BACKGROUND &SUMMARY

Expanded access (often referred to as *"compassionate use"*)***:*** 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. [21 CFR 312.300 (Subpart I)]

> ***Immediately life-threatening disease or condition:*** A stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.
>
> ***Serious disease or condition:*** A disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Expanded Access Programs (EAPs)*:* The FDA uses this term to refer to the various types of allowable expanded access use.

For all expanded access use prior IRB review and approval is needed*, (*with the exception of Emergency Use; see Emergency Use of a Test Article [GUI-6].)

In this guidance:

- Drugs
  - All Expanded Access Programs (basic criteria, etc.)
  - Single (Individual) Patients,
    Emergency Use for single patient (see Emergency Use of a Test Article [GUI-6])
  - Intermediate-Size Patient Populations
  - Treatment IND or Treatment Protocol (widespread treatment use)
- Devices
  - Compassionate Use (Single Patient/Small Group Access)
  - Treatment IDE- Larger Group/More Widespread Use
  - Continued Access
- Resources

Note: Humanitarian Use Devices (HUDs) are covered under separate regulations, and are discussed in guidance Humanitarian Use Devices [GUI-36m].

DRUGS

Basic Criteria for All Expanded Access Uses

All expanded access programs (EAPs) use must meet the basic criteria in 21 CFR 312.305(a), i.e., the FDA must determine:

(1) The patient or patients to be treated have a *serious* or *immediately life-threatening* disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

(2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and

(3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

Note: See *additional criteria* under each EAP category.

Submission to FDA

Prior approval from the FDA is required for every category of EAP. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information contained in an existing IND if the sponsor of the existing IND grants a "right of reference" to the IND. 21 CFR 312.305(b).

Reporting and Monitoring Requirements

Investigators:

- Reporting adverse drug events to the sponsor,
- Ensuring that the informed consent requirements are met,
- Ensuring that IRB review of the expanded access use is obtained,
- Maintaining accurate case histories and drug disposition records/retaining records in a manner consistent with the requirements of 21 CFR 312.62.

Sponsors:

- Submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to FDA
- Ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use,
- Providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (investigator's brochure must be provided if one exists for the drug),
- Maintaining an effective IND for the expanded access use, and
- Maintaining adequate drug disposition records and retaining records (21 CFR 312.57).

Additional responsibilities may apply (see each EAP category).

Drugs: Single (Individual) Patients

Treatment is generally limited to a single course of therapy for a specified duration unless FDA expressly authorizes multiple courses or chronic therapy. The treating physician should request an individual patient IND for treatment use on FDA Form 1571 (specifying whether it is an emergency IND or individual patient IND). See Physician Request for an Individual Patient IND under Expanded Access for Non-emergency or Emergency Use.

Criteria

In addition to the basic EAP criteria (listed above), the FDA may permit an investigational drug to be used for the treatment of an individual patient by a licensed physician if the following determinations are made: (21 CFR 312.310):

(1) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and
(2) FDA must determine that the patient cannot obtain the drug under another IND or protocol.

Emergency Use for single patient: see Emergency Use of a Test Article [GUI-6] for additional requirements.

Reporting and Monitoring Requirements

At the conclusion of treatment, the licensed physician or sponsor must provide a written summary of the results of the expanded access use, including adverse effects to the FDA.

Drugs: Intermediate-Size Patient Populations

FDA may permit an investigational drug to be used for the treatment of a patient population smaller than that typical of a treatment IND or treatment protocol. FDA may ask a sponsor to consolidate expanded access under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use. The use of this EAP is fully addressed in 21 CFR 312.315.

Criteria

In addition to the basic EAP criteria (listed above) the FDA must determine:

(1) There is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under expanded access; and
(2) There is at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

Drugs: Treatment IND or Treatment Protocol (widespread treatment use)

FDA may permit widespread treatment use of an investigational drug under 21 CFR 312.320.

Criteria

In addition to basic EAP criteria (listed above) the FDA must determine:

(1) ***Trial status:***
- (i) The drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, or
- (ii) All clinical trials of the drug have been completed; and

(2) **Marketing status:**
The sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence; and

(3) ***Evidence:***
- (i) *When the expanded access use is for a serious disease or condition*, there is sufficient clinical evidence of safety and effectiveness to support the expanded access use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials; or
- (ii) *When the expanded access use is for an immediately life-threatening* disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

DEVICES

Compassionate Use (Single Patient/Small Group Access)

Compassionate use is typically approved for individual patients, but may be approved to treat a small group. Prior FDA approval is needed before compassionate use occurs.

The sponsor should submit an IDE supplement to the FDA requesting approval for a protocol deviation (21 CFR 812.35(a)); the supplement should include:

- Description of the patient's condition and circumstances necessitating treatment
- Discussion of why alternatives therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition
- Identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient
- Patient protection measures that will be followed, e.g., informed consent, concurrence of IRB chairperson, clearance from the institution, independent assessment from uninvolved physician, authorization from IDE sponsor
- The number of patients to be treated (when use is for Small Groups)

The physician should not treat the patient identified in the supplement until FDA approves use of the device under the proposed circumstances.

Criteria

This provision allows access when:

- There is an existing concurrent clinical trial but the patient(s) do not meet the inclusion criteria, and
- The treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition.

Reporting and Monitoring Requirements

The attending physician should devise an appropriate schedule for monitoring the patient(s), considering the investigational nature of the device and specific patient needs. The patient(s) should be monitored to detect any possible problems arising from the use of the device.

Following the compassionate use of the device:

- A follow-up report should be submitted to FDA as an IDE supplement in which summary information regarding patient outcome is presented
- Any problems which occurred as a result of device use should be discussed in the supplement and reported to the IRB as soon as possible.
- Follow-up information on the use of the device should be submitted in an IDE supplement after all compassionate use patients have been treated.

Devices: Treatment Use - Larger Group/More Widespread Use

FDA will consider this expanded access under a Treatment IDE (21 CFR 812.36).

An approved treatment IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the study. During the course of the clinical trial, if the data suggests that the device is effective, then the trial may be expanded to include additional patients with life-threatening or serious diseases.

The device may be made available for treatment use:

- After completion of all clinical trials – for serious disease
- Before completion of all clinical trials – for immediately life-threatening disease.

Criteria

(1) The device is intended *to treat or diagnose* a serious or immediately life-threatening disease or condition.

(2) There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population.

(3) The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed.

(4) The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

Reporting and Monitoring Requirements

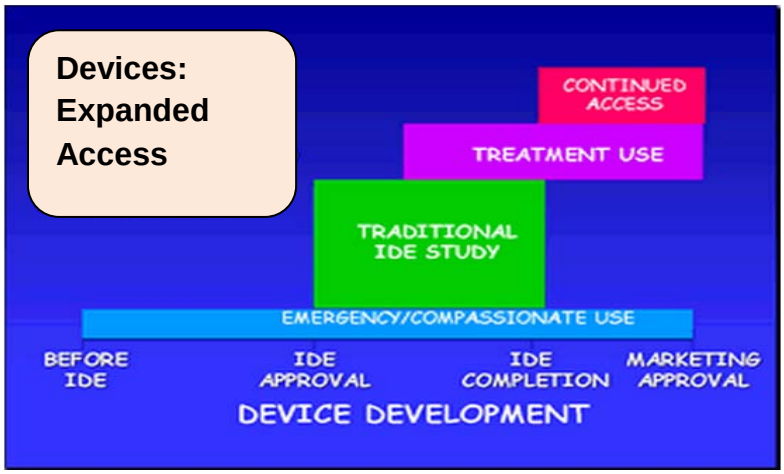
The sponsor (or sponsor-investigator) of a treatment IDE must submit semi-annual progress reports to the IRB and FDA until the filing of a marketing application. *After* filing of a marketing application, progress reports must be submitted annually in accordance with 21 CFR 812.150(b)(5).
See:

- IDE Reports [FDA]
- IDE Early/Expanded Access - Treatment Use [FDA]

Devices: Continued Access

The FDA may allow continued enrollment of subjects after the controlled clinical trial under an IDE has been completed and while the marketing application is being prepared by the sponsor or reviewed by FDA. The Continued Access Policy, which is applied after completion of the clinical trial, *may be considered for any clinical investigation*. See IDE Early/Expanded Access - Continued Access [FDA].

Resources: Regulations and Guidance	
FDA	• 21 CFR 312.300 (Subpart I) Expanded Access to Investigational Drugs for Treatment Use • Physician Request for an Individual Patient IND under Expanded Access for Non-emergency or Emergency Use • IDE Reports [FDA] • IDE Early/Expanded Access
Resources: Other References	
Stanford HRPP	• Chapter 5.8 – Expanded Access • Emergency Use of a Test Article [GUI-6]



[Adapted from FDA guidance]