Expanded Access Programs

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Expanded Access Programs (EAPs)

- What is expanded access?
- History
- Legislative background
- General principles related to expanded access
- The new Expanded Access Regulations
  - 21 CFR 312, Subpart I
- Implementing the process
  - Who is responsible for what?
- Questions/Discussion

What is Expanded Access?

- Use of an investigational drug or biologic to treat a patient with a serious disease or condition who does not have comparable or satisfactory alternative therapies to treat the disease or condition.
- Contrast with investigational drug in a clinical trial where the primary intent is research (systematic collection of data with the intent to analyze it to learn about the drug)

FDA History with Expanded Access

- History of facilitating access to investigational therapies
  - Cardiovascular - metoprolol, nifedipine
  - HIV - pentamadine, AZT
  - Oncology – Group C drugs
- No official regulatory recognition until 1987 when IND regs were revised to provide access for a broad patient population under a Treatment IND/Protocol (21 CFR 312.34
- Implicit recognition of other treatment use for individuals (21 CFR 312.36), though no criteria or requirements described
- Experience with a broad range of scenarios from individual patient access to large scale access for thousands of patients under one IND

1997 FDA Modernization Act

Amended § 561 of the FDC Act to say an individual patient may obtain an investigational drug for treatment use when:

- ✓ The patient's physician determines that the patient has no comparable or satisfactory alternative therapy;
- ✓ FDA determines that there is sufficient evidence of safety and effectiveness to support use of the investigational drug;
- ✓ FDA determines that providing investigational drug will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval; and
- ✓ The sponsor or clinical investigator submits information sufficient to satisfy the IND requirements.

EAPs and Patients - Benefits

- Can provide access to patients with serious/life-threatening diseases who have no other alternatives, and may accept greater risks
- Can provide patients a measure of autonomy over their own health care decision
- The treatment IND can help bridge the gap between the latter stages of product development and approval by making a drug widely available during that period
- Expanded access use can help foster development of additional uses of a drug (e.g., from anecdotal evidence of benefit in a disease other than that being studied)
- May offer hope for patients with no other available options

EAPS and Patients - Risks

- Unknown risks associated with access to investigational products for which there is limited information about safety and effectiveness
  - Some patients may benefit
  - Some patients may experience no effect
  - Some patients may be harmed

What needs to be considered?

Indeterminate Risk

- Minimization of risk is goal
  - Confidence of safety more important than efficacy
- How much evidence of safety is needed to make experimental drug available?
  - for a patient with an immediate life-threatening condition, evidentiary burden is low
  - phase I?
    - Only about 20% of drugs entering phase I end up approved; at least 1/3 are withdrawn for safety concerns
    - Some serious safety concerns may not be apparent until post-marketing (Vioxx)

Could EAP Foster a "Therapeutic Misconception"

- Possible overestimation of benefit, and/or underestimation of risk
- Efficacy (and safety) of early phase investigational drugs not proved; however, might be given in hope of direct benefit to patient

What risk could be WORSE than the risk of death?

New drugs may have toxicities that cause increased suffering and pain, or the acceleration or prolonging of death, with no increase in quality of life

Need for Balance

- Treatment access must be balanced against the systematic collection of clinical data to characterize safety and effectiveness
- Patient autonomy must be balanced against exposure to unreasonable risks and the potential for health fraud, potential exploitation of desperate patients
- Individual needs must be balanced against societal needs
  - Clinical trials are the best mechanism to provide evidence of safety and effectiveness for potential new treatments
  - FDA approval for marketing is the most efficient means to make safe and effective treatments available to the greatest number of patients.

Could EAPs Impair Trial Enrollment?

- Early access to investigational drugs could make phase II and III clinical trials more difficult to perform
  - AZT for HIV, High Dose Chemotherapy + bone marrow transplant for stage IV breast cancer
- General agreement that access to experimental drugs can only be granted if clinical trial enrollment is unimpaired, but how is this practically done?
- Manufacturing capacity is often limitation in early phases – supply of drug for expanded access could limit supply for trials

New Rule Written to Address Limitations of Previous Regulations

- Existing regulations did not reflect how FDA functioned (e.g., the full range of mechanisms FDA used to permit treatment access) or provide flexibility
  - only addressed large groups and emergency treatment access
  - did not define level of evidence required for different categories of EAP
  - May have resulted in inequitable access to EAPs
  - Failed to provide necessary specificity about charging
- New regulations (effective October 13, 2009)
  - Improve access to investigational products for patients thru better understanding of what is accessible, and how
  - Streamline regulatory processes for EAPs

Changes found in the New Regulations

- New Subpart I consolidates treatment use into a separate subpart of the IND regulations
- New Subpart I contains all necessary information
  - Describes the three categories of (Individual, Intermediate-Size, Treatment IND/protocol)
  - Describes the general criteria applicable to all categories of access and additional criteria that must be met for each access category
  - Describes the submission requirements
  - Describes the safeguards applicable to EAPs (e.g., informed consent, IRB review, reporting requirements)
- Provides for possible access to drugs that have a Risk Evaluation and Mitigation Strategy (REMS) that restricts availability of the drug - for patients who do not meet REMS criteria

How does FDA Weigh Safety and Risk for EAPs? (the general evidentiary standard)

Evidentiary basis linked to size of exposed population and seriousness of disease

- Sufficient evidence of safety and effectiveness to support the use of the drug
- Reasonable basis to conclude the therapy may be effective and would not expose patients to unreasonable and significant risk – relative to the risk of the disease
- More rigorous requirements with increasing exposure -- makes access risk-benefit analysis analogous to the clinical trial phase 1, 2 and 3 paradigm of growing exposure

Requirements for Individual Patient EAPs
21 CFR 312.310

- Physician must determine probable risk from drug does not exceed that from disease
- FDA must determine that the patient cannot obtain access under another type of IND
- Procedures for emergency use (where there is not time to make a written IND submission) – FDA may authorize starting access without submission, with very quick turn-around (F/U written submission required within 15 working days of authorization)
- Additional Safeguards
  - Treatment generally limited to one course (though FDA may ok ongoing therapy)
  - FDA requires written summary report and may require special monitoring
  - FDA may request consolidation of multiple cases into single, intermediate size patient population IND

Physician often takes role of sponsor/investigator

Requirements for Intermediate Size Population
21 CFR 312.315

- Drug is
  - Being developed (e.g., patients not eligible)
  - Not being developed (e.g., disease rare)
  - Approved or related (e.g., drug withdrawn, drug shortage situation-e.g., foreign version of a U.S. approved drug)
- Sufficient evidence drug is safe at proposed dose and duration to justify size of exposed population
- Preliminary evidence (clinical or plausible pharmacological) of effect
- Additional Safeguards
  - Require explanation of why drug cannot be developed or why patients cannot be enrolled in clinical trial
  - Annual review to determine whether treatment use should be continued and whether a T-IND would be a more appropriate mechanism

Requirements for Treatment IND or Protocol
21 CFR 321.320

- Drug is being investigated in clinical trial designed to support marketing, or trials are complete
- Company is actively pursuing marketing approval
- Sufficient evidence of safety and effectiveness
  - Serious disease: evidence from phase 3 or compelling data from phase 2 clinical trials
  - Immediately life-threatening disease: evidence from phase 3 or phase 2 studies, but could be based on more preliminary clinical evidence
- Additional safeguards
  - Monitoring
  - 30 day waiting period for FDA review, or on earlier notification by FDA

Human Subject Protections Apply to EAPs

Drugs in EAPs are investigational drugs, and they are subject to the following requirements from 21 CFR:

- Part 50- Protection of Human Subjects (informed consent)
- Part 56- Institutional Review Board
- Part 312 - including Clinical Holds based on safety and reporting requirements (adverse event reports, annual reports)

EAP-Implementing the process

- A community responsibility
  - the patient
  - the doctor
  - the sponsor
  - FDA
  - IRB

EAP-Implementing the process
A community Responsibility

- The patient
  - Facing desperate medical circumstances and difficult decision
  - Patients (and their advising physicians) may have limited information about a drug (e.g., do not have access to the confidential commercial information that FDA has access to), and may not have realistic expectations, may not have access to developing efficacy and/or safety information
  - Patients may face substantial cost that are not reimbursed by health insurers
  - Navigating uncharted waters that differ significantly from standard health care, e.g., IRB involvement

EAP-Implementing the process
A community Responsibility

- The doctor
  - Helps initiate the process for the patient
  - requires commitment to contacting company and filing paperwork
    - may represent unfamiliar processes for many treating physicians
  - responsible for ongoing support and monitoring of patient
  - responsible for adverse event and outcome reporting
  - Physicians costs of providing access may not be fully compensated
  - liability issues

EAP-Implementing the process
A community Responsibility

- The sponsor
  - must be able and willing to provide the product
  - work with doctor to provide and monitor use of product
  - develop mid-size and large scale program protocols and support program infrastructure
    - administration
    - monitoring and reporting responsibilities
    - IRB review and continuing review

EAP-Implementing the process
A community Responsibility
Issues for the Sponsor

- EAPS consume time, energy, and resources – may not be the best use of resources from a commercial perspective

- There may not be enough capacity to produce an investigational drug to meet the additional demand generated by an EAP
  - equitable distribution of limited product – lotteries?

- Logistics of communicating and working with physicians who are outside of research/investigator network
  - challenge to train individual physicians on regulatory requirements, processes and procedures

- Concerns about how data might affect NDA review

- Will toxicity (or lack of efficacy) of the drug effect ability of manufacturer to raise capital?

EAP-Implementing the process
A community responsibility

- FDA
  - resource intensive
    - IND paperwork
    - medical records review
    - quick turn-around time
    - Takes resources from clinical development activities
  - assessment of existing data for safety and evidence of effectiveness
  - assurance of patient protections (IRB review, informed consent)

EAP-Implementing the process
A community responsibility

- IRB
  - not all IRBs are familiar with expanded access protocols and how to review them (intent is treatment, not clinical research)
  - may overestimate risk
  - workload and scheduling issues for IRB can delay review
  - requires entire committee to review (no expedited review procedures at present)
  - liability concerns
  - cost concerns and reimbursement for services

Lingering Issues

- Who pays for investigational drugs?
  - Manufacturers? – possible disincentive to expanded access
  - Insurance carriers? – experimental treatments generally not covered
  - Patients?
    - Access limited to affluent
    - Risk of exploitation and fraud in this very vulnerable population

Lingering Issues

- Risks to physicians
  - Physicians already face pressure from patients who demand medications based on DTC advertising
  - Will "informed consent" be adequate to shield physician if investigational drug is ineffective or injurious?
  - Will physicians be subject to action if they fail to inform patients about alternative, *unapproved treatments*?

Lingering Issues

- How difficult is IRB review to secure?
  - Particularly for single patient access
- Who pays for the cost of review?
- Will IRB requirements continue to discourage access outside of medical research institutions or large urban centers?

Lingering Issues

- How do patients find access programs?
  - Through their healthcare provider
  - Internet
    - ClinicalTrials.gov
    - Patient organizations
    - Patient forums
  - Other patients

Summary

- Patient protection is paramount
- Full evidentiary basis for decision-making is not available to patients, and not always to doctors
- Healthcare system does not pay for resources required to provide expanded access
  - Charging rule may help alleviate this barrier, and increase access
- Patient makes the final decision

Summary

- Improve existing FDA practices on EAPs by consolidating expanded access in one, unified subpart under the IND regulations, clearly differentiating different levels of access, and clarifying evidentiary and filing requirements
- Helps patients, medical professionals and the pharmaceutical industry understand EAP procedures and ensures consistency across FDA divisions
- Reflects a balance between
  - Facilitating patient access to unapproved therapies
    - Serious or immediately life-threatening disease or condition
    - No satisfactory alternatives
    - Minimizing risk to patients
  - The potential for access to impede development and marketing of life-saving therapies

For Further Information

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www.fda.gov, search "expanded access"