatory and statutory requirements of expanded access (EA) to investigational drugs* for treatment use
- Provide responses to common questions related to EA to investigational drugs for treatment use

*Referring to both human drugs and biological products regulated by CDER and CBER

What is Expanded Access?

- Expanded access / treatment use: Using an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease / condition.
  - Subpart I of 21 Code of Federal Regulation (CFR) 312
- Occasionally used terms: "compassionate use" and "preapproval access"
  - Not defined or described in FDA regulations
- Clinical studies of investigational drugs: Primary purpose is to obtain information about the safety or effectiveness of the drug

Subpart I of 21 CFR 312

- Criteria that must be met to authorize expanded access use
- Requirements for expanded access submissions
- Safeguards that are intended to
  - protect patients
  - preserve the ability to develop meaningful data about the safety and effectiveness of the drug through clinical trials or drug development

21st Century Cures Act & EA

- Expanded access policy - Section 561A to the FD&C Act requiring the manufacturer / distributor of investigational drugs to make its policy for evaluating and responding to EA requests public and readily available, e.g., by posting the policy on a publicly available website, including:
  - Contact information,
  - Procedures for submission of EA requests,
  - General criteria for evaluation and response,
  - The anticipated time frame for acknowledgement of such requests,
  - A hyperlink or other reference to the record in ClinicalTrials.gov that contains information about availability of the drug under EA

FDA Reauthorization Act (FDARA) & EA

- Amended the FD&C Act to require that the EA policy for an investigational drug be posted by the earlier of
  - the first initiation of a Phase 2 or Phase 3 study with respect to such investigational drug, OR
  - within 15 days after the drug receives a Fast Track, Breakthrough or Regenerative Medicine Advanced Therapy designation

Clarification

- Posting of the EA policy does not guarantee access to the investigational drug under EA
- It is the sponsor's voluntary action to provide EA to its investigational drug
- FDA - long history of facilitating EA to investigational drugs for treatment use of serious or immediately life-threatening diseases or conditions lacking satisfactory therapeutic alternatives
- FDA cannot compel a sponsor to provide EA to its investigational drug.

What types of regulatory submissions can be used to obtain EA to a drug?

- An EA protocol: A protocol amendment to an existing IND
- An EA IND: Separate and distinct from any existing INDs and is intended only to make a drug available for treatment use under EA

When should an EA protocol submission be used?

- Only if the sponsor seeking EA has an existing IND in effect
  - Typically, a pharmaceutical company or manufacturer of the drug with an existing IND
  - Developing the drug for marketing under the IND
- When there is an existing IND in effect,
  - FDA generally prefers the submission of an EA protocol
  - all EA use and clinical trial use consolidated under a single IND may facilitate the administrative and review processes, less burdensome for sponsors and FDA

When should a new EA IND submission be used?

- No existing IND is in effect for the drug or,
- An existing IND is in effect for the drug, but the sponsor is not intended to be the sponsor of the EA use
  - e.g., for an individual patient use, the sponsor of the existing IND may prefer that a patient's physician be the sponsor-investigator and submit a separate individual patient IND

How does FDA categorize & subcategorize EA submissions?

- EA for individual patients, including for emergency use (21 CFR 312.310)
  - Individual patient EA IND
    - Individual patient EA IND for emergency use
  - Individual patient EA protocol
    - Individual patient EA protocol for emergency use
- EA for intermediate-size patient populations (21 CFR 312.315)
  - Intermediate-size patient population EA IND
  - Intermediate-size patient population EA protocol
- EA for widespread treatment use (21 CFR 312.320)
  - Treatment IND
  - Treatment protocol

EA for individual patients

- EA to an investigational drug for treatment use by a patient
- Individual patient EA IND (aka single patient IND)
  - Submitted under a new IND
  - A 30-day period from the date FDA receives the IND prior to initiation of treatment (FDA may allow treatment to begin earlier)
- Individual patient EA protocol (aka single patient protocol)
  - Submitted as a protocol to an existing IND by the sponsor of the existing IND
  - No 30-day waiting period
  - IRB approval consistent with 21 CFR 254 part 56 prior to treatment
  - FDA may put the protocol on clinical hold (e.g., safety issue)

EA for individual patients for emergency use

- A subset of individual patient INDs / protocols
- Providing EA in an emergency situation
  - e.g., Treating a patient before a written submission can be made, treatments expected to have a rapid effect on an acute clinical emergency
- Often requested and authorized by telephone (or email)
- Must agree to submit a written submission within 15 working days of the initial authorization
- Treatment may start immediately upon FDA authorization
- Must report to the IRB within 5 working days of emergency use If no IRB review prior to treatment

Intermediate-Size Patient Population EA

- EA to an investigational drug can be provided under an intermediate IND / protocol if FDA determines that
  - enough evidence that the drug is safe at the dose and duration proposed for EA to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under EA, AND
  - at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make EA use a reasonable therapeutic option in the anticipated patient population
- > 1 patient, but generally < than a treatment EA
- IRB approval must be obtained before treatment

Treatment IND/Protocol

- EA to an investigational drug can be provided under a Treatment IND / protocol only if
  - the drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application, or
  - all clinical trials of the drug have been completed, and the sponsor is actively pursuing, with due diligence, marketing approval of the drug
- IRB approval must be obtained before treatment

What forms are used for expanded access submissions?

- Form FDA 1571 (Investigational New Drug Application (IND))
  - individual patient INDs and protocols
  - intermediate-size patient population INDs and protocols
  - treatment INDs and protocols
- Form FDA 3926 (Individual Patient Expanded Access—Investigational New Drug Application (IND))
  - May be used by the licensed physician acting as a sponsor-investigator
  - More streamlined alternative for submitting an individual patient EA IND under 21 CFR 312.23

What information should be included in an EA submission?

- Must include all information required by 21CFR 312.305(b)
- Additional information required for the particular category of expanded access
  - 21CFR 312.310(b) for individual patient submissions,
  - 21CFR 312.315(c) for intermediate-size patient population submissions,
  - 21CFR 312.320(b) for treatment submissions

Are there safeguards in place for EA use of an unapproved drug?

- FDA oversight of patient safety
- Investigators responsible for
  - reporting adverse events to the sponsor,
  - ensuring that the ICD requirements are met (21 CFR part 50),
  - ensuring an IRB review consistent with 21 CFR part 56
- Sponsors responsible for
  - complying with expedited IND safety reporting requirements (21 CFR 312.32)
  - submitting to FDA annual reports (when the IND or protocol continues for >1 year) under 21 CFR 312.33
  - ensuring that licensed physicians are qualified to administer the drug
  - providing licensed physicians with the information needed to minimize the risk
  - maintaining an effective IND for the expanded access use

How does FDA address individual patient EA applications for treatment with multiple courses of therapy or treatment of a chronic condition?

- Generally limited to a single course of therapy for a specified duration
- FDA may authorize multiple courses of therapy or chronic therapy, including authorizing individual patient EA to treat a chronic disease or condition that requires extended treatment.
  - When the circumstances of the treatment are well defined and reasonable considering the available evidence to support use of the drug.
  - The patient's physician (as the investigator) proposes the full course of treatment when filing the request for expanded access.
  - To justify the risks and benefits, the planned course of therapy should be well defined.
  - Not usually authorize EA for an unspecified duration at the discretion of the patient's physician.

Is IRB review and approval required for all EA categories?

- Yes, except for emergency EA use when there is not sufficient time to secure prospective IRB review, but IRB must be notified within 5 working days of emergency use
- Non-emergency individual patient EA IND: FDA allows for waivers of the requirement for review and approval at a convened IRB meeting
- Intermediate IND/Protocol and Treatment IND/Protocol:
  - Require a full IRB review
  - Form FDA 1571 requires a commitment that an IRB will be responsible for the initial and continuing review of the studies under an IND

Form FDA 3926

10.b. Request for Authorization to Use Alternative IRB Review Procedures

I request authorization to obtain concurrence by the Institutional Review Board (IRB) chairperson or by a designated IRB member, before the treatment use begins, in order to comply with FDA's requirements for IRB review and approval. This concurrence would be in lieu of review and approval at a convened IRB meeting at which a majority of the members are present.

Are EA submissions subject to the informed consent (IC) requirements?

- EA to an investigational drug for treatment use, including emergency use, requires IC as described in 21 CFR part 50, unless one of the exceptions found in part 50 applies.
- The IC must contain information set out in 21 CFR 50.20 and 50.25 to allow the patient to make an informed decision about receiving experimental treatment.

How does FDA determine that authorizing EA to a drug will not interfere with clinical trials or drug development?

- The potential for EA to interfere with clinical trials/drug development is high for rare disease drug development programs, due to limited number of subjects available
- This potential is highest early in development and decreases as development progresses.
- In general, for rare disease drug development, well-controlled clinical trials should be initiated before treating patients under EA,
- EA should be sought only for patients truly not eligible for or are unable to participate in those well-controlled trials.
- Sponsors should consider study designs that help to minimize barriers to trial participation, e.g., broad inclusion criteria, virtual/at-home visits, or using health facilities closer to potential subjects.

What are some of the reasons for FDA to deny a request?

- Even when there are two (or more) individual patient EA requests for patients with the same disease or condition,
  - there may be significant differences in the clinical presentation of the disease or condition that make the risks acceptable for one patient, but not for another.
  - a patient may be able to enroll in a clinical trial that was not accessible to a previous patient who was granted EA
  - FDA becomes aware since authorizing previous requests for EA that EA is impeding the clinical development of the drug and, on that basis, place further requests for EA on clinical hold

Challenge Question #1

IRB review and approval is required for all expanded access prior to investigational drug treatment except for emergency EA use when there is no sufficient time to secure prospective IRB review

A. True

B. False

Challenge Question #2

Which of the following statements is NOT true?

A. Posting of the expanded access (EA) policy guarantees access to the investigational drug under EA.

B. FDA has long history of facilitating EA to investigational drugs for treatment use for patients with serious or immediately life-threatening diseases or conditions lacking satisfactory therapeutic alternatives

C. FDA cannot compel a sponsor to provide its investigational drug for expanded access use.

D. The primary purpose of EA is not to obtain information about the safety or effectiveness of a drug.

Summary

- Expanded access : The use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease / condition
- FDA - long history of facilitating EA
- It is the sponsor's voluntary action to provide EA to its investigational drug
- Under FDA oversight for patient safety

Resources

- Guidance for Industry: *Individual Patient Expanded Access Applications: Form FDA 3926 (https://www.fda.gov/media/91160/download)*
- Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers

  https://www.fda.gov/media/85675/download
- Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers (draft)

  https://www.fda.gov/media/162793/download

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