Unpacking Expanded Access to Investigational Drugs and Biologics

When All Else Fails

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Office of Health and Constituent Affairs
Food and Drug Administration

September 13, 2016
FDA Drug Approval

• Most effective way to get meaningful therapy to the greatest number of patients
  – Based upon evidence from rigorous clinical trials
  – Adequate labeling to guide use and predict potential risks
  – Third party reimbursement
Why Expanded Access?

• Not all patients can wait for approved drugs
  – No effective therapy for condition
  – Exhausted approved options
  – Intolerant of approved products

• Expanded access 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)
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 therapeutic options, and cannot participate in a clinical trial.
Treatment Access

Named Patient Program

Special Access Programme

Compassionate Use

Single Patient IND

Pre-approval access

Pre-launch Access

Expanded Access
Expanded Access Programs (EAP) Are Considered Option of Last Resort

- Hierarchy of Access -

**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 for treatment
**Historical Underpinnings**

- History of facilitating access to investigational therapies reaches back to 1970s
  - 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 treatment use for individuals (21 CFR 312.36), though no criteria or requirements described
FDA Published Revised Regulations in 2009

21 CFR 312 / IND Regulations

- **Subpart I** 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
21 CFR 312  Subpart I

• 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)
Requirements shared by 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
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)
Individual Patient EAPs

- 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
Intermediate Size Population
21 CFR 312.315

- No fixed numerical requirement
- More than a few ...less than a lot
- 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)
  - Approved (e.g., drug withdrawn, drug shortage situation- e.g., foreign version of a U.S. approved drug)
Intermediate Size Population

• Sponsor can be physician, manufacturer, or 3rd party

• Sufficient evidence drug is safe at proposed dose and duration to justify size of exposed population

• Preliminary evidence (clinical or plausible pharmacological) of effect

• Annual review to determine whether treatment use should be continued and whether a Treatment IND would be a more appropriate mechanism

• Intended for patient populations smaller than intended for Treatment IND (generally up to 100 patients)
Treatment IND
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 or life-threatening disease: evidence from phase 3 or compelling data from phase 2 clinical trials
Categories of Expanded Access

- Commercial Sponsor
  - Treatment IND
  - Treatment Protocol
  - Intermediate Size Population IND
  - Intermediate Size Population Protocol
- Physician
  - Emergency Individual Patient IND
  - Emergency Individual Patient Protocol
  - Individual Patient IND
  - Individual Patient Protocol
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 - Reporting requirements (adverse event reports, annual reports), and Clinical Holds based on safety
EAPs and Patients - Considerations

- 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

- FDA considers:
  - potential harm to patients
  - need to exhaust existing approved treatments
  - the scientific likelihood of an efficacious response
  - patient functionality (health, organ function)
  - patient age (pediatric/geriatric)
EAPs and Patients - Potential 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

• Can be a foothold into marketplace for sponsors

• May offer hope for patients with no other available options
Does Expanded Access Support Approval?

- Patients - not research subjects
- Uncontrolled variables: organ function, overall health, disease stage, comorbidities, concomitant drugs
- Intended to minimize data collection burden on physician
- Limited contribution to safety data
  - Reporting requirements for serious and unexpected adverse events
Clinical Trials

Phase I: Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify immediate side effects.

Phase II: The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.

Phase III: The drug or treatment is given to large groups of people to establish/confirm its effectiveness, further monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

Phase IV and/or Post Market Surveillance: Conducted after the drug or treatment has been marketed to gather information on the drug's effect in various populations and identify any longer term or rare side effects.
Unestablished Risk

- Minimization of risk is primary consideration
  - Confidence of safety is primary consideration
- How much evidence of safety is needed to make experimental drug available?
  - for a patient with a life-threatening condition, evidentiary burden is low
    - Only about 12% of drugs entering phase I end up approved*; at least 1/3 are withdrawn for safety concerns
    - Even in approved drugs, some serious safety concerns may not be apparent until post-marketing (Vioxx)

*(Joseph DiMasi, Tufts, 2014)*
Clinical Trials

- **Drug Discovery**
  - Thousands of Compounds

- **Pre-Clinical Studies**
  - 200 - 300 IND Submissions

- **Clinical Trials**
  - Phase 1: 10 research subjects 10-100
  - Phase 2: 3 research subjects 100-500
  - Phase 3: 1 - 2 research subjects 500-1000s

- **FDA Review**
  - 1 - 2 years

- **Manufacturing & Marketing**
  - 1 year

**Expanded Access Potential**
How do patients view investigational products?

Therapeutic Misconception?

Potential overestimation of benefit
and/or underestimation of risk
How do patients view risk?

New drugs can potentially have beneficial effects - and can have toxic effects that cause increased suffering and pain, or the acceleration, or prolonging of death, with no increase in quality of life.

The understanding of the safety profile comes from trials. Not always considered by patients or families - Often see risks as abstract.
How do IRBs view investigational products and risk?

Traditionally charged with protecting research subjects from undue risk
Direct benefit usually not a requisite for trials

Efficacy (and safety) of early phase investigational drugs are not proven – and often not known
Drug might be given through EA 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, and 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 can the two be practically reconciled?

• If patients believe a new, investigational therapy will be beneficial, would they risk randomization to another option? (Finding out is the point of the clinical trial)
Concern about Trial Enrollment

- Clinical trial enrollment and conduct is a factor in consideration of treatment access to experimental drugs by manufacturers and FDA
- Manufacturing capacity is often limited in early phases – diverting drug for expanded access could limit supply for trials
EAP-I 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
Guidance on FDA web site

Expanded Access to Investigational Drugs for Treatment Use —
Questions and Answers
Guidance for Industry

Charging for Investigational Drugs Under an IND —
Questions and Answers
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2016
Procedural
Filing an Individual Patient IND with FDA

- After ensuring that the sponsor will provide the unapproved drug, submit written request to the appropriate FDA review division

- Brief Clinical History of the patient including: diagnosis, status, prior therapy, rationale

- Proposed Treatment Plan: dose, route, duration, monitoring procedures, modifications (e.g. dose reduction or treatment delay) for toxicity

- Chemistry, Manufacturing, and Controls Information and Pharmacology and Toxicology Information, including a description of the manufacturing facility. Covered by Letter of Authorization (LOA) from sponsor

- Clinical procedures or lab tests/monitoring necessary to evaluate effects, or minimize risks

- Certification of IRB review and consent (except in emergency use)

- Investigator Qualification Statement (Curriculum Vitae) & contact info

- FDA Form 1571 listing treating physician as the sponsor
Form 1571

Typically intended for commercial IND applications

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Contents of Application - The application contains the following items (Select all that apply):

- [ ] 1. Title and Date of INVESTIGATIONAL NEW DRUG APPLICATION (IND) (Title 21, Code of Federal Regulations (CFR) Part 312)
- [ ] 2. Table of Contents (21 CFR 312.20(a)(3))
- [ ] 3. Introductory Statement (21 CFR 312.2(a)(9))
- [ ] 4. Investigational Plan (21 CFR 312.3(a)(8))
- [ ] 5. Study Protocol (21 CFR 312.20(a)(8))
- [ ] 6. Summary of Data (21 CFR 312.20(a)(9)(i)-(iii))
- [ ] 7. Data on the chemical identity and purity of the investigational new drug product (INP) (21 CFR 312.20(a)(9)(ii))
- [ ] 8. Pharmacology, toxicology, and toxicology data (21 CFR 312.20(a)(9)(i))
- [ ] 10. Additional information (21 CFR 312.20(a)(9)(ii))
- [ ] 11. Acknowledgement (INVESTIGATIONAL NEW DRUG APPLICATION (IND) (Title 21, Code of Federal Regulations (CFR) Part 312))
- [ ] 12. Clinical Trials Certification of Compliance (Form FDA 3574)
- [ ] 14. Clinical Trials Certification of Compliance (Form FDA 3574)

Yes | No

If any part of the clinical study is to be conducted by a contract research organization:

- [ ] Yes
- [ ] No

If yes, will any sponsor obligations be transferred to the contract research organization:

- [ ] Yes
- [ ] No

If yes, provide a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred (use continuation page).

Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations:

15. Name(s) and Title(s) of the person(s) responsible for review and evaluation of information relevant to the safety of the drug:

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold or financial hold. I agree that an Institutional Review Board (IRB) that oversees the requirements set forth in 21 CFR Part 56 will be responsible for initiating and continuing clinical review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all applicable regulatory requirements.

Name of Sponsor or Sponsor's Authorized Representative:

17. Name of Sponsor or Sponsor's Authorized Representative:

21. Email Address:

Address 1: Street address, R.O. box, company name city
Address 2: Apartment, suite, unit, building, floor, etc.
City | State/Province Region | ZIP or Postal Code

22. Date of Sponsor's Signature (W/initials):

23. Name of Contact Person:

24. Address of Contact Person:

Address 1: Street address, R.O. box, company name city
Address 2: Apartment, suite, unit, building, floor, etc.
City | State/Province Region | ZIP or Postal Code

25. Name of Counter signer:

26. Signature of Counter signer:

WARNING: A willful false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).
Form 3926
For single patient requests only

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Individual Patient Expanded Access
Investigational New Drug Application (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Patient's Initials

Date of Submission

Initial Submission

Select this box if this form is an initial submission for an individual patient expanded access (IND), and complete only fields 4 through 9, and fields 10 through 11.

Follow-Up Submission

Select this box if this form accompanies a follow-up submission to an existing individual patient expanded access (IND), and complete the items to the right in this section, and fields 8 through 11.

5. Clinical Information

Indication

Clinical History (Patient's age, gender, weight, allergies, diagnosis, prior therapy, response to prior therapy, reason for request, including an explanation of why the patient lacks other therapeutic options)

6. Treatment Information

Investigational Drug Name

Name of the entity that will supply the drug (generally the manufacturer)

FDA Review Division (if known)

Treatment Plan (Including the dose route and schedule of administration, planned duration, and monitoring procedure. Also include modifications to the treatment plan in the event of toxicity.)

7. Letter of Authorization (LOA), if applicable (Obtained from manufacturer if drug)

I have attached the LOA. (Attach the LOA, if electronic, use normal PDF functions for file attachments)

Physician's Qualification Statement (Including medical school attended, year of graduation, medical specialty, state medical license number, current employment, and job title. Alternatively, attach the first few pages of physician's curriculum vitae (CV), provide they contain the information. If attaching the CV electronically, use normal PDF functions for file attachments.)

8. Physician Name, Address, and Contact Information

Physician Name (Sponsor)

Address 1 (Street address, No P.O. Box)

Address 2 (Apartment, suite, unit, building, floor, etc.)

City

State

FAX Number of Physician

ZIP Code

Phone Number of Physician

Physician's Ind No.

Signature of Physician

Date

For FDA Use Only

Date of FDA Receipt

Is this an emergency?

Is this IND for a rare disease (prevalence < 200,000 in the U.S.)?

FORM FDA 3926 (2016)
Page 1 of 2
Form 3926

- 1: Patient’s initials and date of submission
- 2: Clinical information
- 3: Treatment information
- 4: Letter of Authorization (from manufacturer)*
- 5: Physician’s qualification statement
- 6: Physician name, address and contact information
- 7: Request for authorization to use Form 3926
- 8: Certification statements and physician signature
  - When treatment may begin
  - Informed consent and IRB issues
  - Emergency IND procedures

* Attachment
Individual Patient Expanded Access Applications: Form FDA 3926

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2016
Procedural

OMB control number 0910-0814
Expiration Date: 04/30/2019
See additional PRA statement in section V of this guidance.
Where can you find more Information?
Expanded Access (Compassionate Use)

This section of our website provides information about FDA’s current expanded access policies, requirements for enrolling in expanded access programs, and steps you can take to get more information.

Expanded access, sometimes called “compassionate use,” is the use outside of a clinical trial of an investigational medical product (i.e., one that has not been approved by FDA). FDA is committed to increasing awareness of and knowledge about its expanded access programs and the procedures for obtaining access to human investigational drugs (including biologics) and medical devices.
Information for Patients, Physicians and Industry

**Patients**
Learn about what your physician should do before submitting a request for individual patient expanded access use of an investigational medical product, who may be eligible for expanded access, associated costs, FDA contacts and more.

**Physicians**
Learn about your responsibilities under the expanded access pathway, how to submit a request for expanded access for an individual patient (including for emergency use), which forms to use, FDA contacts and more.

**Industry**
Learn about current regulations, what information is required when you provide access to investigational medical products under an individual patient expanded access IND, and view an example of wording that could be used for a Letter of Authorization, FDA contacts and more.
CBER and CDER Expanded Access IND Submissions and Protocols, FY 2010-2015

*For FY 10 and FY 11, the reporting period was October 13 through October 12 of the following year.
# Drugs track record

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## Expanded Access Protocols

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## Totals for Expanded Access

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*** These reporting periods cover a one year cohort starting the day the Final Rule for Expanded Access to Investigational Drugs for Treatment Use and Charging went into effect. Starting with Fiscal Year 2012, the reporting period was changed to a fiscal year to match the reporting period for other IND activity reports.
• There is a single, uniform, national, FDA mechanism in place that creates a pathway to access
• Application is designed to be completed in 30 – 45 minutes
• FDA turns around completed applications quickly – hours to days
• More than 99% of expanded access applications are allowed to proceed
• Patients can’t apply for such access; the request has to come from the sponsor, physician investigator, or a qualified treating physician, either for a single patient or a small group (up to 100 patients). Sponsor companies can request Treatment INDs
• Office of Health and Constituent Affairs staff available to provide information and assistance
• 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 conclusion of treatment
Office of Health and Constituent Affairs

For questions about FDA’s expanded access program, contact the Office of Health and Constituent Affairs’ Expanded Access Team at

301-796-8460 or

PatientNetwork@fda.hhs.gov

Richard.klein@fda.hhs.gov