Expanded Access/Compassionate Use Part 1

Individual Patient and Emergency Use of Drugs: Past, Present, and Right to Try

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Presented by:
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- Established in 1983
- Superior audit history with FDA—five consecutive audits with no findings
- 21 CFR Part 11 compliant electronic systems
- Compliant with FDA, OHRP and Health Canada requirements
- Full board meetings **five days a week**
- Dedicated **daily expedited review** of qualifying minimal risk protocols
About Schulman IRB

- Review outcome provided within **one business day** of new study review
- **One business day** turnaround for complete new site submissions
- **Phase I Board** with streamlined processes tailored to Phase I timelines
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About Today’s Presenter

Rebecca Carson Rogers, MA, CIP, CHRC
IRB Chair, Schulman IRB

- IRB Chair at Schulman IRB since 2014
- Previously served as Assistant Director of Dartmouth College’s IRB and as IRB Member
- Also previously served as Research Regulatory and Compliance Officer at Dartmouth Cancer Center
- Contributor to 1st and 2nd editions of Bankert and Amdur’s *IRB: Management and Function*
- Experienced educator and presenter on human subject protection topics
Objectives

- Share history of FDA expanded access for investigational drugs and biologics
- Review FDA categories of expanded access of investigational drugs for treatment use
  - Differentiate access INDs and access protocols
  - Learn requirements for individual patient emergency use of investigational drugs
- Provide IRB review requirements for expanded access of drugs and biologics
- Contrast FDA expanded access for investigational drugs and “Right to Try” legislation
- Consider expanded access scenarios
patient with unexpected treatment reaction.
• treating physician finds a citation for an unapproved “antidote” drug. calls the research office compliance officer.

compliance officer starts to coordinate the required choreography between the treating physician, the drug company, the fda, the clinical trials office, the patient and family.

drug company and fda are prepared.

antidote drug individual expanded access protocol are reviewed and approved by irb rapid response board.

drug is flown to regional airport and helicoptered to site in less than 12 hours.

patient is doing well monday morning.
Wherever possible, use of an investigational medical product by a patient as part of a clinical trial is preferable.

Clinical trials can generate data that may lead to the approval of products and, consequently, to wider availability.

FDA News/Event Public Health Focus Expanded Access
Compassionate Use webpage
http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm
Expanded access uses are not primarily intended to obtain information/data about the safety or effectiveness of a drug.

The terms *expanded access, access, and treatment use* are used interchangeably to refer to use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient’s disease or condition.
Expanded access, sometimes called "compassionate use," is the use outside of a clinical trial of an investigational medical product 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.

How did we get here?
The Pure Food and Drug Act of 1906 was one of the first consumer protection laws enacted by US Congress.

Initial Federal Food, Drug and Cosmetic Act of 1938 required FDA approval of new drugs PRIOR to being shipped in interstate commerce.

HOWEVER: Section 505(i) allows FDA to exempt, by regulation, investigational drugs from the approval requirements.

- FDA chose to implement this exemption through the IND regulations in 21CFR Part 312.
Since 1987, largely thanks to AIDS patient advocacy, the FDA has had rules in place that have enabled patients, under specific circumstances, to access drugs or biologics that are still in development for treatment purposes.

Concerns:

- Disparate access for different types of patients
- Access primarily limited to patients with cancers and HIV infection
Expanded access program rules were amended in 2009 by the FDA to ensure “broad and equitable access to investigational drugs for treatment.”

In response to State “Right to Try” laws, in Feb 2015, FDA posted a draft of a streamlined application form for use by physicians to expedite the individual expanded access IND application process.
Under FDA’s current regulations, there are three categories of expanded access to Investigational Drugs for Treatment Use:

• Expanded access for individual patients, including for emergency use 21 CFR 312.310
• Expanded access for intermediate-size patient populations 21 CFR 312.315
• Expanded access for large patient populations under a treatment IND or treatment protocol 21 CFR 312.320
1. **Access IND**: a new IND submission, which is separate and distinct from any existing INDs and is intended only to make a drug available for treatment use. 21 CFR 312.305(b)(1)

- An access IND submission generally should be used when:
  - (1) there is no existing IND in effect for the drug, OR
  - (2) there is an existing IND in effect for the drug, but the sponsor of the existing IND declines to be the sponsor of the access use

- Example: for an individual patient use, the sponsor of the existing IND may prefer that a patient’s physician submit a separate individual patient IND.
2. **Access protocol**: submitted as a protocol amendment to an existing IND

- When there is an existing IND in effect, FDA generally encourages the submission of an access protocol, rather than a new access IND:
  - Having all access and clinical trial use consolidated under a single IND may facilitate earlier detection of safety concerns associated with a drug.
  - The administrative process is less burdensome for sponsors and FDA.
What about an emergency?!
FDA may authorize expanded access for an individual patient without a written submission if there is “an emergency that requires the patient to be treated before a written submission can be made.”

FDA believes this regulation means that it is appropriate when treatment of the patient must occur within a very limited number of hours or days.

FDA scrutinizes emergency requests and authorizes access for such requests only when the situation is a true emergency.
Emergency requests for expanded access use under a single patient IND may be submitted over the phone or electronically by a licensed physician, usually the patient's treating physician.

The physician explains how the expanded access use will meet FDA’s requirements and agrees to submit an individual expanded access IND submission within 15 working days of FDA’s initial authorization of the expanded access use.
The FDA expects that, for expanded access uses approved under the emergency procedures, there typically will not be time to obtain prior IRB approval.

For an emergency use, access to the drug may begin upon verbal authorization (usually over the telephone) by the reviewing FDA official 21 CFR 312.305(d)(2)(i)

In such cases, the emergency use must be reported to the responsible IRB within 5 working days of initiation of treatment 21 CFR 56.104(c)
There can be more than one expanded access emergency use of the same drug at the 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 21 CFR 56.104(c)

- Provided that such emergency use is reported to the IRB within 5 working days.
- Any subsequent use of the test article at the institution is subject to IRB review.

HOWEVER: When prior IRB review and approval is not feasible for a subsequent expanded access emergency use at a particular institution, FDA does not intend to deny the subsequent request for emergency use due to lack of time to obtain prospective IRB review, as long as that use will be reported to the IRB within 5 working days of initiation of treatment.

“Expanded Access to Investigational Drugs for Treatment Use - Qs & As”
What about the Drug Company?

- So FDA has processes in place for emergency use or individual patient access for an investigational drug or biologic....
  - Can FDA require a drug company to provide expanded access to its drug?
Can FDA Require a Drug Company to Provide Expanded Access to Its Drug?

NO.

• FDA cannot compel a company to provide expanded access to its drug.
• When a company provides expanded access to its drug, it is doing so voluntarily.
Back to the patient with an unexpected treatment reaction on a Friday. The treating physician found a citation for an unapproved “antidote” drug.

If there was not an individual patient access IND available and the drug company agreed to provide the antidote drug if the site properly uses the FDA emergency use criteria, which of the following circumstances MUST take place:

a) FDA is contacted by treating physician over the phone, who explains how this situation meets the FDA expanded access criteria. FDA agrees. Sponsor ships drug. IRB calls a Rapid Response meeting and approves the emergency use. Patient is consented and received drug.

b) FDA is contacted by treating physician over the phone, who explains how this situation meets the FDA expanded access criteria. FDA agrees. Sponsor ships drug. No IRB approval is needed since this is an emergency use.

c) Treating physician completes the FDA individual IND submission form and emails it to the FDA. FDA emails an approval. Sponsor ships drug. IRB calls a Rapid Response meeting and approves the emergency use. Patient is consented and received drug.
More on the patient with unexpected treatment reaction on a Friday.

If there were no individual patient access IND in place, the drug company agreed to provide the antidote drug if the site properly uses the FDA emergency use criteria, and the FDA authorizes the emergency use, which of the following circumstances MUST take place:

a) Treating physician submits an individual patient access IND to FDA within 15 working days. IRB approval required prior to administration of investigational drug.

b) Treating physician submits an individual patient access IND to FDA within 15 working days. No IRB submission required. The investigational drug has already been administered, and IRBs do not conduct retrospective review.

c) Treating physician submits an individual patient access IND to FDA within 15 working days. Emergency use is reported to the IRB within 5 working days of initiation of treatment.
Start with the drug company that has an IND for the investigational drug.

- When a licensed physician would like to obtain an investigational drug for an individual patient, the physician should first ensure that the manufacturer is willing to provide the investigational drug.

- If the manufacturer agrees, they should provide the physician with a letter of authorization (LOA) that permits FDA to refer to IND submission information the manufacturer has submitted to FDA.

- The physician should then submit an individual patient expanded access IND application to FDA.
  - Use Form 1571. New Form FDA 3926 is now published as draft guidance February 2015.
The physician is considered a sponsor-investigator and is responsible for complying with the responsibilities for sponsors and investigators, including:

- submitting IND safety reports,
- submitting annual reports, AND
- maintaining adequate drug disposition records
The sponsor of the existing IND can submit an individual patient access IND and cross-reference information in its existing IND to support the individual patient access IND.

- The sponsor of the existing IND is also the sponsor of the access IND.
- The patient’s physician is the investigator for the access IND.
The sponsor of the existing IND can submit an individual patient access protocol to its existing IND.

- The sponsor of the existing IND is also the sponsor of the access protocol.
- The patient’s physician is the investigator for the access protocol.
Regardless of who is the sponsor of an individual patient access protocol or access IND:

- The patient can obtain access to the investigational drug **only through a licensed physician.** 21 CFR 312.310
FDA and physician criteria for determination if access for an individual patient is appropriate:

- Physician must determine that probable risk to the patient from the investigational drug is not greater than probable risk from the disease or condition.  
  \[312.310(a)(1)\]

- Determination to be based on available information about the drug and physician’s knowledge of the patient’s clinical situation.
FDA Criteria for Granting Individual Patient Expanded Access

- The potential benefit justifies the potential risks of the treatment use with the drug and those risks are not unreasonable in the context of the disease or condition to be treated.
- The patient has a serious or life-threatening disease or condition.
- There are no other comparable or satisfactory therapeutic options.
- Providing access will not interfere with development of the drug.
- Patient cannot obtain the drug under another IND or protocol (such as clinical study of the drug).
Informed consent requirements apply to treatment provided to patients under expanded access INDs and protocols. 21 CFR part 50

- Informed consent must be obtained before initiating treatment, including in the case of emergency use, unless one of the exceptions found in part 50 applies.

IRB requirements apply. 21 CFR part 56

- IRB approval must be obtained before starting treatment under an expanded access IND unless it is for emergency use.
- IRB must review the expanded access use at a convened (full Board) meeting.
FDA is aware of concerns that this requirement for full IRB review may deter individual patient access to investigational drugs for treatment use.

Concerns:

- Individual patient expanded access programs in settings in which IRB review is not readily accessible (e.g., healthcare settings that do not have IRBs)
- Cost of IRB review
FDA encourages use of central IRBs for review of expanded access uses.

- However, other options may be needed.
- FDA is currently considering whether other options might better facilitate individual patient expanded access while providing appropriate ethical oversight.
IRB Review: Submission Requirements

- Clinical history of subject
- Treatment plan to be executed by submitting practitioner
- Informed consent document
- Written proof that submitting practitioner/investigator or sponsor has sent documents to FDA for expanded access IND approval
- Form 1571 signed by submitting practitioner/investigator or sponsor
- IB and safety reports for drug
Practitioner must be familiar with “information on the drug’s safety and effectiveness derived from previous clinical and nonclinical experience with the drug.” 21 CFR 312.35 (b)(1)(vi)

• Submit signed and dated statement from treating practitioner confirming that he/she reviewed the currently available product information and understands the information contained therein

Appropriate IRB submission forms
CV and license of submitting practitioner/investigator
When can treatment begin under individual patient access INDs not for emergency use?

• All expanded access INDs go into effect 30 days after FDA receives the IND or on earlier notification by FDA.

• The treatment use of the drug may begin when the IND goes into effect and IRB approval has been obtained.
When can treatment begin under access protocols not for emergency use?

• Access to drug can begin once access protocol has been submitted to FDA and has been approved by an IRB.
Individual patient access is generally limited to a single course of therapy for a specified duration. [21 CFR 312.310(c)(1)]

- Unless FDA expressly authorizes multiple courses or chronic therapy.

FDA does not typically authorize access of unspecified duration at the discretion of the treating physician.
Payment for Expanded Access Use

- Often patients may have to pay for the investigational drug and/or for medical care associated with the use of the investigational drug.
- If a manufacturer seeks to impose charges, it may be under pressure from patients to waive costs because they may not be covered by insurance.
  - FDA reports that most manufacturers do not charge for their products.
- Some observers have accordingly argued that expanded access generally favors the rich or well-connected over the poor. 
  
  Darrow JJ, et al. Practical, legal, and ethical issues in expanded access to investigational drugs

- IRBs may charge for protocol review.

  Will cover this in detail in Part 2 of the presentation.
A call comes to a local academic medical center research physician’s office explaining that their family member has a terminal condition, and they have learned of an investigational drug for this condition.

The family has done their homework. They have contacted the drug company and the sponsor is willing to submit an individual patient access IND to the FDA, as they have done successfully in the past.

Which of the following are accurate:

a) Since FDA has previously approved an individual patient access IND for this product and for the same condition, FDA will approve subsequent individual patient access INDs for the same product and medical condition.

b) Since the drug company will submit the individual patient access IND submission, the physician at the medical center does not need to submit anything to FDA.

c) IRB approval is required prior to the administration of the investigational product.

d) The patient’s family may have to cover costs of the investigational product and its administration.
“Right to Try” laws are already in place in 24 states and counting.

http://righttotry.org/in-your-state/
Some interpret these laws as circumventing FDA entirely.

“These laws allow patients and doctors to go directly to a company without asking FDA for permission. And this will expedite the process. The states have a fundamental right to save lives.”

• Kurt Altman, general counsel at Goldwater Institute, a nonprofit that has drafted model bills for several states
Typical provisions:

- Manufacturers “may” provide investigational products that have “successfully” completed Phase 1 clinical trials to terminally ill patients.
- Require informed consent, though not necessarily defined as per federal regs.
- Protections for healthcare providers.
- Clarify insurance coverage issues.
- Protection for manufacturers from tort claims.
Right to Try Laws

- Laws encourage doctors to pursue drugs by providing immunity from lawsuits.
- Some state laws indemnify drug makers if treatment goes wrong.
“No one is obligated to do anything. It gives you the right to ask, but people have been asking drug companies in droves long before these laws existed.”

• Art Caplan, head of bioethics in Division of Medical Ethics at NYU Langone Medical Center

“Right to Try” laws do not compel manufacturers and insurers to supply and pay for experimental therapies.
Right to Try Laws – Limits

- Do not prevent federal government from rescinding Drug Enforcement Administration registration of physicians who prescribe experimental drugs independent of FDA.

- Unlikely to withstand a constitutionality challenge.
  - Under the Supreme Court's long-standing preemption doctrine, state laws that conflict with federal statutes or regulations are “without effect.”

- The frustration that these laws reflect may nonetheless mount pressure on Congress and FDA to reassess the expanded access system.
“The FDA is not the obstacle to access. These laws aren’t doing anything to address understandable obstacles that companies face when a drug is requested.”

- Patti Zettler, former FDA associate chief counsel, now a fellow at Stanford Law School Center for Law and the Biosciences

Drug makers may deny requests in order to meet strict criteria needed to win FDA approval for a medicine.

- Unexpected patient reaction might jeopardize the chance of drug approval.
- Company may lack sufficient supplies for clinical trials and a large number of individual requests.
- Company may not want to reveal potential pricing of a new drug.
The ethical and policy debate on the appropriate balance between access to and protection from potentially useful but also possibly harmful or ineffective medicines began with the passage of the Pure Food and Drug Act in 1906.

The escalation of the battle over expanded access has rekindled this debate a century later. In the ensuing years, Congress has unambiguously delegated authority over striking this balance to the FDA, but growing antiregulatory sentiment has begun to threaten this assumption, with the most persuasive arguments being made concerning patients with terminal illnesses who appear to have much to gain and little to lose by accessing unapproved drugs.

However, this debate will need to take into account the simple concept that led to the regulatory authority of the FDA in the first place: that it may well not be in the interest of patients, however sick they may be, to have easier access to products that are ineffective and may actually worsen their clinical status.

One of the most straightforward means of addressing the issue of expanded access:

- Shorten the time between the determination that a new substance may be clinically useful and the point at which it becomes widely available.
Be prepared.

- Know your institution’s policy on individual expanded access and emergency use, including:
  - Cost coverage.
  - Is an individual physician permitted to be an IND holder?
- Work with the drug company.
- Then work with the FDA.
- Know your institution’s IRB requirements.
- Expect media attention.
  - Plan ahead with your public affairs or media/communications team.
**FDA Resources**

**Form FDA 1571**
This is the currently approved form for submitting requests for an individual patient expanded access to investigational drugs (including biologics).

**Comment on Individual Patient Expanded Access Applications: Form FDA 3926**
When finalized, draft Form FDA 3926 is intended to provide a streamlined alternative for submitting an Investigational New Drug Application (IND) for use in cases of individual patient expanded access.

**FDA's Draft Guidance: Expanded Access to Investigational Drugs for Treatment Use - Qs (PDF - 75KB)**

**FDA's Draft Guidance: Charging for Investigational Drugs Under an IND - Qs (PDF - 57KB)**

**21 CFR 312 Subpart I** FDA’s current expanded access regulations for investigational drugs (including biologics).


**Right to Try**

http://righttotry.org/in-your-state/ Interactive map regarding State Right-to-Try laws

http://goldwaterinstitute.org/en/ Goldwater Institute

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