



# Expanded Access to Investigational Drugs

Anne Pariser, M.D.

Office of New Drugs

Center for Drug Evaluation and Research

Food and Drug Administration

# Outline

## Expanded Access

- Regulatory considerations
- Conducting research in human subjects
- CDER EA History
  - Example
- Interacting with FDA

# Expanded Access

- Purpose
  - Intended to improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions with no satisfactory/comparable alternatives
  - Enables these patients to access products that are still in development for treatment purposes
  - Provides access to investigational products outside of a clinical trial, thus:
    - *Not* likely to describe effectiveness
    - *Not* likely to support marketing applications

# Expanded Access (2)

- FDA's main concern is with safety – requires that:
  - “Potential patient benefit justifies the potential risks, and potential risks are not unreasonable”
- FDA approval is the best form of access to a drug
  - EA use “will not interfere with the initiation, conduct or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use”

# Expanded Access (3)

- In general, 4 types, considered on a case-by-case basis
  - Emergency
  - Single patient
  - Intermediate size
  - Treatment protocol
- Briefly:
  - Emergency use IND (E-IND)
    - FDA authorizes use in an emergency situation that doesn't allow time for an IND submission
    - Usually requested by phone or other "rapid means of communication"
    - IRB notification must follow within 5 days
    - Written submissions to FDA within 15 days
    - Generally limited to one course of treatment
  - Single patient & intermediate size
    - Single patient or small groups of patients with similar treatment needs
    - For patients who do not otherwise qualify to participate in a clinical trial
  - Treatment protocol
    - Experimental drugs showing promise in clinical testing for serious or life-threatening conditions while final clinical work is conducted and FDA review takes place

# Expanded Access (4)

- Single Patient: non-emergency
  - Written request (Investigational New Drug Application) must be submitted to FDA. Must include:
    - Brief clinical history, rationale and criteria for selecting appropriate patient(s) for study
    - Proposed treatment plan
      - Clinical protocol
      - Description of procedures, lab testing and monitoring necessary to evaluate the effects of the drug and minimize risks
    - Investigator qualification statement (e.g., CV)
    - Chemistry, manufacturing, controls (CMC) information
      - Proper identification, quality, purity, strength, and manufacturing facility information
      - Can provide a Letter of Authorization from the manufacturer if previously submitted (e.g., an existing IND or NDA)

# Expanded Access (5)

- Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for use
  - Nonclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans, or
  - any previous clinical experience with the drug (usually foreign)
- What is usually required to give a new drug to humans for the first time (e.g., commercial IND)?
  - Repeat dose toxicology study in two species (14-28 days)
  - Safety pharmacology
    - CV, CNS, pulmonary
  - Genetic toxicology
- Are these requirements immutable? No --
  - Pre-clinical requirements depend on the clinical protocol
    - Variables: patient population, duration, proposed doses

# INDs – a few FAQs

- First step for any EA IND:
  - Manufacturer must be willing to supply the investigational product
  - FDA cannot make anyone supply drug
- All information about/in an IND is confidential
  - “The existence of an investigational new drug application will not be disclosed by FDA” ( 312.130)
  - For unapproved applications “no data or information in an application... is available for public disclosure” ( 314.430)
  - FDA will communicate only with the IND holder (e.g., PI, drug manufacturer)
    - Otherwise, can only discuss information already in the public domain

# IND FAQs (2)

- Investigational plan expected to vary widely depending on many factors
  - E.g., novelty of drug, patient population, previous experience, developmental phase, etc.
- Independent review by an IRB is also required
  - Include an informed consent form and statement that IRB approval will be obtained prior to initiating treatment
- For any initial IND (except E-INDs)
  - FDA has 30 days to review
    - Trial may not proceed before Day 30
    - Multi-disciplinary review team evaluates application, typically involving:
      - Chemistry, Manufacturing and Controls (CMC)
      - Animal pharmacotoxicology
      - Clinical

# Conducting Research in Human Subjects

- US requirements for human experimentation
  - Derived from internationally shared ethical principles
  - Principles codified in US law in Code of Federal Regulations (21 CFR 312)
- FDA's primary objectives in overseeing all phases of clinical investigations are:
  - To assure the safety and rights of subjects
  - That quality of scientific evaluation of drugs is adequate to permit an evaluation of the drug's safety and, for later phase trials, effectiveness

# Ethical Principles

- Ethical principles broadly state
  - Medical research must conform to generally accepted scientific principles (i.e., Good Clinical Practice)
    - Based on thorough understanding of scientific information from all relevant sources
    - Of sufficient quality to assure that results are credible and accurate
  - Before trial is initiated, a careful assessment of foreseeable risks to subjects should be weighed against anticipated benefit for the subject
    - Using all available nonclinical and clinical information which “should be adequate to support the proposed clinical trial”

# Research (2)

- *Primum non nocere*
- Jesse Gelsinger (1981-1999)
  - First person publically identified as having died in a clinical trial for gene therapy
  - Investigation revealed many concerns with study conduct, reporting, non-clinical safety testing, informed consent and others
- TGN1412 (anti-human CD28 mAb; TeGenero)
  - Orphan designation in Europe (e.g., malignancies)
  - Near-fatal side-effects in first-in-human, single-dose trial in 6/6 healthy volunteers who received the product
  - CHMP subsequently developed a guideline for biologic product trials
    - Changes for first-in-human biologics trials, non-clinical safety evaluations, calculation of safe starting dose and conduct of trials, E.g., “rigorous and structured approach for the evaluation of pre-clinical experiments...” [MHRA] <sup>12</sup>

# Common Concerns

- Early/Pre-IND Phase
  - Usually safety related
  - Clinical Hold criteria – two most common ( 312.42)
    - Subjects would be exposed to an unreasonable and significant risk of illness or injury
    - Insufficient information to assess risks to subjects, e.g.
      - Lack of characterization of drug/biologic (CMC)
      - Lack of pre/non-clinical data
        - » E.g., Animal toxicology
- Later phase - Safety concerns (as above), and
  - Plan/protocol for the investigation is clearly deficient in design to meet its stated objectives.

# Clinical Hold

- If assessed as not safe to proceed then:
  - Usually receive a phone call from review team
    - Often will attempt to resolve issues, if possible/feasible
  - Unable to resolve → Day 30 goes on Clinical Hold
    - Subjects *may not* be given the investigational drug
    - Initial notice of Hold is via phone call to the IND sponsor
    - Hold letter from the review division will follow within 30 days listing hold issues and what's needed to resolve
  - In some situations, may be placed on Partial Clinical Hold
    - A delay or suspension of only part of the clinical work requested under the IND
      - E.g., a specific protocol or part of a protocol is not allowed to proceed
        - » For example, may limit dose escalation or to single-dose administration

# Hold Letter

- Letter will include
  - Listing of Clinical Hold deficiencies
    - That is, the specific items that result in the hold, such as inadequate non-clinical toxicology data
  - Listing of information needed to resolve Clinical Hold deficiencies
    - Such as specific non-clinical studies needed to support dosing
  - Instructions on “Complete Response” procedures and who to contact



# Recent Regulatory History

## Expanded Access Submissions Received by CDER CY 2010

<b>New INDs</b>	<b>Requests Received</b>	<b>Allowed to Proceed</b>	<b>Denied</b>
Emergency	446	434 (97)	12 (3)
Single Patient	428	428 (100)	0
Treatment	0	0	0
Intermediate Size	1	1 (100)	0
<b>Protocols Submitted to Existing INDs</b>			
Emergency	0	0	0
Single Patient	15	15 (100)	0
Treatment	6	6 (100)	0
Intermediate	4	4 (100)	0



# E-INDs - previous 3 years

## E-IND Requests Received at CDER CY 2007-2009

<b>E-INDs</b>	<b>Requests Received</b>	<b>Allowed to Proceed</b>	<b>Denied</b>
CY 2007*	657	640 (97)	17 (3)
CY 2008	316	311 (98)	5 (2)
CY 2009	360	347 (96)	13 (4)

\*Atypically high number driven by special situation with one drug

# Hypothetical Hold Example

- Fictitious EA for an unapproved drug in serious, life-threatening disease
  - Over-the-Counter drugs or food additives at times proposed for investigational use in serious disorders
  - Many of these described as “Generally Regarded as Safe” (GRAS)
  - However, GRAS refers to food additives or OTC drugs for which “the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use” ([www.fda.gov](http://www.fda.gov))
    - Based on exposure, e.g., mg/day
    - “Drug X” GRAS level = X/day
  - Drug X proposed dose of 100X/day
    - No animal toxicology studies conducted
    - Search of literature revealed severe toxicity in animals at human-equivalent dose lower than that proposed in EA protocol
    - In this situation, FDA would generally request additional non-clinical testing to identify a safe dose prior to human testing, or starting at a lower dose supported by available safety data

## Example (2)

“All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy”

– Paracelsus (16<sup>th</sup> century)

- E.g., Table salt (NaCl)
  - RDA ~90 mg/kg in adults
    - To use the previous example 100-fold dose increase  
→ 9,000 mg/kg or ~600 g for 70-kg man
  - LD50 in mice 3,000 mg/kg

# Interactions w/FDA

- For IND and marketing applications
  - May request meetings with FDA
  - Early and frequent communication with FDA is essential for successful programs
- Milestone meetings
  - Pre-IND, EOP1, EOP2A, EOP2, pre-NDA/BLA
  - Type A → development at a standstill (e.g., on Hold)



# Questions

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# References

## 1. Expanded Access

- US FDA. *Code of Federal Regulations Title 21: Subpart I -- Expanded Access to Investigational Drugs for Treatment Use*. Pt. 312.305-.320. (2010)

## 2. Physician request for Expanded Access

- <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm107434.htm>

## 3. Good Clinical Practice Guidelines:

- US Dept. of HHS, FDA, CDER, CBER. Guidance for Industry. ICH E6 Good clinical practice: Consolidated guidance. April 1996.  
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073122.pdf>.

## 4. Articles relating to Jesse Gelsinger

- McCarthy M. US FDA rejects defence of gene-therapy trial. *Lancet*. 2000;355:997.
- McCarthy M. US tightens oversight of gene-therapy trials. *Lancet*. 2000;355:997.
- Yarborough M, Sharp R. Public trust and research a decade later: What have we learned since Jesse Gelsinger's death? *Mol Genet Metab* 97(1):4

# References (2)

## 5. TGN1412

- Stebbings R, Poole S, Thorpe R. Safety of biologics, lessons learnt from TGN1412. *Curr Opin Biotechnol* 2009;20(6):673-677.

## 6. Clinical Hold

- US FDA. *Code of Federal Regulations Title 21: Clinical holds and requests for modification*. Pt. 312.42. (2010)

## 7. Requesting Meetings with FDA

- US Dept. of HHS, FDA, CDER, CBER. Guidance for Industry. Formal meetings between the FDA and sponsors or applicants. May 2009.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.