US FDA Expedited Programs and Expanded Access

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Optimising the development of ATMPs to meet patient needs
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Disclosures

I have no financial relationships to disclose.

I will not discuss off-label use of products.

Outline

- US FDA Expedited Programs
  - Priority Review Designation: 1992
  - Accelerated Approval: 1992
  - Fast Track Designation (FTD): 1997
  - Breakthrough Therapy Designation (BTD): 2012
- US FDA Expanded Access

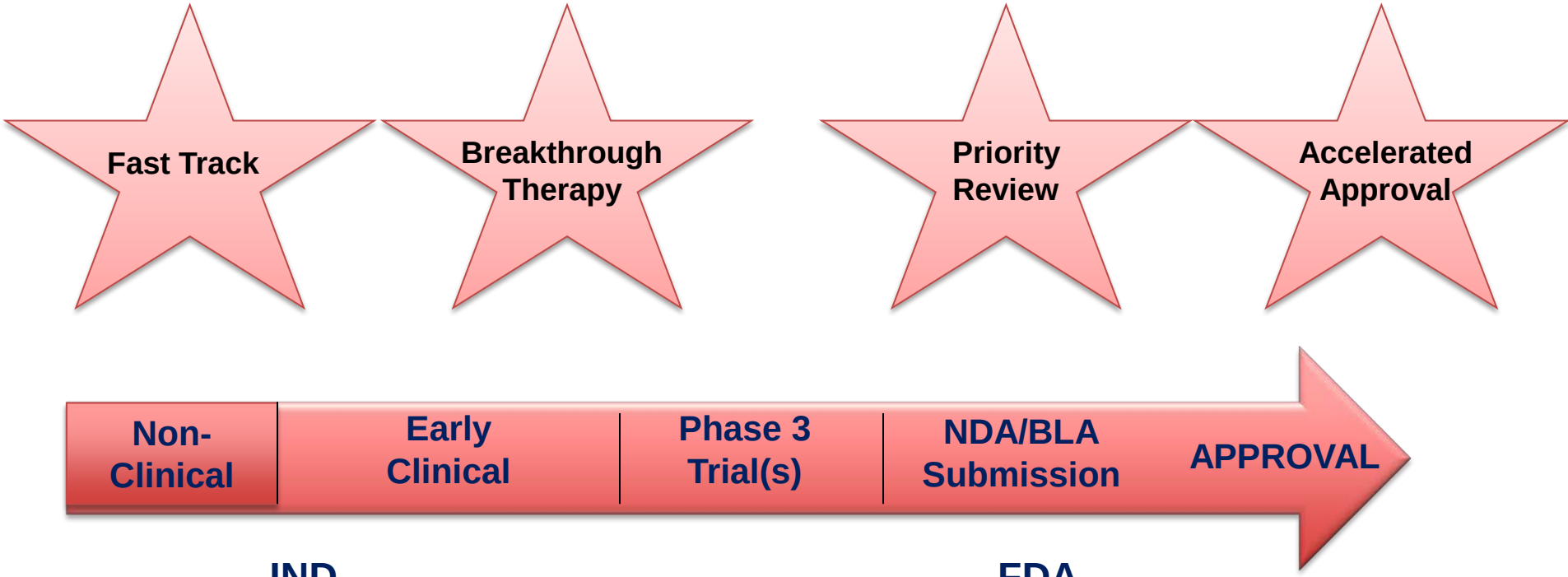
FDA Expedited Programs: Goals

- For drugs that address an unmet medical need in the treatment of a serious or life-threatening condition
- Intended to help ensure that drugs for these conditions are approved & available to patients as soon as it can be concluded that the therapies' benefits justify their risks
- Allow for earlier attention to drugs that have promise in treating such conditions
  - Early consultation with FDA

FDA Expedited Programs Guidance

- Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (2014)
  - Single resource for information on FDA's policies & procedures for four expedited programs
  - Describes threshold criteria applicable to concluding that a drug is a candidate for an expedited development and review program

FDA Expedited Programs



Breakthrough Therapy Designation (BTD)

- Qualifying criteria
- Features
- Breakthrough vs. Fast Track

BTD: Qualifying Criteria

- A drug that
  - Is intended to treat a serious condition ***AND***
  - Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies on one or more clinically significant endpoints

BTD: Qualifying Criteria

❖ Serious Condition

- "*condition*" : A disease or illness
- Including life-threatening conditions
- A clinical judgment, based on the condition's impact on factors, such as:
  - Survival
  - Day-to-day function, ***OR***
  - The likelihood that the condition, if left untreated, will progress from a less severe condition to a more serious one

BTD: Qualifying Criteria

- **Intended to have an effect on a serious condition or a serious aspect of a condition**
  - A direct effect on a serious manifestation or symptom of a condition
  - Other intended effects, such as
    - A product intended to improve or prevent a serious treatment-related side effect
    - A product intended to prevent a serious condition or reduce the likelihood that the condition will progress to a more serious condition or a more advanced stage of disease

BTD Qualifying Criteria

- Preliminary clinical evidence of substantial improvement over available therapy on one or more clinically significant endpoints
  - Is approved or licensed in the United States for the same indication, *AND*
  - Is relevant to current US standard of care (SOC) for the indication

BTD Qualifying Criteria

- **Preliminary clinical evidence**
  - Not sufficient (quality and/or quantity) to establish safety and effectiveness for purposes of approval
  - Generally derived from Phase 1 or 2 trials
  - Should involve a sufficient number of subjects to be considered credible
  - Ideally derived from a study comparing the drug to an available therapy (or placebo, if no available therapy), or from a study comparing the drug + SOC to the SOC alone
  - Single-arm studies comparing the study subjects' clinical course with well-documented historical experience, if the magnitude of difference is large

BTD Qualifying Criteria

- Substantial improvement
  - A matter of judgment
  - Depends on:
    - The magnitude of the drug's effect on a clinically significant endpoint (including duration of the effect) **AND**
    - The importance of the observed effect to the treatment of the serious condition or serious aspect of the condition

BTD Qualifying Criteria

- Approaches to demonstrate substantial improvement
  - Direct comparison of the drug to available therapy shows a much greater response
  - If there is no available therapy, the drug shows a clinically meaningful effect on an important outcome when compared to placebo
  - The drug plus available therapy result in a much greater response compared to available therapy alone
  - The drug reverses or inhibits disease progression, in contrast to available therapy that provides only symptomatic improvement
  - The drug has an important safety advantage compared with available therapy, and has similar efficacy

BTD Qualifying Criteria

- Clinically significant endpoint
  - An endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease.
  - An endpoint that suggests an effect on IMM or serious symptoms, including:
    - An effect on an established surrogate endpoint that typically would be used to support traditional approval
    - An effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)
    - A significantly improved safety profile compared with available therapy (e.g., less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy

Benefits / Features of Granted BTD

- All benefits of Fast Track designation
  - FDA takes actions to expedite development and review
  - Eligible for rolling review of NDA or BLA (submission and review of portions of an application before submission of the complete application)
- Intensive guidance on efficient drug development during IND, beginning as early as Phase 1
- Organizational commitment involving FDA senior managers

FTD vs BTD: Similarities

- Nature of programs: Designation
- Timeline for FDA response: Within 60 calendar days
- Intend to treat serious condition
- Benefits: FDA's Actions to expedite development and review
  - Frequent interactions with the review team
  - May be eligible for priority review if supported by clinical data at the time of BLA / NDA submission
  - May qualify for rolling review
- Designation may be rescinded if no longer meeting the qualifying criteria

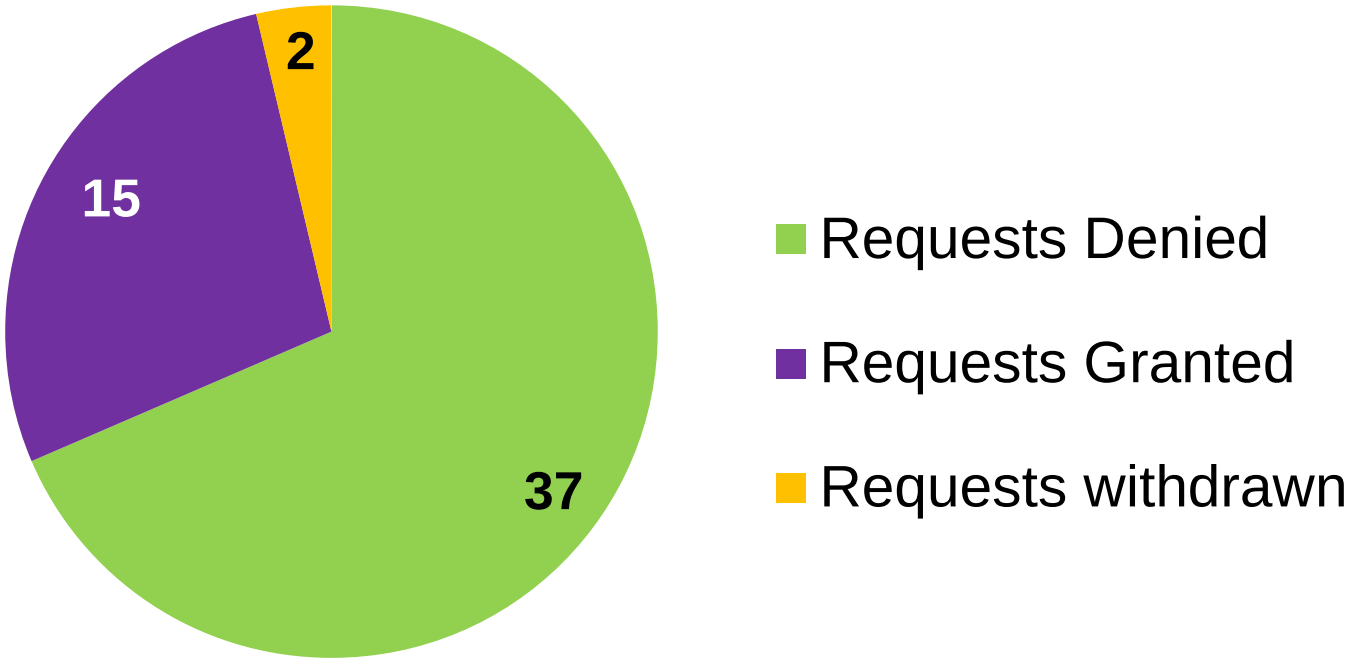
FTD vs BTD: Differences

		FTD	BTD
Requirements for Designation	**Source of Data**	Non-clinical or clinical data	Preliminary clinical evidence
	Strength of Evidence	The potential to address unmet medical need	Substantial improvement on a clinically significant endpoint(s) over available therapy
	Development Plan	Specify how this potential will be evaluated in the drug development program (e.g., a description of the Phase 3 trials)	Not required
Benefits		FDA takes actions to expedite development and review	• All benefits of FTD • Intensive guidance on an efficient drug development program • Involvement of FDA senior managers

Breakthrough Designation Experience in CBER OTAT

BT Requests in OCTGT (12/2012 – 06/2016)

- **Total Requests: 54**
  - 47 products
  - 7 Repeated requests



BTDs by Product Types

Products	Requested BTDs	Granted BTDs
Gene	26	12
Cellular	16	1
Tumor Vaccine	4	1
Oncolytic Virus	1	1

BTDs by Indications

Indications	Requests	Granted
Oncology	**33**	**9**
Non-oncology	**21**	**6**
Hematology	4	3
Ophthalmology	3	1
Cardiology	3	1
Neurology	4	1
Transplantation	2	0
Nephrology, Peripheral Vascular, Burn, Hepatology	1 in each specialty	0

Common Reasons for BTD Denial

- Evidence is too preliminary (quantity and/or quality) to be considered reliable
  - Small sample size
  - Lack of appropriate control
  - Post-hoc analyses of failed studies that identify a subset that may benefit
- Improvement over available therapy does not appear to be "substantial"
- Modification of product

What OTAT Has Learned

- BTD decisions are complex.
  - There is no one-size-fits-all characterization of a BT product.
- The reliability and persuasiveness of clinical evidence is critical to making the BTD decision.
  - There is not a definitive threshold for substantial improvement.

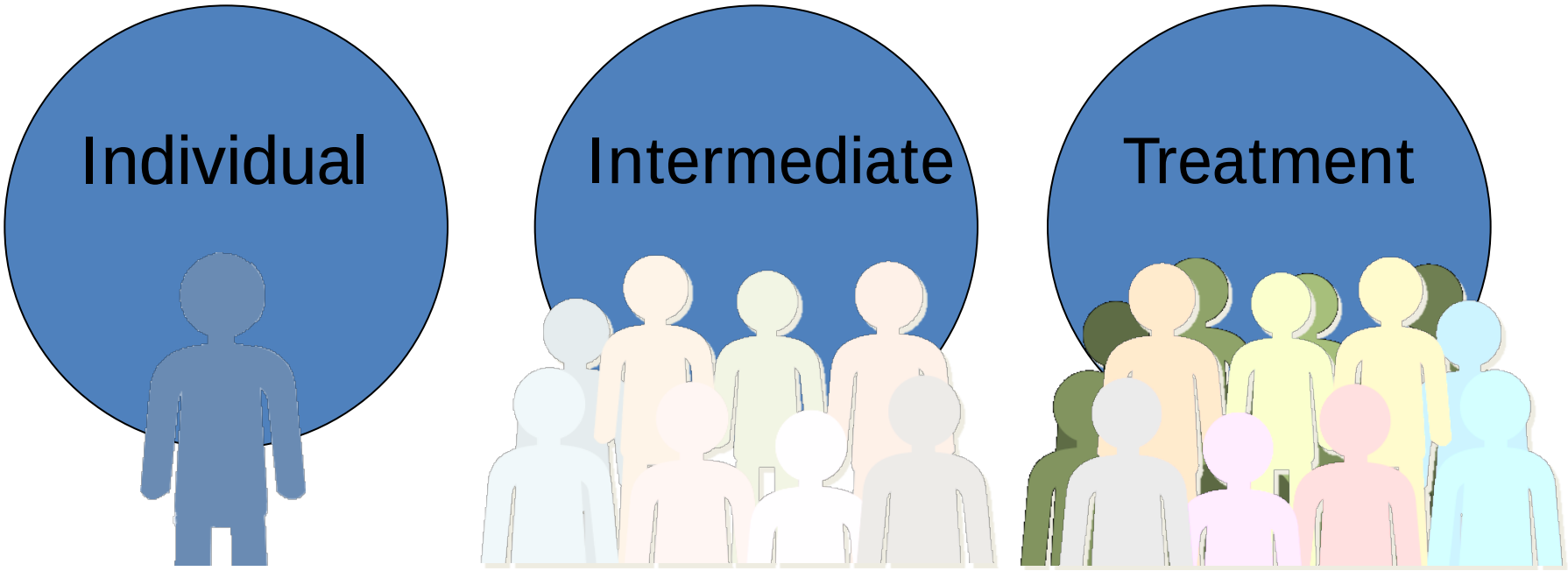
Expanded Access to Investigational Drugs

What is Expanded Access?

- Use of an investigational drug to treat a patient with a serious disease who has no other satisfactory options
- Intent is TREATMENT; also called "Compassionate Use"
- Contrast with using an investigational drug in a clinical trial, where the primary intent is RESEARCH

Types of Expanded Access Programs (EAPs)

There are three types of EAPs defined in the code of federal regulations:



Requirements for 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 (risks are not unreasonable in the context of the disease / condition being treated)
- Providing drug will not compromise product development

Human Subject Protections Apply to <u>All</u> EAPs

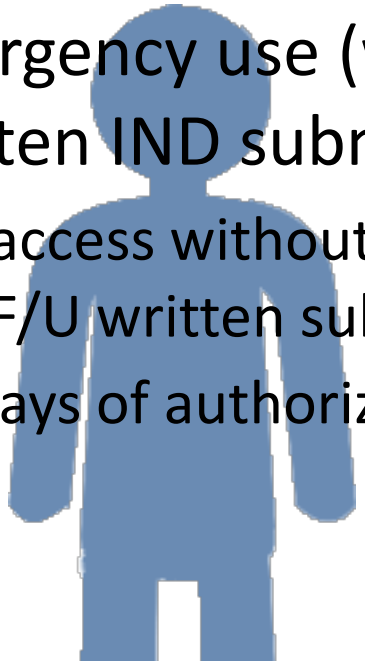
Drugs in EAPs are *investigational drugs*, and they are subject to the following requirements from 21 CFR:

- Part 50 - Protection of Human Subjects
  (informed consent)
- Part 56 - Institutional Review Board
- Part 312 - including Clinical Holds based on safety and reporting requirements (adverse event reports, annual reports)

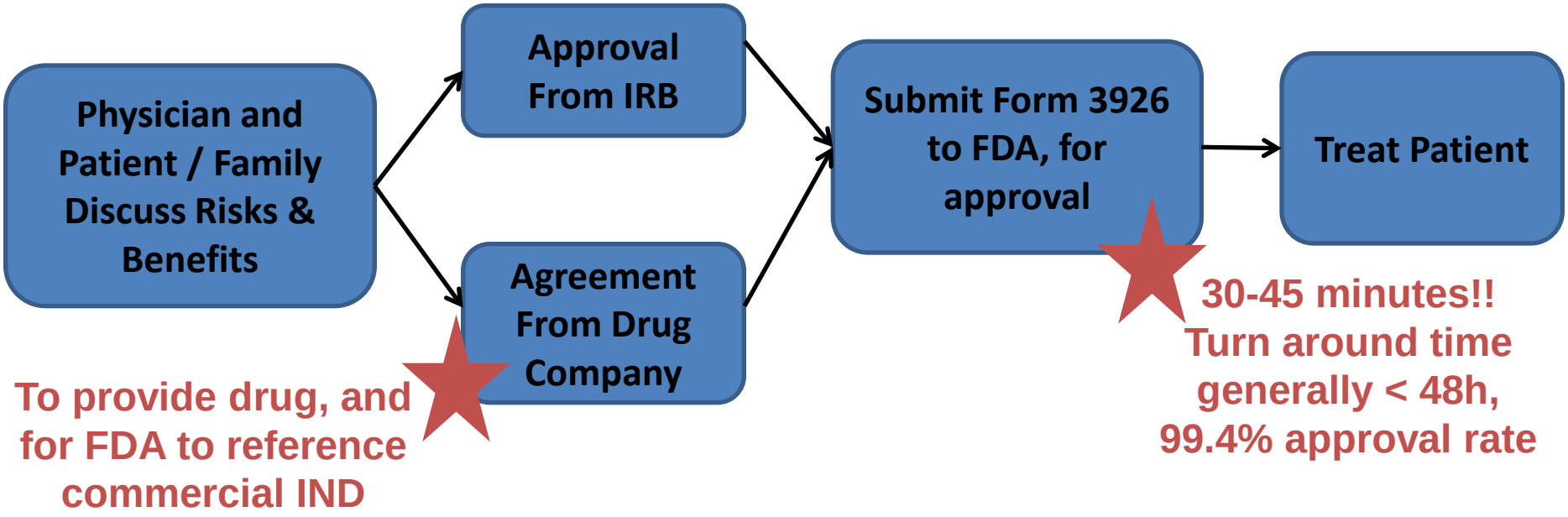
Individual Patient EAPs

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 (when there is not time to make a written IND submission)
  - FDA may authorize access without submission, with very quick turn-around (F/U written submission required within 15 working days of authorization)



Obtaining a Single Patient IND



- **Form 3926 is 2 pages and includes**:
  - Brief medical history and rationale for trying drug
  - Proposed treatment plan with safety /efficacy monitoring
- **Also submit:**
  - Letter of authorization from sponsor
  - Investigator qualification statement / form 1571

Intermediate Size Population

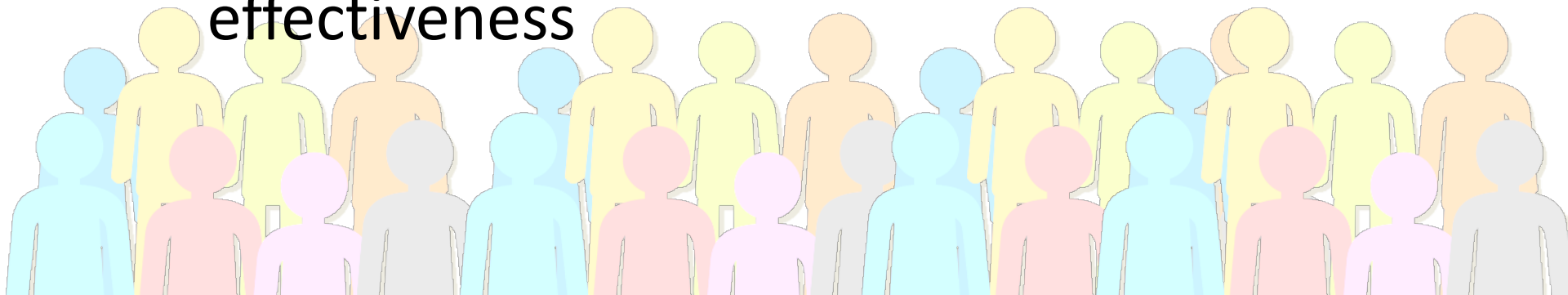
21 CFR 312.315

- Intended for situations where multiple patients with the same condition might benefit from a particular investigational product
- No set numerical parameters – meant to be practical
  - more than a few, and less than a lot

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 approval
- Sufficient evidence of safety & effectiveness



Cautions for EAP Use

- Risk has not been established for investigational drug
  - Confidence in safety more important than consideration of efficacy
  - For a child with an immediate life-threatening condition, evidence burden is low
- Potential benefit is often overestimated
  - Drug given under EAP with intention to provide benefit
  - Anecdotal evidence of even overwhelming efficacy may hold up only in a very small subset of patients, but have toxicities that increase suffering and/or hasten death in everyone else
- Potential for negative impact on clinical development plan

Benefits and Barriers

BENEFITS:

- Provide access and hope to patients with no alternatives, willing to accept potentially greater risk
- May provide patients with a measure of autonomy over their own health care decisions

- Can be a foothold into marketplace for sponsors

BARRIERS:

- Paperwork/time (New! Form 3926)
- Manufacturing (drug availability)
- Fear that adverse events may disrupt clinical product development

CBER OTAT DCEPT
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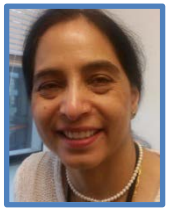
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- OCTGT Learn Webinar Series:
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm