FDA 101: CLINICAL REGULATORY CONSIDERATIONS AND APPROVAL PATHWAYS FOR (CAR-T) CELL & GENE THERAPIES

Kristin Baird, MD
Division of Clinical Evaluation, Pharmacology and Toxicology
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

CAR-TCR Summit 2017 Boston, MA
Tuesday September 5, 2017

Disclosures

I have no financial relationships to disclose.

Outline

- FDA: Basics and overview
- IND Process
- Regulatory considerations for clinical development of Cell Therapies / CAR T Therapy
- Basis for US regulatory approvals
  - Expedited Programs
- Expanded Access Programs
- Post Marketing Risk Evaluation & Mitigation Strategies (REMS)
- Questions / Discussion
- Resources and Contact Information

Outline

- **FDA: Basics and overview**
- IND Process
- Regulatory considerations for clinical development of Cell Therapies / CAR T Therapy
- Basis for US regulatory approvals
  - Expedited Programs
- Expanded Access Programs
- Post Marketing Risk Evaluation & Mitigation Strategies (REMS)
- Questions / Discussion
- Resources and Contact Information

FDA Regulation of Oncology Products

CDER

Office of Hematology and Oncology Drug Products (OHOP)

- Drugs (small molecules)
- Biologics
  - Monoclonal Antibodies
  - Therapeutic Proteins
  - Cytokines

CBER

Office of Tissues and Advanced Therapies (OTAT)

- Cell therapies
- Gene Therapies
- Oncolytic viruses
- Therapeutic vaccines and immunotherapies

CDRH

Office of In Vitro Diagnostics and Radiological Health (OIR)

- Companion Diagnostics

Oncology Center of Excellence (OCE)

What do all of those medical officers do?

- Work with an interdisciplinary team to provide regulatory oversight of investigational and approved cancer therapies
  - Review investigational new drug applications (INDs)
  - Provide advice regarding clinical development of new cancer therapies to sponsors
  - Analyze clinical data for New Drug Applications (NDAs) and Biologics License Applications (BLAs) and provide clinical risk and benefit assessments for use in approval decisions
  - Oversee postmarketing safety of approved cancer therapies
- Stakeholder outreach
- AND MORE…

Reviews require multidisciplinary input

Pharmacology & Toxicology

Statistics

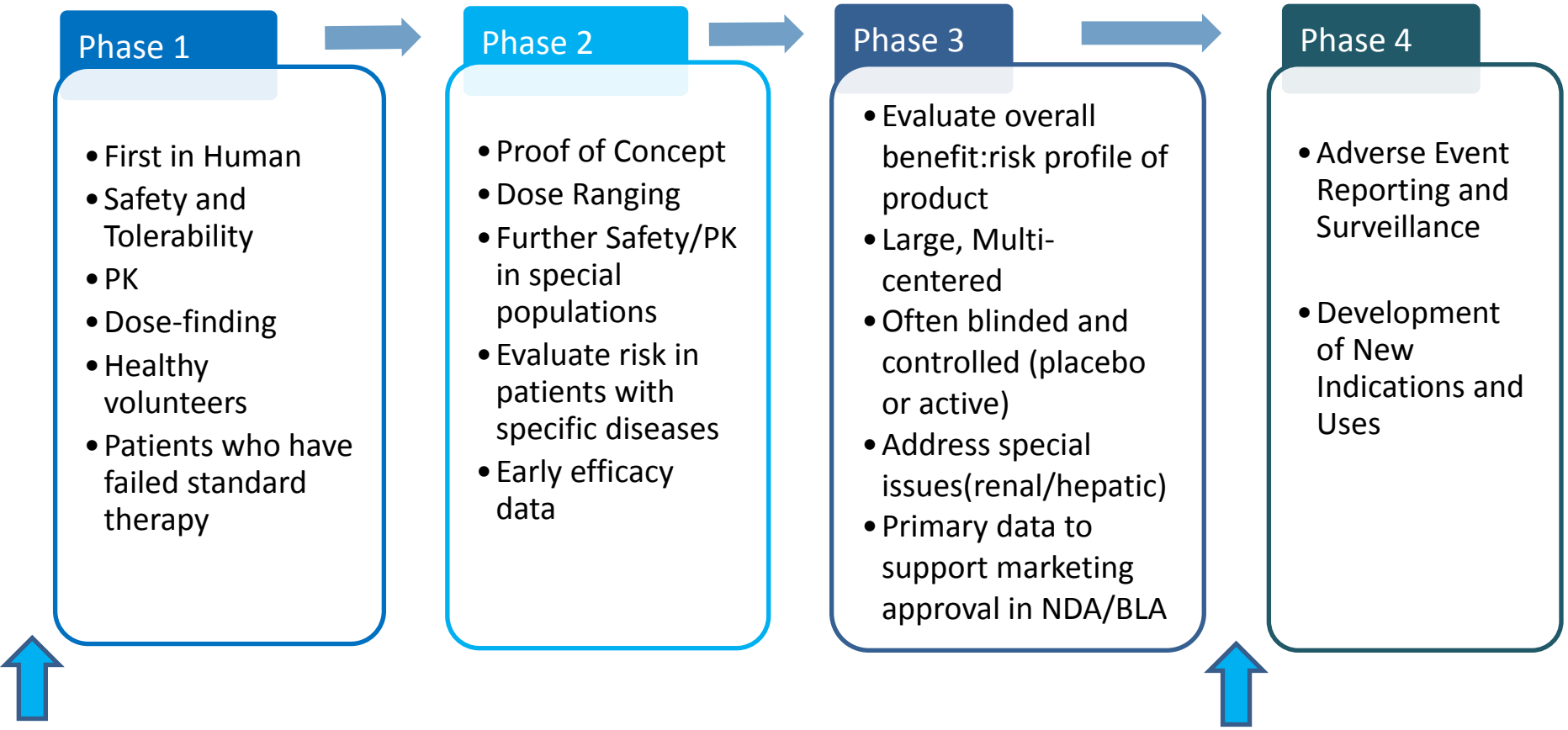
Clinical Pharmacology & Biopharmaceutics

Regulatory
Project
Management

Clinical

Product Quality (CMC)

Traditional Drug Development Progression

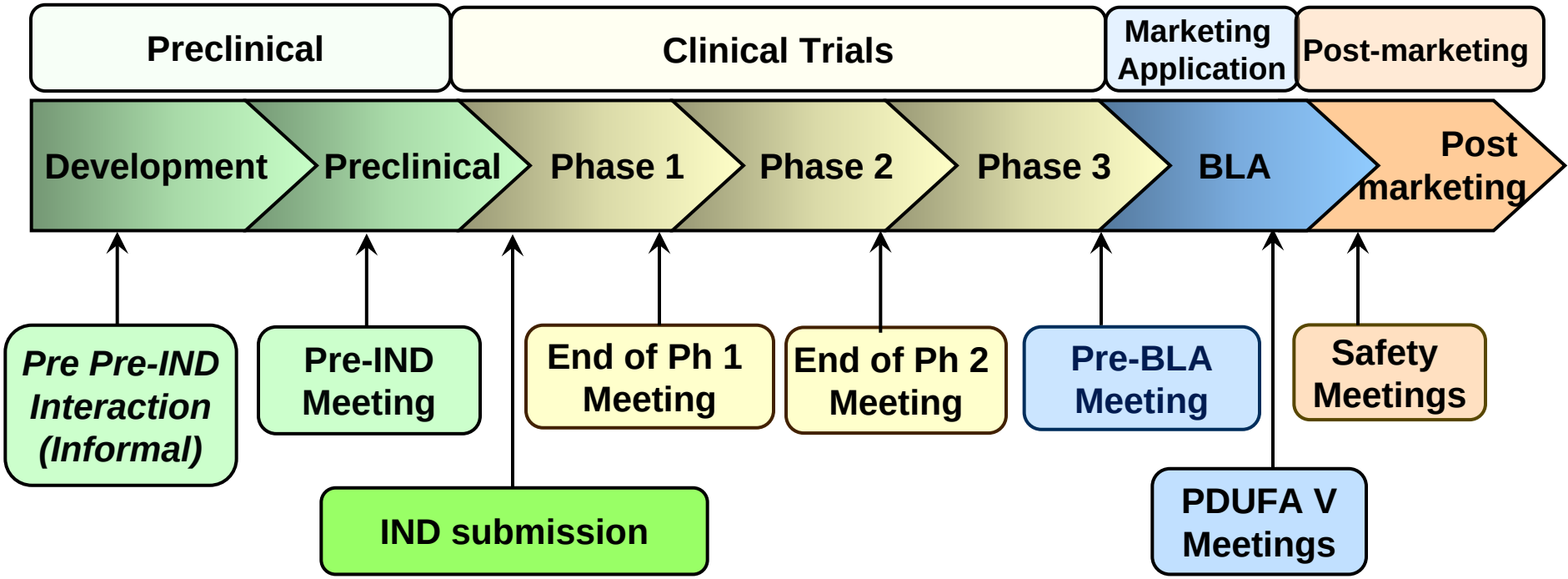


IND deemed safe to proceed

But distinctions between Phase 1, Phase 2, and Phase 3 trials are often blurred in today's environment

NDA/BLA approval

When to Approach FDA for Product Development Discussions



https://www.fda.gov/downloads/drugs/guidances/ucm153222.pdf

Outline

- FDA: Basics and overview
- **IND Process**
- **Regulatory considerations for clinical development of Cell Therapies / CAR T Therapy**
- Basis for US regulatory approvals
  - Expedited Programs
- Expanded Access Programs
- Post Marketing Risk Evaluation & Mitigation Strategies (REMS)
- Questions / Discussion
- Resources and Contact Information

What happens after you submit your IND to FDA?

The 30-day IND safety review

Regulatory Decision: Hold or Proceed

- FDA determines whether the following criteria are met in order for the IND to be considered "safe to proceed"
  - The study does not pose an unreasonable or significant risk of illness or injury
  - The study is adequately designed to meet its stated objectives

https://www.fda.gov/RegulatoryInformation/Guidances/ucm240323.htm

For Safety, Context is Important

- Who are the subjects?
  - Healthy volunteers
  - Patients with chronic disease
  - Patients with life-threatening cancer
  - Patients with potentially curable cancer
- Is there prior clinical experience with the drug/product?
  - Is this first-in-human, first-in-class?

https://www.fda.gov/RegulatoryInformation/Guidances/ucm240323.htm

Eligibility Criteria

FDA considers

- Available therapies
- Seriousness of the disease
- Known toxicities and / or toxicity in animals
- Special populations (e.g., age, pregnancy)

Patient Monitoring

- Provide a calendar of events and ensure consistency with protocol and consent form
- Animal studies may be informative, e.g.:
  - ECGs if QTc concern
  - MUGA if cardiomyopathy is a concern
  - PFTs if pneumonitis is a concern
- Consider half life of drug
  - mAbs may require longer-term monitoring
- FIH studies may need frequent monitoring and labs due to unknown toxicities

Dosing / Dose Escalation

- Is the dose safe?
  - Based on toxicology data or first-in-humans study
  - Prior human experience?
- In a phase 1 study, what is the *next* dose?
  - Generally consider
    - Half-log increments for biological drugs (log is generally aggressive)
    - Percentiles for small molecules (100% is generally aggressive)
- Intrapatient dose escalation typically not allowed for biologics
- Staggering of treatment between subjects / dose cohorts

Dose Limiting Toxicity

- Prevents excess toxicity during dose escalation
- Context important
  - Healthy volunteer versus late stage cancer
  - Monitoring as outpatient versus hospital or ICU
- Ensure *clear* definition
  - e.g., for cytotoxic drugs: Grade 4 (life-threatening) hematological toxicity or ≥ Grade 3 non-hematological toxicity (except alopecia or Grade 3 nausea, vomiting, or diarrhea lasting less than 48 hours).
- Provide justification for non-standard rules
- For continuous dosing or long half-life: consider extension of DLT period of observation or incorporation of additional rules
- Early dose-escalation studies frequently find a recommended Phase 2 dose (RP2D) that is overly toxic (just by chance)

Study Stopping Rules

- Temporary pause in enrollment and treatment of additional subjects to prevent excess subjects from experiencing toxicity
  - Death
  - Increased incidence of expected toxicity
- Dose escalation studies usually consider DLTs
  - 3+3 or rolling-6 design
  - Bayesian or Continuous Reassessment Method (CRM) design
  - Other
- Recommend stopping rules for safety after dose-escalation phases
  - Can be based on severe/serious toxicity
  - Higher than expected cumulative incidence of a known toxicity
  - DSMB oversight may be sufficient

Dose Modification / Interruption

- Ensure clear and internally consistent rules
- Ensure rules are reasonable (e.g., interrupt /delay for life threatening cardiomyopathy, infection, etc.)
- Dose reduction may be appropriate following resolution of toxicity
  - For severe / life threatening diseases
  - For dose-related toxicities (e.g., neutropenia with a cytotoxic antibody)

Informed Consent Process

- Be truthful, clear, and consistent
- Do not “oversell” benefits
- Do not minimize risks
- Ensure there is a detailed discussion of available alternative therapies

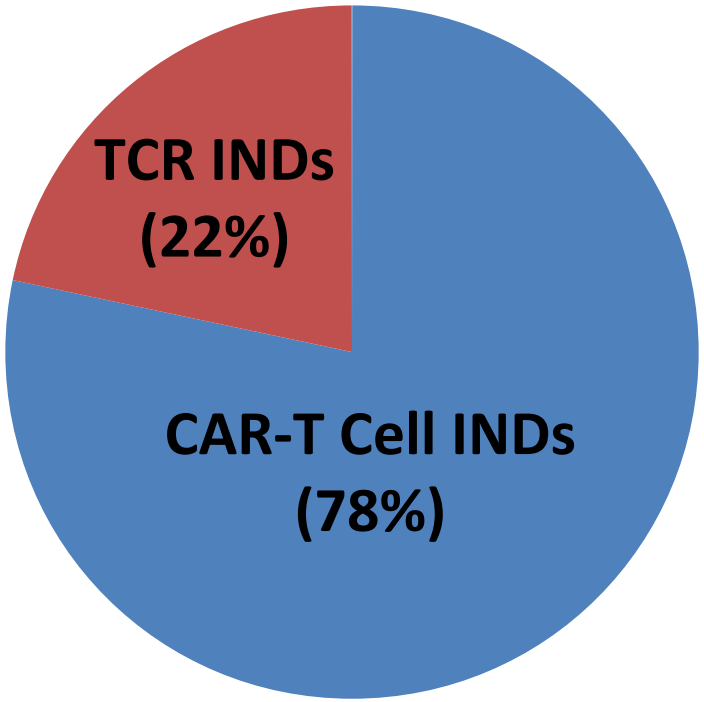
IND Rules of Thumb

- **DO**
  - Provide justification for dose
  - Provide adequate monitoring plan
  - Expect comments from FDA that need a quick turn-around (~2-7 days)
  - Consider requesting a pre-IND meeting if trial / product is complex
- **DON'T**
  - Go "off the grid" after submitting an IND (without providing a contact who can be easily reached)
  - Copy/Paste irrelevant or incorrect information from other protocols

Outline

- FDA: Basics and overview
- IND Process
- **Regulatory considerations for clinical development of Cell Therapies / CAR T Therapy**
- Basis for US regulatory approvals
  - Expedited Programs
- Expanded Access Programs
- Post Marketing Risk Evaluation & Mitigation Strategies (REMS)
- Questions / Discussion
- Resources and Contact Information

TCR and CAR-T cell products under CBER review

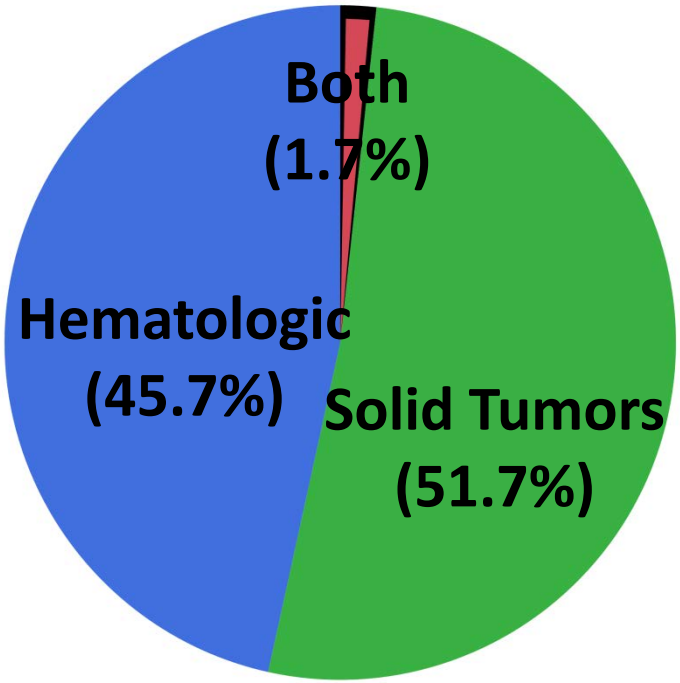


A total of ~120 TCR / CAR-T Cell INDs regulated by OTAT/CBER

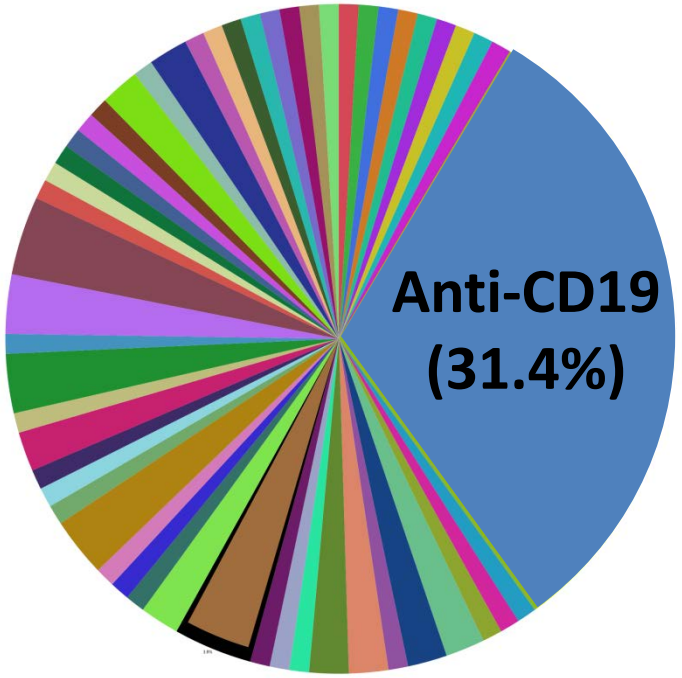
As of August 2016

TCR and CAR-T cell products under CBER review

TCR / CAR-T Cell INDs for Cancer Therapy



CAR–T Cell INDs



As of August 2016

Regulatory Considerations

Patient Population - 1

Conventional	CAR-T
• Testing the efficacy and safety in a defined patient population with a given malignant type, e.g., CLL • Move to another stage of the same tumor type or different disease	• Targeting a specific antigen regardless of tumor type • May consider enrolling patients with different tumor histology as long as the tumors express the antigen that the CAR-T cells target

Regulatory Considerations

Patient Population - 2

- Challenges in enrolling patients with different tumor histology
  - Prior treatment requirement
  - Patient performance and organ function
  - Disease stage or severity
    - Risk-benefit considerations – most severely affected should not be the default choice
    - Lack of other treatment options
- Companion diagnostic for target identification
- Enrolling pediatric subjects / conducting pediatric studies

Regulatory Considerations

Treatment Plan

- Dose Selection
  - Role of preclinical data (allometric scaling for CGT products may be less precise than for small molecules)
  - Previous clinical experience with related products might be helpful
- Dose Description
  - Products mixture of various cell types
  - Variable gene transduction rates
  - Variable *in vivo* expansion
- Repeat administration
  - Staggering doses

Regulatory Considerations

Trail Design / Efficacy Endpoint

- Single-arm trial
  - Tumor response rate
  - Magnitude of the treatment effect
  - Duration
- Randomized controlled trial
  - Time to event (overall survival, progression-free survival)
  - Feasibility
  - Appropriate control
- Impact of concurrent treatments
  - Lymphodepletion
  - Chemotherapy tailored to patients with different tumor types
- Other factors confounding study results

Regulatory Considerations

Toxicities – 1

- Infusion reactions
- Cytokine release syndrome
  - Specify criteria used (CTCAE not sufficient)
  - Importance of monitoring cytokine levels
- Neurotoxicity
  - Type
  - Evaluations
    - Baseline
    - During Toxicity
    - End of treatment
- Other (cytopenias, cardiac)
- Optimal management for toxicities
  - Consideration for specific algorithms

Regulatory Considerations

Toxicities – 2

- On-target / off-tumor effects
- Off-target effects
- Long-Term safety concerns
  - Monitoring cell persistence over time
- Optimal management for toxicities
  - Short-term vs. long-term

Regulatory Considerations

Manufacturing and Quality Control

- Dose of transduced CAR-T cells
- Reproducibility and consistency
- Standardization
- Production Scale-up vs Scale-Out
- Issues related to Product Comparability
- Long-Term Follow-Up Requirements
- Co-development of Companion Diagnostics

Outline

- FDA: Basics and overview
- IND Process
- Regulatory considerations for clinical development of Cell Therapies / CAR T Therapy
- **Basis for US regulatory approvals**
  - **Expedited Programs**
- Expanded Access Programs
- Post Marketing Risk Evaluation & Mitigation Strategies (REMS)
- Questions / Discussion
- Resources and Contact Information

Regulatory Standard for FDA Approval of New Treatments

- Requires substantial evidence of effectiveness derived from adequate and well controlled investigation (1962 amendment to Food, Drug and Cosmetic act)
  - Clinical benefit demonstrated by showing an improvement in survival or quality of life, or an established surrogate for either (regular approval)
  - "An effect on a surrogate endpoint that is reasonably likely… to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity." (accelerated approval)

Kefauver Harris Amendment –FD&C Act § 505(d), 21 USC 355(d) (1962)
See Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998

Requirements for BLA/NDA Approval

- Substantial evidence of effectiveness with acceptable safety in adequate and well-controlled investigations
- FDA examines the evidence in the context of the disease state, available therapy, study design, endpoints selected, and strength of the evidence
- Ability to generate product labeling that:
  - Defines an appropriate patient population
  - Provides adequate information to enable safe and effective use

Federal Food, Drug, and Cosmetic Act, Section 505

Expedited Development Programs

- Fast Track (FT)*
- Breakthrough Therapy (BT)*
- Accelerated Approval (AA)
- Priority Review (PR)
- Regenerative Medicine Advanced Therapy (RMAT) Designation*

* FT, BT, and RMAT may be rescinded if the product ceases to qualify under these categories

Comparison of Expedited Programs

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Criteria	-**Serious condition** AND -Nonclinical or clinical data demonstrate the *potential* to address unmet medical need Note: Information to demonstrate *potential* depends upon stage of development at which FT is requested	-**Serious condition** AND -Preliminary clinical evidence indicates that the drug may demonstrate **substantial improvement over available therapy** on one or more clinically significant endpoints	-**Serious condition** AND - Meaningful advantage over available therapies - Demonstrates an **effect on** either: a **surrogate endpoint or an intermediate clinical endpoint**	-**Serious condition** AND -Demonstrates potential to be a significant **improvement in safety or effectiveness**

https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

Comparison of Expedited Programs

	Fast Track (FT)	Breakthrough Therapy (BT)	Accelerated Approval (AA)	Priority Review (PR)
Features	**Frequent meetings** Frequent written communication Eligibility for *: ✓ **Accelerated Approval** ✓ **Priority Review** **Rolling Review** *if relevant criteria are met	**All of FT Features +** ✓ **Intensive guidance** on an efficient drug development program, beginning as early as Phase 1 ✓ Organizational commitment **involving senior managers**	Approval based on surrogate or intermediate clinical endpoints ✓ **Save valuable time** in the drug approval process. ✓ **Reduce waiting period to obtain clinically meaningful benefit.**	✓ **Short Review Clock** ✓ **FDA will Take action on an application within 6 months** (compared to 10 months under standard review).

https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

Regenerative Medicine Advanced Therapy (RMAT) Designation

- 21st Century Cures Act: Title III, Sections 3033-3036
  - Section 3033: Accelerated Approval for Regenerative Advanced Therapies
  - Creates program for designation as a regenerative advanced therapy
- A drug is eligible for designation if:
  - It is a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, gene modified cell therapy, or any combination product using such therapies or products
  - The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and
  - Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition

https://blogs.fda.gov/fdavoice/index.php/2017/03/this-is-not-a-test-rmat-designation-goes-live/
https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm

Regenerative Medicine Advanced Therapy (RMAT) Designation

- Benefits of RMAT Designation
  - Early interactions with FDA to discuss any potential surrogate or intermediate endpoints to support accelerated approval
  - Interactions as specified for products granted breakthrough therapy designation
  - May be eligible for priority review
  - May be eligible for accelerated approval, as agreed upon during product development, based on:
  - Surrogate or intermediate endpoints reasonable likely to predict long-term clinical benefit, or
  - Reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate

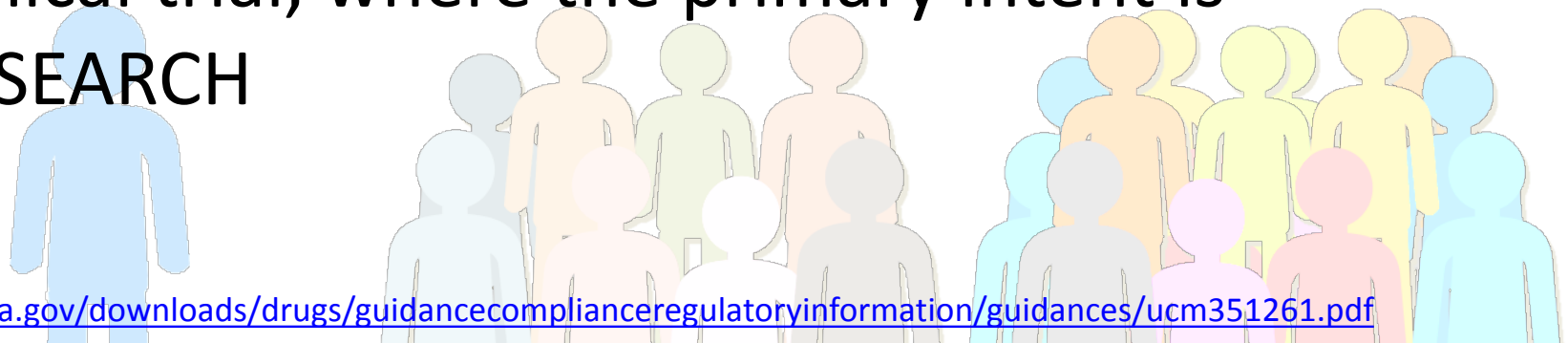
https://blogs.fda.gov/fdavoice/index.php/2017/03/this-is-not-a-test-rmat-designation-goes-live/
https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm

Outline

- FDA: Basics and overview
- IND Process
- Regulatory considerations for clinical development of Cell Therapies / CAR T Therapy
- Basis for US regulatory approvals
  - Expedited Programs
- **Expanded Access Programs**
- Post Marketing Risk Evaluation & Mitigation Strategies (REMS)
- Questions / Discussion
- Resources and Contact Information

What is Expanded Access?

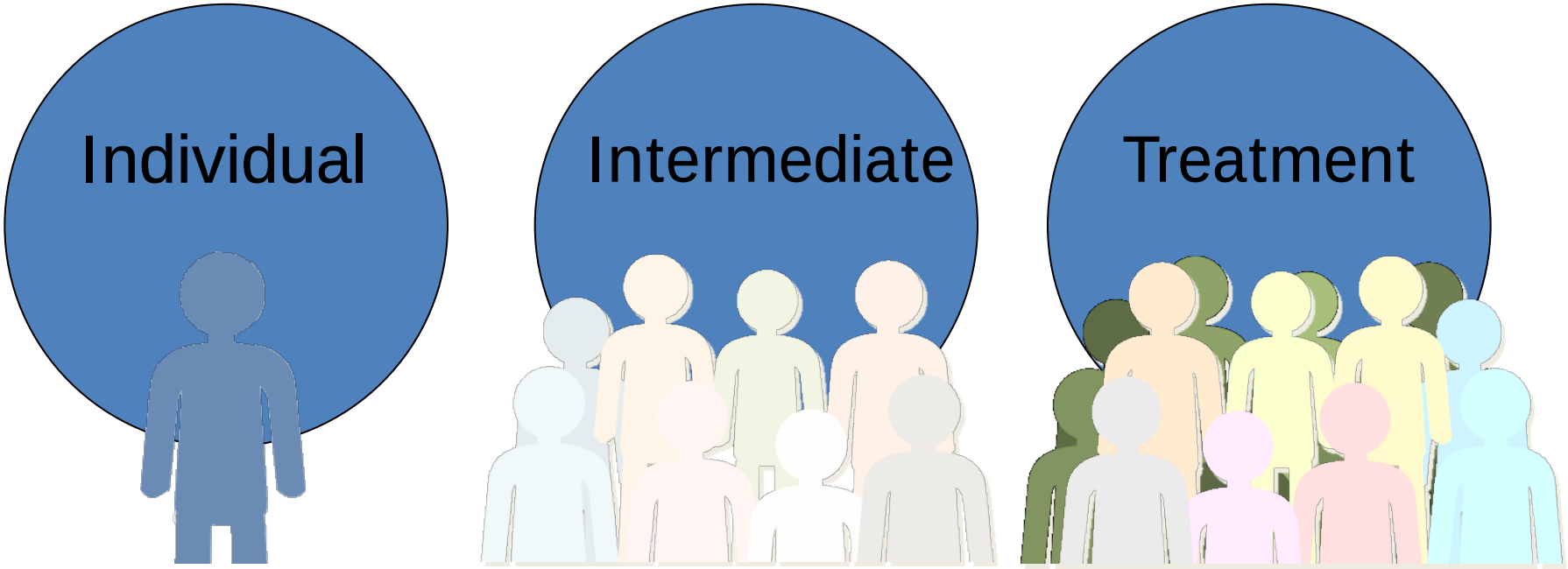
- Use of an investigational drug to treat a patient with a serious disease who has no other satisfactory options
- Intent is TREATMENT; also called "Compassionate Use"
- Contrast with using an investigational drug in a clinical trial, where the primary intent is RESEARCH



https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

Types of Expanded Access Programs (EAPs)

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



https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

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

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

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

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

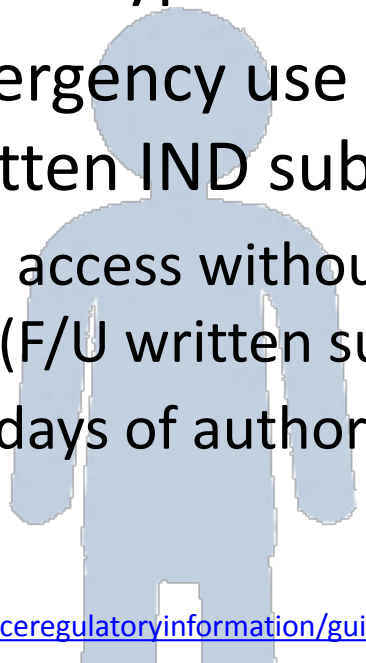
- Part 50 - Protection of Human Subjects (informed consent)
- Part 56 - Institutional Review Board
- Part 312 - including Clinical Holds based on safety and reporting requirements (adverse event reports, annual reports)

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

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)



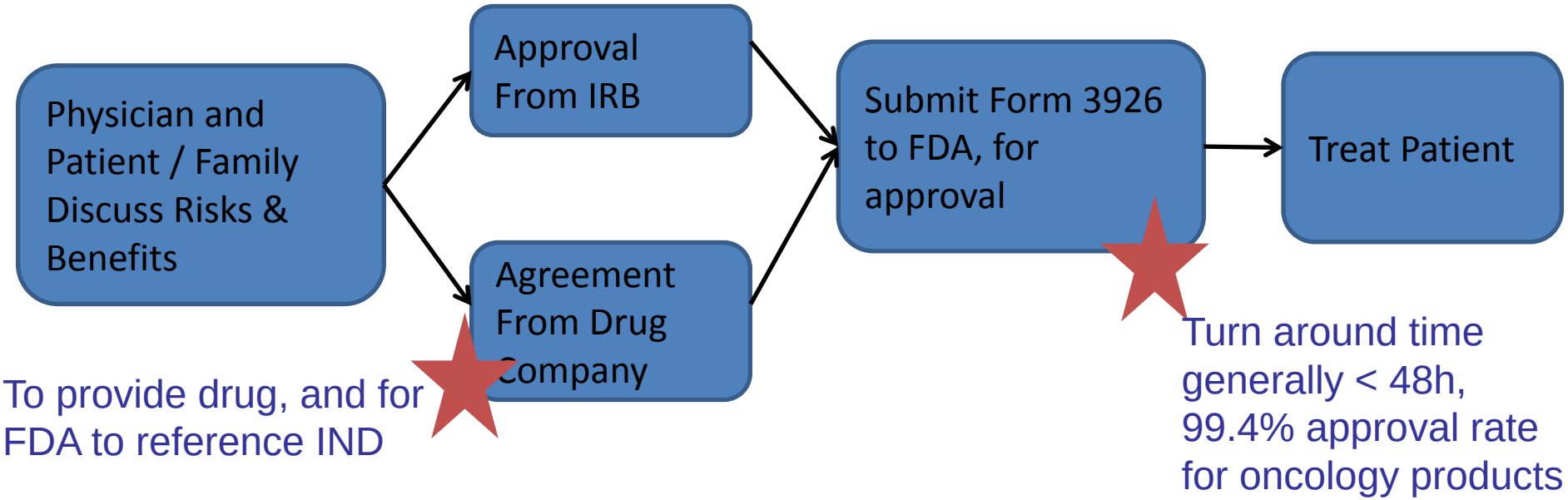
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

Individual Patient Expanded Access

- Usually multiply-relapsed, refractory patients
- Reasons for requesting expanded access may include:
  - Promising evidence of activity with a similar molecular target or histology
  - Previous benefit from a clinical trial
  - Ineligible for clinical trial, but potential benefit is thought to outweigh potential risk
  - Clinical trial is closed to accrual
  - Drug is not currently being developed

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

Obtaining a Single Patient IND

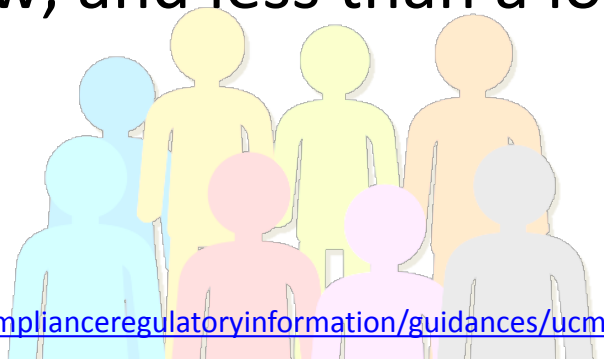


- Form 3926 is 2 pages and includes:
  - Brief medical history and rationale for trying drug
  - Proposed treatment plan with safety /efficacy monitoring
- Also submit:
  - Letter of authorization from sponsor
  - Investigator qualification statement / Form 1571

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

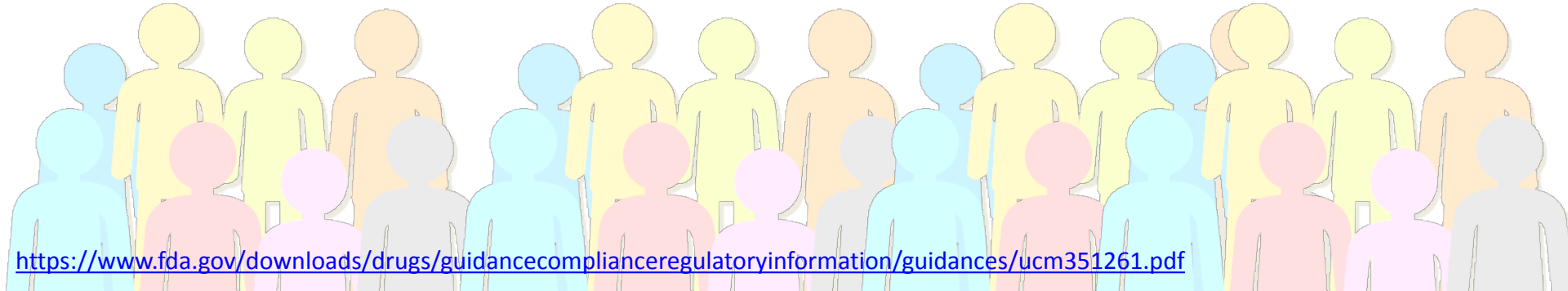


https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

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



https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf

Outline

- FDA: Basics and overview
- IND Process
- Regulatory considerations for clinical development of Cell Therapies / CAR T Therapy
- Basis for US regulatory approvals
  - Expedited Programs
- Expanded Access Programs
- **Post Marketing Risk Evaluation & Mitigation Strategies (REMS)**
- Questions / Discussion
- Resources and Contact Information

Risk Evaluation & Mitigation Strategies (REMS)

REMS are required risk management plans that use risk minimization strategies beyond the professional labeling to ensure that the benefits of certain prescription drugs outweigh their risks.

FDA REMS web site http://www.fda.gov/REMS

Risk Evaluation & Mitigation Strategies (REMS)

- Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks
- Pursuant to 505-1(f)(1), Elements To Assure Safe Use (ETASU) may be required if the drug has been shown to be effective, but is associated with a serious adverse event and can be approved only if, or would be withdrawn unless, such elements are required as part of a strategy to mitigate the specific serious risk(s) listed in the labeling of the product.
  - ETASU under section 505-1(f)(3)(B): health care settings that dispense the drug are specially certified

Examples of the Types of Risk REMS Requirements Aim to Mitigate*

Risk Example	Possible REMS Action
Serious infection	Patient education of initial warning signs of infection prior to prescribing
Severe allergic reaction	Healthcare professional must be certified to administer the product
Liver damage	Liver function monitoring while the patient is taking the drug
Severe birth defects	Negative pregnancy test prior to dispensing each prescription

* A list of approved REMS is available at:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

REMS : Key Points

- FDA can require a REMS if the agency determines that safety measures are needed beyond the professional labeling to ensure that a drug's benefits outweigh its risks
- Drug Sponsors develop REMS programs
- FDA reviews and approves them
- FDA can require a REMS before or after a drug is approved
- REMS can be required for a single drug or a class of drugs
- Healthcare professionals and distributors may need to follow specific safety procedures prior to prescribing, shipping, or dispensing the drug
- Each REMS has specific safety measures unique to the safety risks associated with a particular drug or class of drugs (i.e., no two REMS are exactly alike)

FDA REMS web site http://www.fda.gov/REMS

REMS Elements

- All REMS required for an NDA or BLA must contain a timetable for submission of assessments of the REMS
- A REMS for an NDA or BLA may also contain any of the following elements:
  - Medication Guide or Patient Package Insert
  - Communication Plan
  - Elements To Assure Safe Use (ETASU)
  - Implementation System

FDA REMS web site http://www.fda.gov/REMS

REMS Elements: Medication Guides

- Not usually required as part of a REMS unless the REMS includes ETASU
- Required to be dispensed with the drug
- Written in non-technical language
- Standardized format (font size, headers, etc.)
- Provided in *addition to* general information sheets (Consumer Medication Information or CMI)

FDA REMS web site http://www.fda.gov/REMS

REMS Element: Communication Plan

- A communication plan is developed by the drug's sponsor to support implementation of an element of the REMS, and can inform key audiences (health care providers) about the risks of the drug.
- This could include:
  - Sending letters to healthcare providers (e.g., Dear Healthcare Provider letters)
  - Disseminating information about the REMS to encourage implementation or to explain certain safety measures
  - Disseminating information through professional societies about any serious risks of the drug and any measures to assure safe use

A communication plan educates, informs, and raises awareness of risk.

REMS Elements: (ETASU) Elements to Assure Safe Use

ETASU are required medical interventions or other actions healthcare professionals need to execute prior to prescribing or dispensing the drug to the patient. Some actions may also be required in order for the patient to continue on treatment.

ETASU requirements are the most extensive elements of a REMS program.

FDA REMS web site http://www.fda.gov/REMS

REMS Elements: (ETASU) Elements to Assure Safe Use

ETASU requirements are intended to reduce a specific serious risk listed in the labeling of the drug.

Depending on the risk, a REMS may require any or all of the following:

- Prescribers have specific training/experience or special certifications
- Pharmacies, practitioners or healthcare settings that dispense the drug be specially certified
- Drug be dispensed only in certain healthcare settings (e.g., infusion settings, hospitals)
- Drug be dispensed with evidence of safe-use conditions such as laboratory test results
- Each patient using the drug be subject to monitoring
- Each patient using the drug be enrolled in a registry

REMS Elements: (ETASU) Elements to Assure Safe Use

FDA understands that ETASU should not unduly burden patients, healthcare professionals, or the healthcare system.

The following provisions help ensure REMS are as efficient as possible:

- ETASU requirements must be commensurate with the specific serious risk listed in the drug's labeling
- Cannot be unduly burdensome on patient access to the drug, especially those who have serious or life-threatening diseases and/or difficulty accessing healthcare, and
- To the extent practicable, ETASU must conform with other components for other drugs with similar serious risks and be designed to be compatible with established distribution, procurement, and dispensing systems for drugs.

REMS Elements: (ETASU) Implementation System

Implementation system: The drug's sponsor may be required to take reasonable steps to monitor and evaluate those in the healthcare system who are responsible for implementing ETASU measures, if certain ETASU are required.

Assessment Examples: Information Needed

- Survey data: healthcare professionals' understanding regarding the safe use of the drug as measured through surveys
- Summary of adverse events associated with the drug that the REMS was designed to address
- Prescriber compliance with certification and REMS requirements:
  - Completing training and enrollment procedures
  - Completing patient baseline form
  - Complying with discontinuation procedure
- Use data: what patients are getting the drug and under what conditions of use
- Number and percentages of patients who were monitored for potential serious adverse events during treatment with the drug

REMS Component: Timetable for Assessments

- All REMS for NDAs and BLAs must include a timetable for assessing the effectiveness of their safety measures
- Timetable for assessments must be at least by 18 months, 3 years, and in the 7th year after the REMS is approved
- Can be eliminated after 3 years

Assessment results may be used to modify the REMS, or even eliminate it, if the assessment shows changes are needed or that the REMS has met its goals

REMS

End Note: REMS help keep products on the market

Some drugs would not be able to be approved, or be able to stay on the market, unless a REMS with ETASU was required to ensure that their benefits outweigh their risks.

For more information:

FDA REMS web site
http://www.fda.gov/REMS

Outline

- FDA: Basics and overview
- IND Process
- Regulatory considerations for clinical development of Cell Therapies / CAR T Therapy
- Basis for US regulatory approvals
  - Expedited Programs
- Expanded Access Programs
- Post Marketing Risk Evaluation & Mitigation Strategies (REMS)
- **Questions / Discussion**
- Resources and Contact Information

Question 1:

Can the Agency provide guidance on the appropriate toxicology studies needed for proper safety predictions?

A: Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products

https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm376136.htm

Also consider a pre-pre IND or pre-IND meeting

Question 2:

Can the Agency provide more guidance on the core requirements of a cell production facility?

Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for **Human Gene Therapy** Investigational New Drug Applications (INDs) 4/2008

https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072587.htm

Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for **Human Somatic Cell Therapy** Investigational New Drug Applications (INDs) 4/2008

https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm074131.htm

Question 3:

Does the agency have any guidance regarding how to implement cost recovery of novel cell therapeutics after FDA approval to obtain cost recovery for a product manufactured under IND has been granted?

SOPP 8203: Evaluation of Cost Recovery Requests for Investigational New Drugs and Investigational Device Exemptions

https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/proceduressopps/ucm336287.htm

Contact Information

- **Kristin Baird, M.D.**

  Kristin.Baird@fda.hhs.gov

- **Regulatory Questions:**

  OTAT Main Line – 240 402 8190

  Email: OTATRPMS@fda.hhs.gov and

  Lori.Tull@fda.hhs.gov

FDA Headquarters

- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.gov
- **Follow us on Twitter:** https://www.twitter.com/fdacber


FDA
U.S. FOOD & DRUG
ADMINISTRATION