Expanded Access Programs

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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.

- Intent is clearly treatment

What is Expanded Access?

- 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)

EAP Should Be Option of Last Resort

- Approved Drugs
- Clinical Trials
- EAP

FDA Published New Regulations in 2009

- New Subpart I consolidates treatment use into a separate subpart of the IND regulations containing all necessary information
  - Describes three distinct categories of access (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 requirements for submission
  - 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 all EAPs
21 CFR 312.305

- Serious or immediately life threatening illness or condition
- No comparable or satisfactory alternative therapy
- Potential benefit justifies the potential risks of the treatment, and those risks are not unreasonable in the context of the disease or condition being treated
- Providing drug will not interfere with or compromise development for the expanded access use

Human Subject Protections Apply to All 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)

EAPs and Patients - Benefits

- Can provide access to patients with serious/life-threatening diseases who have no other alternatives, *and* may be willing to accept greater risk
- 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
  - How early access? 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 proven – and sometimes not known; however, might be given in hope of direct benefit to patient

Are there risks that could be WORSE than the inherent risk of death from the condition?

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 therapies could make phase II and III clinical trials more difficult to perform
  - E.g., 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

EAP-Implementing the process

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

EAP-Implementing the process

- 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

- 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

- 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

- 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

- 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

- IRB
  - outside physician looking for review for their patient
  - 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?
- Do IRB requirements discourage/restrict access outside of medical research institutions or large urban centers?

How do patients find access programs?

- Through their healthcare provider
- Internet
  - ClinicalTrials.gov
  - Patient organizations
  - Patient forums
- Other patients

For Additional Information

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www.fda.gov, search "expanded access"