Expanded Access and Expedited Approval Programs for Biomedical Products: A Global Perspective
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Expanded Access = Early Access = Compassionate Use

- Program regulated by FDA
  - To improve access to investigational drugs for Rx of patients with a serious or immediately life-threatening disease or condition who do not have comparable or satisfactory alternative therapeutic options and who may benefit from such therapies
- Intent is treatment of patients with most to gain & least to lose
  - Differs from use of an investigational drug in a clinical trial where primary purpose is research (i.e., systematic collection of data)
- Method of obtaining access
  - FDA approval of an Expanded Access Submission, which is a type of Investigational New Drug (IND) application (i.e., a new IND or protocol amendment to existing IND)
  - Nearly 6000 applications in last 4 years
- Mfr decides whether or not a patient can participate in a “compassionate use” trial!

Subpart I of 21 C.F.R. Part 312

- Expanded Access IND
- Expanded Access Protocol
- Single-Patient IND
- Single-Patient Protocol
- Intermediate Size IND
- Intermediate Size Protocol
- Treatment IND
- Treatment Protocol

- General standards AND specific standards based on the size of population and seriousness of the disease
- Requirements for obtaining access
- Safeguards, including IRB review, informed consent, and reporting requirements to FDA

General Requirements (21 CFR 312.305)

- FDA must determine that:
  - Patients to be treated have a serious or immediately life-threatening illness or condition
  - No comparable or satisfactory alternative therapy exists
  - Potential patient 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 the drug will not interfere with or compromise clinical investigations that could support marketing approval for the Expanded Access indication
21 CFR 312.300

- Immediately Life-Threatening Disease or Condition = “A stage of disease in which there is a 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. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease of condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.”

Can Manufacturer Charge for Investigational Drug Under Expanded Access Program?

- **YES**, under 21 CFR 312.8, mfr must request authorization from FDA and demonstrate:
  - Sufficient enrollment in any ongoing clinical trial needed for marketing approval to assure FDA that it will be successfully completed as planned;
  - Evidence of adequate progress in drug development for marketing approval;
  - Information specifying drug development milestones the sponsor plans to meet in next year; and
  - Amount to be charged recovers only direct costs of manufacturing, shipping, and handling; for Expanded Access, may also charge for costs of monitoring, complying with FDA reporting requirements, and other administrative costs.
- **If company is not the sponsor of the Expanded Access IND, it is not required to obtain authorization from FDA to charge for the investigational drug.**

Expanded Access at FDA (FY 2010-2014)

Expanded Access Requests Accepted by FDA

<table>
<thead>
<tr>
<th>Expanded Access Requests Accepted by FDA</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
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<td>158</td>
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<td>Single Patient Protocol/Single Patient</td>
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<tr>
<td>Single Patient Emergency/Single Patient</td>
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<td>12</td>
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<tr>
<td>Total</td>
<td>1,066</td>
<td>313</td>
<td>287</td>
<td>442</td>
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Expanded Access Requests Rejected by FDA (0.5% of all apps)

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<tr>
<th>Expanded Access Requests Rejected by FDA</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
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<tr>
<td>Total</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>16</td>
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</tbody>
</table>

Expanded Access Requests Accepted by FDA

- **Yes**, if mfr meets 4-part test:
  - Drug must exhibit evidence of clinical benefit;
  - Data from trial is essential to obtaining future approval for it;
  - Trial could not be conducted without charging;
  - Amount being charged is reasonable
Physician Views on Compassionate Use

Should compassionate use be allowed for unapproved drugs or therapies?

- Yes, but only if the patient has no other options: 74%
- Yes, clinical trials take too long: 19%
- No, it’s unethical to do so: 7%

SERMO Physician Poll • Feb 2015 • 2,182 Votes • blog.sermon.com

FDA Form 3926

- Physician must submit 8 pieces of information:
  - Patient’s initials
  - Clinical indication, history, rationale for request
  - Drug name and Rx plan
  - Letter of authorization from mfr
  - Physician qualification statement
  - Physician contact information
  - Formal request for authorization
  - Certification statement – no Rx for at least 30d after FDA receipt of application, also ICF, IRB, IRB within 5d of emergency

Multiple Expanded Access Emergency Uses of Same Drug at Same Institution

- “Once an investigational drug is used in an emergency situation without prior IRB approval, any subsequent uses of the investigational drug at that same institution would ordinarily require prior IRB review and approval…” but FDA will not deny further emergency access if prior IRB review is not feasible. Draft Guidance, Q11

Medicare Coverage in Expanded Access Programs

- Medicare coverage policies do not specifically address the situation where unapproved/investigational drugs are used for treatment purposes
- Two paradigms:
  - (1) “Reasonable and Necessary” Standard
  - (2) Clinical Trial Policy (NCD)
- Under either paradigm, the investigational drug itself is usually not covered, but other items and services associated with clinical care and/or treatment of the patient are likely covered. Examples include:
  - Costs of infusion of an investigational drug and overnight observation services to monitor the patient
  - Costs of hospital stay to monitor/treat cardiac complications resulting from use of the investigational drug
  - Costs of follow-up visits to physician office for examination of potential side effects from investigational drug regimen

Medicare Coverage in Expanded Access Programs

- Look to Medicare clinical trial policies to determine likely Medicare coverage of Expanded Access Programs—consult your Medicare Coverage Analysis document prepared for the clinical trial
- Investigational drugs used in Expanded Access Programs are typically not covered by Medicare, so providers/patients may be responsible for costs, depending on whether a manufacturer charges for the investigational drug
- Other treatment costs associated with the use of investigational drugs in Expanded Access Programs are typically covered by Medicare, including investigational drug administration costs, diagnosis/treatment of complications, monitoring of side effects
- Items/services performed solely for data collection or analysis, provided free of charge, or not ordinarily covered by Medicare are typically not covered by Medicare in Expanded Access Programs
- “Coverage with Evidence Development” – evolving concept for devices
### Expanded Access Issues for Physicians
- Emergency requests
- Want access outside the program
- Want full indemnities
- Want promises of no cost to patients
- Want funding
- Locations; number of sites
- Qualified in this role?
- Not properly fulfilling investigator role
- Don’t want program to end
- Pros/cons of company-sponsored submissions

### Expanded Access Issues for Manufacturers
- Supply chain
- How to say “No”
- Other stakeholders
- Distraction from clinical trials/application
- Transparency and Availability of Process Information
- Updating of information
- Monitoring and other efforts/burdens/costs
- Letting product out of tightly controlled environments
- Remove incentive to enroll in clinical trials
- Liability exposure?

### Expanded Access Issues for FDA
- Tremendous discretion
- Evidence of safety
- Can get different decisions from FDA
- Is drug being developed for population to be treated, and if not, why not, or under what circumstances could it be?
- EAP vs. open-label safety study
- Risk of interference with clinical investigations
- “Significant number” of similar requests can result in FDA request for more sponsor involvement
- Does EAP mean less incentive for FDA to approve?

### Legal Challenges in EAP
- U.S v. Rutherford (no constitutional right to access to amygdalin (Laetrile)(1979)
- Abigail Alliance v. von Eschenbach (2007)(no fundamental right...to experimental drugs for terminally ill)
- Contract right of access if received drug during clinical trial? (but investigator promises don’t bind a manufacturer)

### Abigail Alliance v. von Eschenbach
**D.C. Cir. (2007)**
- “[O]ur Nation’s history evidences increasing regulation of drugs as both the ability of government to address these risks has increased and the risks associated with drugs have become apparent. Similarly, our legal traditions of allowing a necessity defense, prohibiting intentional interference with rescue, and recognizing a right of self-defense cannot justify creating a constitutional right to assume any level of risk without regard to the scientific and medical judgment expressed through the clinical testing process.”

### “Right to Try” laws
- First passed in Colorado
- Currently 24 states
- Leading Proponent—Goldwater Institute
- Do not compel companies to grant access
- As of today, no patient has received compassionate access via right to try laws
State “Right-to-Try” Laws

- CO, LA, MI, AZ, MO versions – right to “mitigate extreme suffering and to enhance self-preservation” supported by different risk-benefit thresholds among individuals
- Constitutionality suspect if conflict with FDA enabling legislation and EAP regulations (preemption doctrines)
- Inadequate data = inadequate risk assessment?
- Inadequate data = inadequate informed consent?

Pearls to Remember

- How do we distinguish those who are dying from those who are not?
- Does a right presume a duty?
- Right to Ask = Right to Beg
- Right to Ask ≠ Right to Receive
- Right to Ask ≠ Right to Try
- ? Loss of hospice coverage or benefits?
- Will FDA say “If recipient dies, you can’t sue the manufacturer”?

Pearls to Remember

- “Compassionate Use” – a potentially misleading term
- Manufacturer is not required to provide investigational drug or provide it free of charge
- Physician always incurs regulatory obligations as investigator, including obligations as sponsor-investigator, if the physician is holder of the Individual Patient IND
- Potential medical costs may be incurred by the patient, including costs of the drug and medical expenses for injury

Pearls to Remember

- Use of drug at stage of early and incomplete understanding of its safety risks means possible overestimation of benefit and underestimation of risk
- State laws cannot prevent DEA from rescinding registration of physicians who prescribe experimental drugs independent of FDA
Possible Paths Forward for EAPs

- FDA attempts to shorten interval between “determination of clinical utility” and “point of wide availability”

- FDA-State collaboration
  - Fund specialized IRBs
  - Mfr places profits in interest-bearing escrow until drug is “approved”

Expanded Access in UK
Expanded Access in UK

Resources on Expanded Access


Resources on Expanded Access

- [http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm?utm_source=FDA.Facebook](http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm?utm_source=FDA.Facebook)

- [http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/accesstoinvestigationaldrugs/default.htm](http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/accesstoinvestigationaldrugs/default.htm)

- [http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccesstoInvestigationalDrugs/ucm176098.htm](http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccesstoInvestigationalDrugs/ucm176098.htm)


- Expanded Access ≠ Expedited Approval
Compare EMA and FDA

Who’s Faster: EMA or FDA?

Comparison of Licensing Flexibilities

**EMA**
- Conditional Approval
- Allows approval of a drug for serious or life threatening conditions based on less complete data than is normally required, subject to certain specific obligations to be reviewed annually

**FDA**
- Accelerated approval
- Allows approval of a drug for serious or life threatening conditions based on an effect observed on a surrogate endpoint that is reasonably likely to predict clinical benefit

Comparison of Licensing Flexibilities

**EMA**
- Approval under exceptional circumstances
  - Applicants must demonstrate that they are unable to provide comprehensive data on the efficacy and safety under normal conditions of use (e.g. rare conditions)

**FDA**
- No direct equivalent procedure

Comparison of Licensing Flexibilities

**EMA**
- Accelerated assessment
  - CHMP opinion given within 150 days as opposed to 210 days

**FDA**
- Priority review
  - Regulatory review period shortened from standard 10 months to 6 months

Comparison of Licensing Flexibilities

**EMA**
- Similar supportive mechanisms to fast track designation
  - Innovation task force/SME office/CHMP scientific advice & protocol assistance/Qualification of novel methodologies for medicine development

**FDA**
- Fast track designation
  - Facilitate development and expedite review of drugs through more frequent FDA interaction and rolling review of data
Comparison of Licensing Flexibilities

**EMA**
- Similar supportive mechanisms to breakthrough designation
- Innovation task force/SME office/CHMP scientific advice & protocol assistance/Qualification of novel methodologies for medicine development

**FDA**
- Breakthrough designation
- Expedite the development and review of drugs through more intensive FDA guidance and commitment to involve senior management

**EMA**
- Orphan Designation
- A supportive legislative framework for medicines for rare diseases was adopted in Europe in 2000 (Regulation (EC) 141/2000). Although similarities exist, the criteria and processes for designation are not internationally harmonised. However, a common joint EMA/FDA orphan designation application form is available.

**FDA**
- Orphan Designation
- A supportive legislative framework for medicines for rare diseases was adopted in the USA in 1983 (the Orphan Drug Act).

Australia

[Image of a flowchart related to the Australia section]


- Since the 1980s, FDA has expedited drug development using a number of programs.
- In 2012, the Food and Drug Administration Safety and Innovation Act created a new program, Breakthrough Therapy designation, for drugs intended to treat a serious condition that preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies.
- All of these expedited programs are available to all drugs intended to treat serious conditions, it is in the area of rare diseases where these programs have the greatest potential to favorably effect new drug development.
- Speed and precision in developing the clinical evidence needed to support regulatory approval are not mutually exclusive goals.
- Demonstration of comprehensive scientific evidence of product quality, effectiveness, and safety and careful assessment of this evidence by FDA remain the most important determinants for application approvals.
"Guidance for Industry: Expedited Programs for Serious Conditions-Drugs and Biologics" (May 2014)

Comparison of Expedited Processes at FDA

<table>
<thead>
<tr>
<th>Program</th>
<th>Fast Track</th>
<th>Accelerated Approval</th>
<th>Priority Review</th>
<th>Breakthrough Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying criteria</td>
<td>Must be intended to treat a serious condition or a drug designed as a Qualified Infectious Disease Product (QIDP)</td>
<td>May address an unmet medical need</td>
<td>Supporting data can be clinical or nonclinical</td>
<td>Must treat a serious condition</td>
</tr>
<tr>
<td>Time frame for application and FDA response</td>
<td>Can be requested with an investigational new drug (IND) submission or any point after applying. The FDA has sixty days to respond to the request.</td>
<td>No formal process.</td>
<td>Drug sponsors discuss the possibility with the FDA during drug development and decide the planned endpoint.</td>
<td>Requested at time of drug approval application. The FDA has sixty days to respond to request.</td>
</tr>
<tr>
<td>Key features</td>
<td>Earlier and more frequent communication with the FDA during development</td>
<td>Rolling review of application</td>
<td>Designation may be withdrawn if drug no longer meets qualifying criteria</td>
<td>Approval is granted on a conditional basis. Drug sponsor must conduct post approval confirmatory trials to confirm clinical benefits</td>
</tr>
</tbody>
</table>

EMA Adaptive Licensing for Orphan Drugs (Fast Track Market Access)

- Pilot as of March 2015 to explore AL for conditions with unmet medical need
- Progressive licensing approach with meds in early-stage development
- Goal is to refine AL pathways for compatibility with a range of products
**Early Access to Medicine Scheme (EAMS)**

- Initiated April 7, 2014 by MHRA (UK)
- Designation as “promising innovative medicine” (PIM)
- Analyze data from clinical trials
- Issue benefit/risk opinion on whether product should be used before license is approved
- Renewable opinion good for ONE year or until MA granted
- Public Assessment Reports (PARs)

**MHRA – PIM Designation Statistics**

<table>
<thead>
<tr>
<th>EAMS step I PIM designations - April 2014 to November 2015</th>
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<tr>
<td>Applications received</td>
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<tr>
<td>PIM designations granted</td>
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<tr>
<td>PIM designations refused</td>
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<tr>
<td>PIM designations pending</td>
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**MHRA – Scientific Opinion Statistics**

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<th>EAMS step II applications - April 2014 to December 2015</th>
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<td>Applications received</td>
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<td>Opinions awarded</td>
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<tr>
<td>Opinions refused</td>
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<tr>
<td>Opinions pending</td>
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</table>

**Criteria of an EAMS Application**

- (a) Life threatening or seriously debilitating condition and (b) High unmet need, i.e., there is no methods available or existing methods have serious limitations
- Medicinal product is likely to offer significant advantage over methods currently used in the UK
- Potential adverse effects of the medicinal product are considered to be outweighed by the benefits, allowing for the reasonable expectation of a positive benefit/risk balance
- Applicant is able to supply the product and to manufacture it to a consistent quality standard (GMP)

**EAMS Timeline Options**

**Comparison of Breakthrough therapy designation and MHRA processes**

**FDA**
- Holding meetings with the sponsor and the review team throughout the development of the drug.

**MHRA**
- The MHRA offers a scientific advice service in face to face meetings, which can be requested during any stage of the development of a medicinal product.
Comparison of Breakthrough therapy designation and MHRA processes

**FDA**

- Providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable.

**MHRA**

- Following a scientific advice meeting, a final scientific advice letter is sent to the company within 30 working days of the meeting. The MHRA has launched an ‘Innovation Office’, aimed at providing regulatory advice and to support research and development. The EU system also provides extensive guidance to applicants outlining requirements.

Comparison of Breakthrough therapy designation and MHRA processes

**FDA**

- Taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment.

**MHRA**

- Internal MHRA procedures are in place to ensure quality and consistency of the final scientific advice letters (multidisciplinary in house review group). MHRA has dedicated product lifecycle assessment teams (PLATs) for different therapeutic areas, comprising clinical, non-clinical, and pharmaceutical assessors and the same specialist assessors handle products throughout the licensing process. The MHRA clinical trials unit works alongside the PLATs and are also present at scientific advice meetings, alongside statistical and standards/inspection colleagues as required.

Comparison of Breakthrough therapy designation and MHRA processes

**FDA**

- Assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the cross-discipline members of the review team (i.e., clinical, pharmacology-toxicology, chemistry, manufacturing and control (CMC), compliance) for coordinated internal interactions and communications with the sponsor through the review division’s Regulatory Health Project Manager.

**MHRA**

- Internal MHRA procedures are in place to ensure quality and consistency of the final scientific advice letters (multidisciplinary in house review group). MHRA has dedicated product lifecycle assessment teams (PLATs) for different therapeutic areas, comprising clinical, non-clinical, and pharmaceutical assessors and the same specialist assessors handle products throughout the licensing process. The MHRA clinical trials unit works alongside the PLATs and are also present at scientific advice meetings, alongside statistical and standards/inspection colleagues as required.

Definitions of “Biosimilars”

<table>
<thead>
<tr>
<th>Name/Category</th>
<th>Agency</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Similar biological product</td>
<td>FDA</td>
<td>A biological product that is similar in terms of safety, purity, and potency to an already approved biological product.</td>
</tr>
<tr>
<td>Similar biological product</td>
<td>EMA</td>
<td>A biological product that is similar in terms of safety, purity, and potency to an already approved biological product.</td>
</tr>
<tr>
<td>Replicating biological product</td>
<td>EMA</td>
<td>A biological product that is intended to be used as a substitute for the approved biological product.</td>
</tr>
<tr>
<td>Supplemental new biological product</td>
<td>Canada</td>
<td>A biological product that is similar in terms of safety, purity, and potency to an already approved biological product.</td>
</tr>
<tr>
<td>Orphan designation</td>
<td>FDA</td>
<td>A biological product that is intended to be used as a substitute for the approved biological product.</td>
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Orphan Designation

- 21st Century Cures Act • Right-to-Try Laws • FDA Guidance • EAP Task Force
- Program Planning and Design • Supply Equity • Product Forecasting
- Stakeholder Collaboration • Global Request Management
- Country-Specific Regulations • EAP Partnerships • Outsourcing Strategies
- Reimbursement Models • Benefit/Risk Assessment • Real-World Data
- Patient Reported Outcomes • EAP Close Out and Transition

- Expanded Access Programs, Early Access Programs, Compassionate Use Programs, Named Patient Programs and Managed Access Programs.
- best practices around providing investigational, pre-launch or end-of-lifecycle drugs to patients for treatment purposes
• http://slideplayer.com/slide/6259059/#