Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs

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Objectives

• Define Expanded Access Programs (EAPs)

• Define the regulations involved in expanded access programs

• Describe the physician, patient, and industry perspective on expanded access programs
The New Drug Development Process
(Steps from Test Tube to New Drug Application Review)

Pre-clinical Research

Clinical Studies

NDA Review

Synthesis and Purification

Phase 1

Phase 2

Phase 3

Accelerated Development/Review

Treatment IND

Parallel Track

Institutional Review Boards

Industry Time

FDA Time

IND Submitted

NDA Submitted

Review Decision

Sponsor/FDA Meetings Encouraged

Early Access: Subpart E

Sponsor Answers Any Questions From Review

Advisory Committees
THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS

From drug discovery through FDA approval, developing a new medicine takes at least 10 years on average and costs an average of $2.6 billion.* Less than 12% of the candidate medicines that make it into Phase I clinical trials will be approved by the FDA.

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* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

How is it actually done

- **Components**
  - Budget
  - Regulations
  - **Protocol** development
  - Investigator/site initiation
  - Investigational Review Board (IRB)
  - Trial/ study participant enrollment /data maintenance
  - Study closure/statistical analysis/reporting
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

- 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
What is Expanded Access?

- A process (or pathway) regulated by the Food and Drug Administration (FDA) that allows manufacturers to provide investigational new drugs to patients with serious diseases or conditions who have exhausted approved therapy, and cannot participate in a clinical trial.

- It allows access to unapproved/investigational drugs that might potentially provide benefit, when company is willing to provide, and ethical protections are in place (IRB/informed consent).
Why Expanded Access (AE)

- Not all patients can wait for approved drugs
- No standard effective therapy for condition
- Exhausted approved options
- Intolerant of approved products
- Ineligible or otherwise unable to participate in trials
When EAPs occur

- EAPs can occur in phase 2, during phase 3, or after phase 3
- They occur before FDA/health authority approval and marketing of approved agent
- Key criteria: sufficient safety and efficacy
  - This criteria is relative to the patient population and need
Expanded Access is a Balance!

IND in clinical trials have not been proven safe and effective yet

Patient has exhausted all Other treatment options AND Doesn’t meet criteria for clinical trial
Expanded Access

Treatment Access

  Named Patient Program

  Special Access Programme

  Compassionate Use

  **Single Patient IND**

  Pre-approval access

  Pre-launch Access
Expanded Access Programs (EAPs) Should Be Considered the Option of Last Resort

**Approved Drugs**
- Studied and characterized
- Labeled
- Brodest Availability
- Reimbursement by 3rd party

**Clinical Trials**
- Provide necessary data to determine safety & effectiveness
- Most efficient path to market and broad availability

**Expanded Access**
- Represent opportunity when other options exhausted
- Goal is access to treatment
Requirements shared by all EAPs

- 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
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
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
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
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?
Reasons Company May Deny Expanded Access Requests

Companies may deny a request for a number of reasons:

• Available clinical trials

• Manufacturing capacity is often limited in early phases
  – diverting drug for expanded access could limit supply for trials

• Concern adverse events would undermine the development program
Managed Access Program Implementation

- Enhance and streamline the delivery of specialty pharmaceuticals that address unmet medical needs around the world
- Match patients across the globe with serious diseases to needed therapies prior to registration or product approval
- Understand the requirements that are associated with charging for treatment
- Establish a cost share model for an expanded access program and protect global pricing for future sales
- Garner insight on the reporting and reimbursement process on an international scale
FDA Published Revised Regulations in 2009

21 CFR 312 / IND Regulations

- Consolidated treatment use into a separate subpart of the IND regulations containing all necessary information in one place
- Describes **three distinct categories** of access

- Individual
- Intermediate size population
- Treatment IND
Expanded Access Options

Large Population

Intermediate-size population

Individual Patient
Large Population-Treatment IND

- 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
- Can have hundreds to thousands
- Company sponsored trial
- Incorporated into a Treatment Use Protocol for EAP
  - **Treatment Use Protocol**: Allows physicians to provide investigational new drugs to patients OUTSIDE of clinical trials.
Large Population-Treatment IND

Pros:
- Proper conduct: high quality controlled safety data
- Allows all regions to have access
- Increase awareness: pt population / drug

Cons:
- Resources and costs (drug supply, human capital)
- Low number of requests
Intermediate-size population

- More than one patient, but does not enough to constitute a treatment use protocol
- Can be used when a drug is
  - Being developed (e.g., patients not eligible for trial)
  - Not being developed (e.g., rare disease, cannot recruit for a trial)
- Sponsor can be physician, manufacturer, or 3rd party
- Can have multiple intermediate-size EAPs at once
  - FDA can request to consolidate these under a Treatment use Protocol
Individual Patients/Single Patient IND

- 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

**Pros:**
- Less resources
- Could start quickly
- Fits with a low number of request

**Cons:**
- Limited monitoring of safety
- Spontaneous requests: unpredictable
Individual Patients/Single Patient IND

- Physician often takes role of sponsor/investigator (responsible for sponsor activities: tracking, reporting, etc.)
- FDA requires written summary report, and may require special monitoring
- FDA may request consolidation of multiple cases into a single, intermediate size patient population IND
Human Subject Protections Apply to All EAPs

Drugs in EAPs are *investigational drugs*, and they are subject to the following requirements:

- Protection of Human Subjects (informed consent)
- Institutional Review Boards (IRBs)
- Clinical Holds based on safety and reporting requirements (adverse event reports, annual reports)
EAP-Implementing the process: A community responsibility

- The Patient: Consults with their doctor to find and decide about alternative options
- The Doctor: Works with manufacturer, files paperwork with FDA, IRB, and is responsible for patient care and reporting
- The Industry Sponsor: Provides the investigational product, and permits cross-reference to their original IND information
- FDA: Determines eligibility, judges safety data, ensures patient protections
- IRB: Reviews consent to assure patient is informed about nature of treatment
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 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
## EAP Governance

<table>
<thead>
<tr>
<th>Region</th>
<th>Stage</th>
<th>Governing Body and Legislation</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>Mature</td>
<td>FDA: CRF 21 Sec 312.300-320</td>
</tr>
<tr>
<td>Europe (EU)</td>
<td>Mature</td>
<td>EMA: Implementation governed by individual country legislation. Patient W.A.I.T. 116-241 days; Launch lag in EU from 2-12 mo.</td>
</tr>
<tr>
<td>Europe (non-EU)</td>
<td>Complex; Evolving</td>
<td>Complex to navigate; Evolving markets re: regulatory pathway</td>
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<tr>
<td>Asia Pacific</td>
<td>Mature</td>
<td>Local Legislations</td>
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<tr>
<td>South America</td>
<td>Evolving</td>
<td>Local Legislations</td>
</tr>
<tr>
<td>Central America</td>
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<td>Local Legislations</td>
</tr>
<tr>
<td>Middle East</td>
<td>Evolving</td>
<td>Local Legislations</td>
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| Lebanon          | Evolving            | Each patient requires approvals and coordination from the physician/patient, local pharmaceutical company, and the headquarter pharmaceutical company (sponsor)  
**Headquarter:** either US or EU → FDA or EMA is implemented. |

## Challenges and Opportunities

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Opportunities</th>
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<tbody>
<tr>
<td>• Compassionate use is extremely challenging and resource intense</td>
<td>• Many bodies currently examining this issue</td>
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<tr>
<td>• Can be seen as a “back door”</td>
<td>• Support from patient/advocacy organizations</td>
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<tr>
<td>• Each company manages independently</td>
<td>• Conversation around the need to prioritize trials</td>
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<td>• Patients have to navigate when they don’t know</td>
<td>• Navigator– sparked stakeholders coming together</td>
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<td>• Huge burden for a requesting HCP</td>
<td>• Explore ability to leverage ClinicalTrials.gov</td>
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<tr>
<td>• Risk for all organizations</td>
<td>• Transcelerate for Compassion Use?</td>
</tr>
<tr>
<td>• Guidelines are vague</td>
<td>• Standard Application?</td>
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<tr>
<td>• Many players involved</td>
<td>• Network of referrals?</td>
</tr>
<tr>
<td>• Patient dependent on knowledge of treating clinician and industry</td>
<td>• Strength in numbers – we can take action</td>
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<td>representative</td>
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*HEALTH INSIGHT*
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

• We need to work on refining a fairer, faster, safer system for pre-approval use of experimental medical products that doesn’t undermine the clinical trial process

• The purpose of these programs is treatment, not research, so sponsors do not have to submit efficacy data from an expanded access study, but must report serious/unexpected adverse reactions and submit a written summary report at the conclusion of treatment

• Patient makes the final decision
2nd Annual Middle East Neuro-Oncology Conference
September 12-14, 2019
American University of Beirut Medical Center, Beirut - Lebanon

Save the Date

[Logos of NAFF K. Basile Cancer Institute, Heidelberg University Hospital, Brigham Health, and AUBMC]
Thank You!

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