Access to Investigational Drugs

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Outline

- What is expanded access?
- 1997 FDA Modernization Act
- Expanded access programs – Benefits and Risks
- Implementing the process
  - Who is responsible for what?
- Questions/Answer

For Patients Seeking Treatment…

- FDA-approved drugs should be the first option
- If patients do not respond to, or are intolerant of approved therapy, investigational drugs may be available through two potential pathways designed to help protect patients from unknown potential risks to patients, where we do not know if a drug is effective.
  - Some may be eligible to receive an investigational drug as a participant in a **clinical trial.**
  - Some may pursue an **expanded access program (EAP)** also known sometimes as “compassionate use.”

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)

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.

Expanded Access Programs (EAP) 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?**

EAP Could Foster a Therapeutic Misconception

- 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

Publication of New Rule

effective October, 2009

- New Subpart I consolidates treatment use into a single, separate subpart of the IND regulations containing all necessary information
  - Describes the three 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 the submission requirements
  - Describes the safeguards applicable to EAPs (e.g., informed consent, IRB review, reporting requirements)

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)

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.

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 model of growing exposure based on increasing knowledge about the drug

EAP-Implementing the process

- A community responsibility
  - the patient
  - the doctor
  - the sponsor
  - FDA
  - Institutional Review Board (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), or developing efficacy and/or safety information
  - May not have realistic expectations
  - Patients may face substantial costs 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
  - For mid-size and large scale programs, develop 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

- Institutional Review Board (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

How do patients find access programs?

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

Lingering Issues

- Who pays for investigational drugs?
  - Manufacturers? – disincentive to drug development
  - 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 may face pressure from patients who demand investigational medications they've read about.
  - 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 discourage treatment access outside of medical research institutions or large urban centers?

For Further Information

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www.fda.gov, search “expanded access”

Access to Investigational Drugs information for patients

Physician Request for an Individual Patient IND under Expanded Access for Non-emergency or Emergency Use