

Facilitating IRB Review for Single Patient Treatment Use of Investigational Drugs and Biologics

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What is FDA Expanded Access?

21 C.F.R. 312.300 (2011)

- FDA may authorize the use of an investigational drug or biologic product to treat patients with serious or life-threatening diseases or conditions who have no satisfactory or comparable alternative therapy to diagnose, monitor, or treat the disease or condition.
 - Authorized by the Food & Drug Administration Modernization Act of 1997 (FDAMA)

Disease or Condition

21 C.F.R. 312.300(b)

- Immediately Life-Threatening Disease or Condition
 - A stage 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.

FDA's Responsibilities

21 C.F.R. 312.305(a)

- For all expanded access requests, FDA must determine that certain criteria are met to authorize access.
 - The patient has a serious or life-threatening disease or condition and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
 - The potential benefit justifies the potential risk and that the risks are not unreasonable in light of the disease or condition to be treated; and
 - The provision of the investigational product will not interfere with the clinical investigation that could support marketing approval or otherwise compromise potential development.

Safeguards for all Expanded Access Protocols

21 C.F.R. 312.305

- “Investigators” (Physicians)
 - Must report adverse drug events to the sponsor
 - Ensure that the Informed Consent requirements are met
 - Ensure that IRB Review is obtained
 - Maintain accurate case histories and records and retain those records
 - Other investigator responsibilities under Subpart D of 21 CFR part 312 may also apply

Safeguards for all Expanded Access Protocols

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- “Sponsors”
 - Submit IND safety reports and annual reports to FDA
 - Ensure the physician is qualified to administer the investigational drug
 - Provide physicians with information needed to minimize risk and maximize benefit to the patient
 - Maintain adequate drug disposition records and retain records
 - Maintain an effective IND for the expanded access use
 - Other sponsor responsibilities under Subpart D of 21 CFR part 312 may also apply

Three Population Levels of Expanded Access

- Individual Patients (21 C.F.R. 310)
- Intermediate-Size Patient Populations (21 C.F.R. 312.315)
- Treatment IND or Protocol for “widespread treatment use” (21 C.F.R. 312.320)

Expanded Access for Individual Patients

- Individual expanded access protocols must meet the following criteria, in addition to meeting the criteria in 312.305(a):
 - 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.
 - FDA determines that the patient cannot obtain the product under another IND or protocol
- Individual expanded access protocols also must have safeguards in addition to the safeguards in 312.305(c), including:
 - Treatment duration is limited to a single course of therapy unless FDA authorizes multiple courses or chronic therapy

Applicable Regulations

- Expanded Access protocols are subject to regulations other than those in part 312.

They include:

- 21 C.F.R. 50 – FDA’s Informed Consent Regulations
- 21 C.F.R. 56 – FDA’s Institutional Review Board Regulations

The Problem

- FDA continues to hear from individual patients, caregivers, IRB members, and health care professionals that the administrative burdens associated with IRB review of expanded access are onerous and diminish its practicality, negatively impacting access to investigational drugs for treatment under EAPs – particularly single patient treatment access protocols.
 - Full Review - Institutional Review Board
 - Cost
 - Time involved with scheduling review for a single patient
 - Physicians not affiliated with an institution with an IRB

Evidence of the Problem

- FDA's Office of Special Health Issues
 - Works with patients, patient advocacy groups, and health professionals
 - Received numerous complaints about the process
 - Full IRB review inhibits access because of the time involved
- Comments to Expanded Access Final Rule - 74 Fed. Reg. 40900, 40903 (2009)
 - At least two comments (Comment 4) noted that the burdens would be greatest among those patients with physicians who practice outside of institutional settings (e.g., universities, hospitals).
 - Independent IRBs would have to be used at significant additional cost to the patient

Evidence of Problem

- Comments to Expanded Access Final Rule - 74 Fed. Reg. 40900, 40920-21 (2009)
 - Some additional comments (Comment 59) expressed concern that IRB review is an obstacle, particularly for individual patient INDs.
 - Recommendations included: 1) FDA standardizing expanded access review for all IRBs; 2) Creating a centralized IRB for small-to-medium expanded access protocols; 3) FDA reduce or limit the scope of the IRB review because of the time and expense involved.

Objectives

- Reduce burden on patients and treating physicians not affiliated with research institutions
- Reduce delays to access, and cost to patients who may find cost of review a barrier to access
- Reduce workload and scheduling burdens for IRBs
- Reduce regulatory/administrative barriers to treatment access, without sacrificing patient protections

Possible Solution

- FDA is considering whether to amend its regulations, or take other appropriate actions, to allow for expanded access IRB review to mimic, in part, the expedited review procedure found in FDA regulation (21 C.F.R. 56.110), while maintaining patient protections.
 - Expedited review procedures allow the IRB chair or his/her designee(s) to review a protocol and approve it.
 - If the protocol is not approved, the full IRB must then convene to review the changes to the protocol and approve or disapprove.
 - Individual patient expanded access protocols are not currently on the list of categories of protocols which are eligible for expedited review (21 CFR 56.110(a)).

Possible Solution

- Adding to or amending current FDA regulations, or taking other appropriate actions, to:
 - Remove the need for a full IRB review of expanded access applications
 - Allow the chair to designate one (or a few) IRB members to review expanded access protocols
 - Disapprovals must be made by the full IRB

Other Factors to Consider

- Risk/Benefit Analysis
 - Reducing IRB requirements could reduce awareness of risk
 - However important safeguards would still remain
 - Risk/Benefit Analysis is arguably different for expanded access protocols
 - By definition, expanded access patients are willing to take on greater risk – to be eligible for expanded access they must have exhausted ALL other treatment alternatives – including clinical trials
 - Informed consents will still be required – should mimic the current informed consents available to those in the clinical trial
 - Physicians still must provide disclosure of risks and benefits

Other Factors to Consider

- Expanded Access should be available to those eligible and without significant burden (cost, time), including patients who are not located at or near major research centers
- FDA must still perform its own review of the application and ensure all Expanded Access requirements and safeguards are met, including whether all other treatment options have been fully exhausted
- IRBs will still have a significant role and must still approve and review the protocol and informed consent – only under an abbreviated procedure

Questions to Committee

- FDA requests discussion involving several questions:
 - What is the Committee's experience with IRB reviews of expanded access protocols? How quickly are they reviewed? Is there a charge to the individual? Are EAPs able to be scheduled ahead of studies already on the calendar?
 - Does providing for something like expedited IRB review seem a reasonable solution, based on the problem cited?
 - If a reduction in the number of IRB members to approve an expanded access protocol is satisfactory to the Committee, does the Committee believe that mimicking the expedited review procedure is the best approach?
 - What is the Committee's opinion on the risk/benefit analysis of expanded access protocols following the IRB procedure discussed in this presentation?