FDA Regulation of Cell Therapies for Autoimmune Diseases

Autoimmune Diseases Coordinating Committee (ADCC)
October 17, 2014

Wilson W. Bryan, M.D.
Division of Clinical Evaluation and Pharmacology / Toxicology (DCEPT)
Office of Cellular, Tissue, and Gene Therapies (OCTGT)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)
Outline

• US History of Drug Regulation
• FDA Structure and Mission
• Investigational New Drug (IND) Applications
• Product (CMC) Regulation
  – Cheng-Hong Wei, Ph.D.
• Preclinical Regulation
  – Allen Wensky, Ph.D.
• Clinical Regulation
  – Wilson W. Bryan, M.D.
US History of Regulation

US Constitution: Article 1, Section 8 (Commerce Clause):

The Congress shall have power … To regulate commerce … among the several states, …
Thalidomide Phocomelilia
US History of Regulation

• Food and Drug Act (1906): Product must not be misbranded or adulterated.
• Kefauver-Harris Drug Amendments to FD&C Act (1962): Product must be effective.
FDA Mission Statement

- The FDA is responsible for **protecting the public health by assuring the safety, efficacy**, and security of human and veterinary **drugs, biological products, medical devices**, our nation’s food supply, cosmetics, and products that emit radiation.

- The FDA is also responsible for **advancing the public health by helping to speed innovations that make medicines** and foods **more effective, safer**, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.
Regulatory authority: 3-tiered system

1. **Statutes** – Law, as passed by Congress and signed by the President

2. **Regulations** – Details of the law, as written by the FDA and approved by the Executive Branch; particularly, the Code of Federal Regulations (CFR)

3. **Guidance** – FDA’s interpretation of the Regulations
Authority for Review of Investigational Products

• A new biologic, drug, or device may not be entered into interstate commerce unless:
  – It is approved by the FDA as safe and effective (e.g., new drug application (NDA) or biologics license application (BLA))

• OR…
  – An Investigational New Drug application (IND) is in effect
Investigational New Drug (IND)

- An IND is required to conduct a clinical trial of an unapproved drug or an approved product for a new indication or in a new patient population.

- IND regulations are in 21 CFR 312:
  - IND content and format, sponsor responsibilities, other

- Sponsor:
  - Responsible for the IND (initiates and conducts the clinical trial)
  - Sponsor can be a company, institution, or an individual investigator
IND: Clinical Hold

FDA may place … [an] investigation on clinical hold if it finds that …

– Human subjects are or would be exposed to an unreasonable and significant risk … [or]

– The IND does not contain sufficient information … to assess the risks to subjects of the proposed studies …

IND Regulations [21 CFR 312.42 – Clinical Holds and Requests for modification]
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Product (Chemistry, Manufacturing, and Controls) Regulation of Cellular Therapies

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Somatic cell therapy definition

• “…autologous, allogeneic, or xenogeneic cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo to be administered to humans and applicable to the prevention, treatment, cure, diagnosis or mitigation of disease or injuries”.
  - October 14, 1993. 58 FR 53248
Cell therapy products regulated as…

- Human Cell & Tissue Products (HCT/Ps)
  - 21 CFR 1271
- Biologics
  - 21 CFR 600s
- Drugs
  - 21 CFR Part 312 --Investigational New Drug (IND)
  - 21 CFR Parts 210/211 Current Good Manufacturing Practices
- Device regulations could apply in certain cases
  - 21 CFR 800s
Potential advantages of cellular therapies

- Cells are dynamic
  - Migrate, proliferate, differentiate, and respond to their environment in vitro (during manufacture) and in vivo (after administration)
  - Multiple cell types and mechanisms of action can be involved
- Therapeutic outcome can be curative and permanent
- Targets may not need to be defined (i.e. tumor antigens)
- Cells can act locally as well as secrete factors systemically
Product testing & characterization challenges

- Small lot size / limited sample volume
- Limited shelf life due to cell viability
- Limited availability of starting material for process, product, and test method development
- Patient to patient variability and cellular heterogeneity
- Multiple potential mechanisms of action
- Lack of reference standards
- Inability to terminally sterilize products
- Difficulty in controlling cells
Importance of product testing

- **Product Understanding**
  - Patient to patient variability
  - Mechanism of action
  - Cellular diversity/homogeneity

- **Product Control**
  - Product safety and quality
  - Process performance
  - Manufacturing consistency
When is product testing important?

All phases of the product life cycle!
• Product and process development
• Product characterization
• Component qualification and control
• Manufacturing control
  – In-process testing
  – Lot release
• Stability
Product characterization during product development

- The farther along in product development the more product manufacturing should become fixed & lot release refined
- Evaluate many parameters at phase I & progressively prune by phase III
- It’s important that the product (as defined by release testing) isn’t substantially changed between preclinical testing & phase I, and between phase III & licensure
- Be aware: significant manufacturing changes may require product comparability studies to ensure the product hasn’t changed
Product Development (PD) Tips for All Phases:

#1: Be data driven:
Clinical studies should be developed around good data:
- Proof of concept (POC) & P/T data that supports clinical research,
- PD data that supports manufacturing process.
- Supportive Data vs. Suppositions to Answer FAQs, e.g.:
  - “Is my cellular starting material free of infectious viruses?”
  - “Do the antibiotics in my culture media interfere with my sterility assay?”
  - “Does my dose of irradiation render the cells replication incompetent?”

#2: Provide complete & accurate documentation:
FDA isn’t able to make an independent assessment of product safety when documentation is missing, incomplete, contradictory, or incorrect.
Product Development (PD) Tips for All Phases:

#3: Be informed of cell therapy PD resources, e.g. online:
- Code of Federal Regulations (eCFR) Title 21
- FDA Guidance Documents
- International Conference of Harmonization (ICH) Guidelines
- "OCTGT Learn" online courses
- USP General Chapters

#4: Plan ahead:
Many product development problems can be avoided via better product understanding earlier in development.

#5: Communicate with FDA:
Formal meetings: pre-IND, end of phase 2, pre-BLA, etc.
Informal discussions: FDA reviewers’ sponsor outreach
Opportunities for Formal FDA Interaction

Development
Pre-Clinical
Pre-IND Meeting (Informal)
Pre-IND Meeting
IND Review
Pre-IND Phase
IND Review Phase
CLINICAL TRIALS
Ph 1
Ph 2
End of Ph 2 Meeting
Pre-BLA Meeting
BLA Review
Post-BLA Meeting
Post-marketing Phase
Post Marketing
Post-marketing Meetings

Product development is an iterative process, with frequent FDA & sponsor interactions
Regulatory expectations for product characterization

- Product testing must cover aspects of both:
  - safety with regards to microbial contamination: sterility, endotoxin, mycoplasma
  - and quality attributes such as viability, identity, purity, and ultimately potency (all of which can affect safety)
- The product is defined by the release specifications: assay method + release criteria

- Specification = Test + Assay + Cutoff

<table>
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<tr>
<th>Parameter/test</th>
<th>Assay</th>
<th>Acceptance criterion</th>
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<tbody>
<tr>
<td>Sterility</td>
<td>USP &lt;71&gt; (14 days, aerobic and anaerobic)</td>
<td>No growth</td>
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In-process & lot release testing

**In-process testing:**
Sometimes required if a safety issue could be present:
- Qualification of cell banks to be sure they are free of adventitious agents

In other cases it is recommended:
- Upstream sterility testing during lengthy culture periods
- Evaluating multiple cell populations

**Final product lot release testing:**
Always required
- May include some of the same tests done in-process
- Results are available prior to use in patients
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)

Additional copies of this guidance are available from the Office of Communication, Training, and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20853-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/ober/guidance.htm.

For questions on the content of this guidance, contact the Office of Cellular, Tissue, and Gene Therapies at 301-827-5102.
III. PRODUCT MANUFACTURING AND CHARACTERIZATION INFORMATION TO BE SUBMITTED BY SPONSORS AND DOCUMENTED BY FDA REVIEWERS

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Additional considerations for cell product testing

- Cellular starting material should be qualified
  - Appropriate donor testing when applicable
  - Cell banks need to be qualified to assure they are free of adventitious agents
- Selection, differentiation, growth, activation and other processing steps should be monitored and controlled
- Tumorigenic potential of cells should be measured, if applicable
- Cellular composition should be understood
- Viability of living cells should be confirmed
- Cell number often determines dose
Who decides on lot release assays & criteria used to define a product?

Some lot release specifications are dictated by regulations (but alternate methods could be used (21 CFR 610.9)):
- Mycoplasma for cultured cells per 21 CFR 610.30

Some are based on guidance documents:
- Viability of at least 70% for cell therapies
- Viral testing of cell banks

However, most lot release specifications are established by the sponsor and justified based on their manufacturing experience and clinical need:
- Identity
- Potency
- Dose / volume / concentration
- Purity / impurities profile
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General recommendation for establishing specifications

- Begin early in development
  - Characterization data obtained during product development may provide support for the use of a given assay or acceptance criteria
- Measure a wide range of product attributes
  - molecular, biochemical, immunologic, phenotypic, physical and biological properties
  - Consider all cells including those not expected to directly contribute to activity
- Determine the critical attributes of your product
- Establish meaningful acceptance criteria
- Specifications can serve multiple roles:
  1) Release
  2) Stability
  3) Comparability
Endotoxin and pyrogens
• Other aspects of impurities profile:
  – Residual solvents, antibiotics, aggregates & particulates, extractables & leachables, etc.
    • Develop & validate appropriate detection methods
    • Set limits
    • Validate removal from product
  – Cell populations other than desired cells
    • Quantitative assessment of each cell type present

21 CFR 600.3 (r):
Means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product.

Purity- 21 CFR 610.13
Identity- 21 CFR 610.14

- Must adequately identify the product designated on the final container, and distinguish it from any other product being processed in the same facility
- For example, >85% CD3+CD8+ (T cell); >85% CD3-CD56+ (NK cells);
- Identity testing for cellular therapy products may not distinguish one patient-specific lot from another
  - Tracking, labeling, segregation systems are of critical importance
The word potency is interpreted to mean the specific ability or capacity of the product...to effect a given result.

Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency...
Potency

- Regulations are flexible with regards to the kind of assay that can be used and what you are measuring as long as it is measuring a meaningful biological parameter related to how you think the product works.

- Potency tends to be one of the hardest assays to establish.

- The FDA recommends developing an assay early and evaluating multiple potential measures of potency.

- A potency assay must be in place by phase III and validated for licensure.

Establishing a potency assay

• Should be guided by the underlying proposed mechanism of action and in vitro and pre-clinical proof of concept data
• Recommend evaluating multiple measures of product potency until you are confident you have an assay that is suitable for your needs
  – In some cases you may wish to choose one assay for product release while continuing to collect data on other assays
  – In some cases a single measurement may not be fully informative and a matrix approach may be needed
• Potency assay should be chosen based on successful qualification of the test method using your product
Summary

• Cell therapies offer unique advantages in specific situations
• Cell therapy product development can be challenging and early development work can greatly facilitate late phase studies
• Communicate with FDA to ensure agreement on critical decisions prior to execution
Acknowledgements

Keith Wonnacott, Ph.D.
Brian Niland, Ph.D.
Andrew Byrnes, Ph.D.
Sources for more information

Important regulations

• Good manufacturing practices: 21 CFR parts 210, 211, 225, & 226
• IND regulations: 21 CFR part 312
• Biologics regulations: 21 CFR parts 600, 601, & 610
• Tissue rules: 21 CFR part 1271
• Device regulations: 21 CFR part 800

Relevant guidance documents

Cell therapy IND submission: 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)

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Preclinical Considerations in the Development of Cellular Therapies

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Autoimmune Diseases Coordinating Committee
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Overview

• Regulatory review principles
• Safety concerns for cell therapy products
• Preclinical evaluation
  – Animal species / model considerations
  – Study design considerations
• Pharmacology / Toxicology section of an IND
• Communication with FDA/CBER/OCTGT
## Components of an IND Application

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What Regulations Govern Preclinical Testing?

Pharmacologic & Toxicologic Studies

Content of application should include “Adequate information about the pharmacological and toxicological studies...on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.”

[IND Regulations [21 CFR 312.23 (a)(8) - Pharmacology and Toxicology]
“FDA’s primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug’s effectiveness and safety…”

[ IND Regulations [21 CFR 312.22 (a) - General Principles of the IND Submission ] ]
CBER Review: Product-Based

- There is no “one size fits all” regulatory approach
- Data necessary to support development depends on the characteristics of the product
- Preclinical studies are designed to support use of a specific product for a specific clinical indication
- Review approach is based on balancing benefit and risk
Preclinical Regulatory Testing Strategy

• A ‘standard set’ of preclinical tests and testing parameters uniformly applicable to all products does not exist

• The diversity and inherent biological properties of cell therapy products necessitate a case-by-case testing strategy

• However, there is an overarching set of general considerations to guide preclinical testing
Final Guidance

- Current Thinking of the Agency on this Topic
- First Comprehensive FDA Guidance on Preclinical Assessment of Cell and Gene Therapy (CGT) Products
- Explicitly Incorporates 3 R’s: Recommendations to reduce, refine, and replace animal use in a preclinical program
Potential Safety Concerns for Cell-Based Products

- Risks of the delivery procedure
- Ex vivo manipulation (e.g., expansion, genetic modification, encapsulation, scaffold seeding)
- Potential inflammatory / immune response to the administered cellular product
- Inappropriate cell proliferation (e.g., tumor formation)
- Inappropriate cell differentiation (e.g., ectopic tissue formation)
- Cell migration to non-target areas / tissues
- Interactions with concomitant therapies
Expectations from Preclinical Data

• To support a **rationale** for the first-in-human clinical trial
  – For cell therapy products, the trial is typically conducted in the disease population, not in healthy volunteers

• To make **recommendations** regarding clinical trial design
  – Initial safe starting dose level, dose-escalation scheme, dosing schedule, organ toxicity, eligibility criteria, clinical monitoring

• To meet **regulatory requirements**
  – 21 CFR 312.23 (a)(8)
  – 21 CFR 58 (GLP compliance)
Preclinical Study Design(s)

- Assess pharmacology / proof of concept (POC) / cell fate in relevant animal model(s) of autoimmune disease / injury, as feasible
- Assess safety / toxicology (T) / cell fate in healthy animals
- Hybrid pharmacology-toxicology study design
  - POC + T + product fate – incorporate activity and safety endpoints into an animal model of autoimmune disease
  - Local microenvironment and pathophysiology status of the model may impact the safety / bioactivity of the product
- Apply the 3 R’s – Reduce, Refine, Replace – in preclinical study designs
  - We encourage you to explore opportunities for reducing, refining, and replacing animal use in your preclinical program.
  - Consider in vitro or in silico testing to complement or replace animal studies
  - We encourage the submission of proposals with justification for any potential alternative approaches
Selection of Appropriate Animal Species / Model

- There is no ‘default’ to the use of nonhuman primates
- There is no ‘default’ to the use of both a rodent and a non-rodent species or multiple species
- Understand the limitations of the species / model(s) used
- Scientific justification should be provided for the animal species / model(s) used
Considerations for Appropriate Animal Species / Model

- Comparative physiology of animal to human
  - Model of disease / injury (e.g., NOD mice, EAE mice, etc.)
  - Local microenvironment may impact the safety of the product
- Route of administration – comparability to clinical
  - Systemic vs. targeted delivery (e.g., intravenous, intraportal, implanted device, intrathecal, etc.)
  - Delivery system / delivery procedure
- Species specificity of the product
- Species specificity of the innate / adaptive immune response
Preclinical Study Design: Specifics

• Appropriate controls and multiple dose levels of product
• Dosing regimen / procedure – mimic clinical
• ‘Standard’ endpoints
  – Mortality, clinical observations, body weights, appetite
  – Serum chemistry, hematology, coagulation, urinalysis
  – Pathology – target & non-target tissues
• Terminal / non-terminal assessment
  – Various imaging modalities
  – PCR, Immunohistochemistry, In situ hybridization
Preclinical Study Design: Specifics (cont’d)

- Other endpoints / biomarkers
  - Cell fate (distribution, survival, engraftment, differentiation, persistence)
  - Functional outcome, ‘PK’ / PD
  - Product-dependent (tumorigenicity, immunogenicity, etc…)
  - Disease-dependent (cardiac, neurological, autoimmune status, etc…)

- Sufficient study duration
- Endpoints measured in surviving animals at multiple intervals
- Attempt to reduce bias as much as possible
Preclinical Study Design: Examples of Disease-specific Assessments

• Cell therapy for Type 1 Diabetes (islets, progenitors, etc.
  – Fasting and non-fasting glucose
  – Glucose tolerance testing
  – Species-specific insulin measures
  – HbA1c, etc.
  – Graft/tissue immunohistochemistry and viability

• Cell therapy for Multiple Sclerosis (EAE model)
  – Measures of disease incidence and severity
  – Histological assessments
    • Location and severity of demyelination and cell death
    • Cell distribution, persistence, differentiation, etc.
Pharmacology / Toxicology Section of an IND

• For each toxicology study intended primarily to support safety, a full tabulation of data should be submitted

• Each toxicology study submitted should be performed in compliance with Good Laboratory Practice (GLP), or an explanation provided
  • For non-GLP studies conducted in-house, oversight of the conduct of the study and the resulting final study report by an independent QA unit / person - 21 CFR Part 58.35
Submit Complete Reports for Toxicology Studies

• Detailed description of the study performed:
  – Test articles (i.e., relevance to the clinical product)
  – Test system (i.e., animal species / model)
  – Delivery device information if applicable
  – Dose levels / dose regimen / study duration
  – Study groups (controls, test article groups, group size, etc)
  – Prospective study endpoints

• Results: for all parameters evaluated-
  – Submit individual animal data for all parameters evaluated
  – Submit summarized and tabulated results

• Interpretation of the data
Sources of Data to Support an IND

- GLP-compliant toxicology studies conducted by a certified testing facility
- Well-controlled studies conducted in-house
- Published data in peer-reviewed journals
- Cross-reference to similar products in previously submitted Master Files (MFs) / INDs
- Detailed clinical study reports from clinical trials
Potential Pitfalls when Submitting an IND

- Insufficient information to assess subject risk
  - Lack of preclinical safety data
  - Incomplete safety study reports
  - Insufficient product characterization
- Inadequate preclinical study design(s)
  - Insufficient numbers of animals
  - Lack of / inappropriate concurrent controls
  - Inappropriate route of administration / anatomic site of delivery
  - Insufficient safety monitoring (safety / activity endpoints)
Early Communication with OCTGT

- **Pre-preIND interactions**
  - Non-binding, informal scientific discussions between CBER/OCTGT nonclinical review disciplines (P/T & CMC) and the sponsor
  - Initial targeted discussion of specific issues
  - Primary contact: Mercedes Serabian
    mercedes.serabian@fda.hhs.gov

- **PreIND meetings**
  - Non-binding, but formal meeting between FDA and sponsor (with minutes generated)
  - Meeting package should include summary data and sound scientific principles to support use of a specific product in a specific patient population
Summary

Preclinical Study Goals:

• Employ study designs that address safety and scientific basis for conducting a clinical trial
  – Robust study designs based on product and risks
  – Preclinical data should be adequate to support the proposed clinical trial

  Important to understand your product

• Work to minimize the number of studies and number of animals necessary to adequately address the safety and potential efficacy of the investigational product

  Apply the 3 R’s – Reduce, Refine, Replace
Selected Guidances

• Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013)

• Draft Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (July 2013)

• Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage (December 2011)
Selected Guidances

- Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines (October 2011)

- Guidance for Industry: Cellular Therapy for Cardiac Disease (December 2010)

- Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products (September 2009)
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Drug Development Process

• Understanding the disease process
• Target identification
• Drug discovery
• Preclinical (esp., animal) study objectives:
  – Safety, biodistribution, proof-of-principle
  – Guide design (including dosing, population, and monitoring) of subsequent clinical studies

• Clinical Development
Clinical Development

• Phase 1 objectives:
  – Safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics, and (if feasible) activity / efficacy
  – Guide dosing and monitoring of subsequent Phase 2 studies

• Phase 2 objectives:
  – Determine dose, route, regimen, population, endpoints, and estimated magnitude of effect
  – Guide design of subsequent confirmatory (Phase 3) studies

• Phase 3 objectives:
  – Evidence of effectiveness and safety to support a marketing application (New Drug Application (NDA) or Biologics License Application (BLA))
Errors in Early (incl. Preclinical) Drug Development

- Insufficient understanding of the disease pathophysiology (poor target identification)
- Insufficient drug discovery
- Poorly designed, seldom reproduced, and imaginatively interpreted “proof-of-principle” studies
Errors in Early-Phase Clinical Development

• Insufficient exploration of dose, regimen, and route of administration
• Over-interpreting biomarkers as surrogates (i.e., activity does not reliably predict clinical efficacy)
• Constantly tweaking the product, and never moving past Phase 1
Errors in Late-Phase Clinical Development

- Proceeding to Phase 3 when Phase 1 - 2 results suggest that the product is ineffective
- Proceeding to Phase 3 with inadequate Natural History or Phase 1 - 2 data to guide the study design (e.g., to determine population, sample size, endpoints, study duration)
- Ignoring FDA advice regarding the evidence necessary to support a marketing application
Errors in Drug Development

Not planning ahead.

Early in drug development, write a Target Product Profile (TPP): The TPP is an evolving draft of the product labeling and should be revised as development proceeds.
Regulatory Requirements

• Approval of all drugs – for both rare and common conditions – must be based on substantial evidence of effectiveness and evidence of safety.

• Evidence of effectiveness should be obtained from adequate and well-controlled studies.

• Certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases. FDA regulations provide flexibility in applying regulatory standards.
Regulatory Requirements

- FDA “exercise[s] its scientific judgment” in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs. This flexibility extends from early phases of development to design of adequate and well-controlled studies required to demonstrate safety and effectiveness to support marketing approval.

21 CFR 314.105
Special Programs
IND: Breakthrough Therapy Designation

• Requirements
  – Drug is intended to treat a serious condition
  – Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies

• Benefits
  – All benefits of Fast Track designation
  – Intensive guidance on efficient drug development during IND, beginning as early as Phase 1
  – Organizational commitment involving senior managers
Serious Condition

“a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.”

21 CFR 312.300(b)(1)
Accelerated Approval of NDA / BLA

• Requirements
  – Drug is intended to treat a serious condition
  – Provides meaningful advantage over available therapies
  – Demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit …

• Benefit
  – Approval based on an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict a drug’s clinical benefit

• Requirement
  – Conduct any required post-approval trials to verify and describe the anticipated clinical benefit …
Expanded Access INDs

- Use of an investigational drug outside of a clinical trial, for the sole purpose of treating a patient or patients with a serious or life-threatening disease who have no acceptable medical options.

- Includes “Single-patient IND” as well as larger-sized INDs (e.g., treatment INDs).

- Often referred to as “compassionate use.”
Orphan Drug Designation

• Requirement:
  – Drug intended to treat rare disease / disorder that affects fewer than 200,000 people in the U.S., or that affects more than 200,000 persons but is not expected to recover the costs of developing and marketing a treatment drug

• Benefits
  – Market Exclusivity
  – Tax Credits
  – Fee Exemptions
  – FDA Orphan Grants Program
Cell and Gene Therapy
Investigational New Drug Applications

- Rare
- Common
Recommendations

• Plan ahead (e.g., Target Product Profile)

• Collaborate: scientists, clinicians, patients, advocacy groups, industry, regulatory bodies

• Early and regular communications with FDA
Resources
(how to get help)
FDA Guidances


Meetings with FDA

Guidance for Industry:
Formal Meetings Between the FDA and Sponsors or Applicants (2009)
References

• Quantum of Effectiveness Evidence in FDA’s Approval of Orphan Drugs; Cataloguing FDA’s Flexibility in Regulating Therapies for Persons with Rare Disorders; FJ Sasinowski, National Organization for Rare Disorders; Drug Information Journal 2012;46(2):238-263

• Clinical research for rare disease: Opportunities, challenges, and solutions; RC Griggs, M Batshaw, M Dunkle, R Gopal-Srivastava, E Kaye, J Krischer, T Nguyen, K Paulus, PA Merke; For the rare diseases clinical research network; Molecular Genetics and Metabolism 96 (2009) 20–26
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