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Oncology Biopharmaceuticals and Preclinical Development: Evolving Regulatory Challenges

Mike Orr, Ph.D., D.A.B.T.
Division of Biologic Oncology Products
OODP/OND/CDER/FDA

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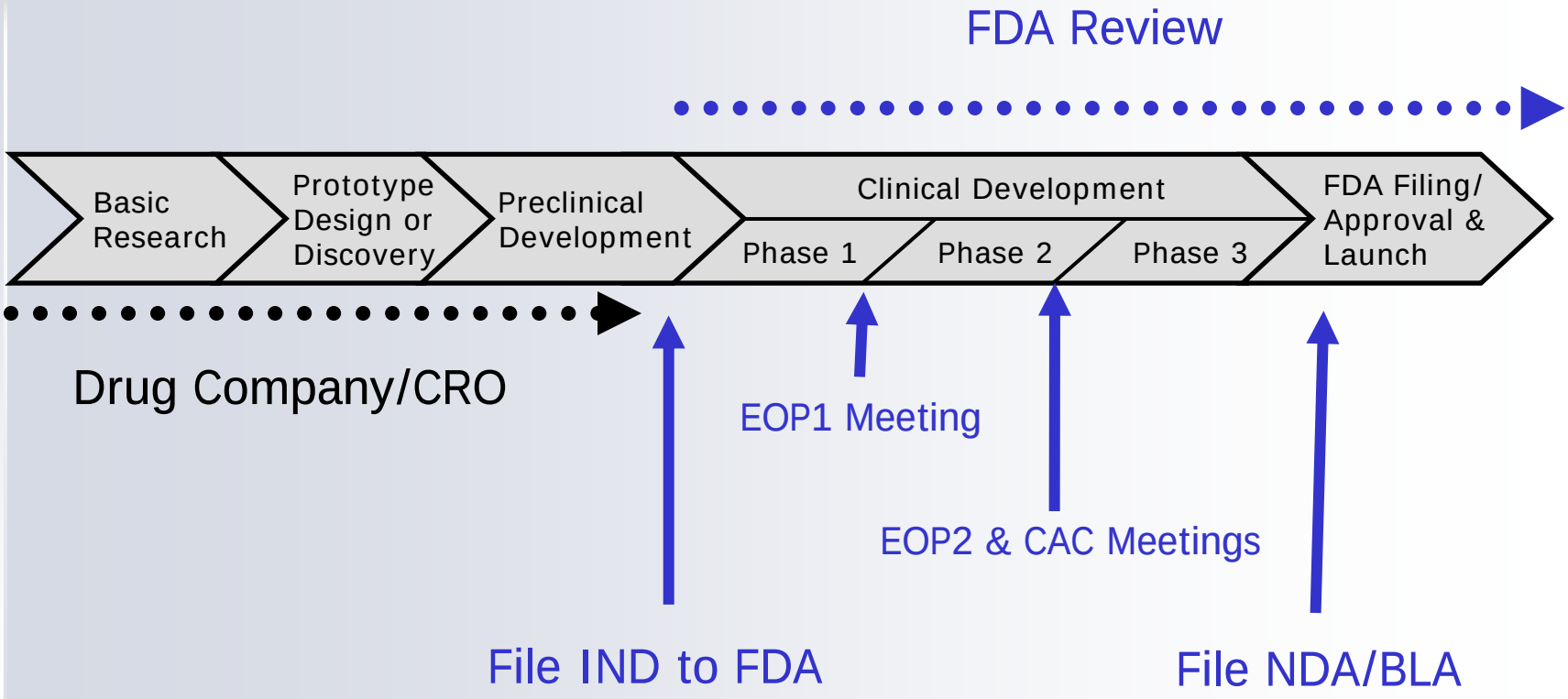
Overview

- **Goals of safety testing and key questions to be addressed**
- Nonclinical Tools used
- Basic differences between small molecules and biologics
- Safety pharmacology, Reproductive, Carcinogenicity studies
  - Challenges

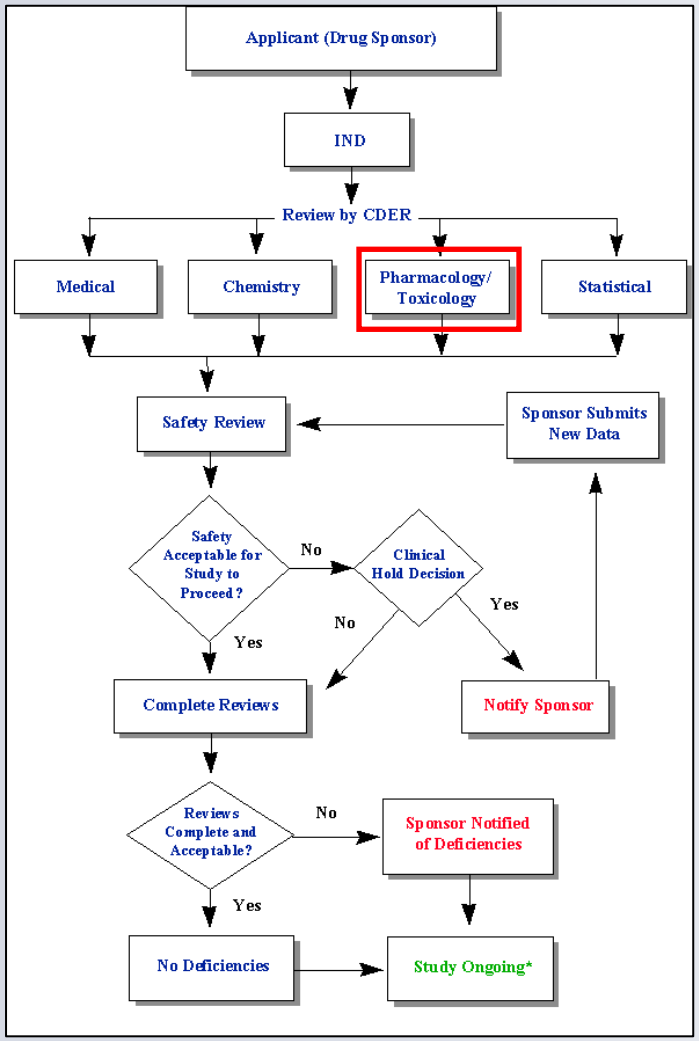
Key Legal Points

- 1902 Biologics Control Act
  - Deaths of children caused by contaminated vaccines
- 1938 Federal Food, Drug, and Cosmetic Act (FDCA)
  - Title 21: Food and Drugs
- 1946 Public Health Service Act currently authorizes FDA to ensure the safety, purity, potency of biologics for licensure
  - Title 42: The Public Health and Welfare (authority of NIH)
  - Emphasis on the importance of manufacturing controls
- Regulatory functions of biologics to FDA in 1972
- In 2003, therapeutic biologic products moved from CBER to CDER
  - Biologics subject to dual regulation by FDCA and PHS during development (Phase I to Phase III studies)

Overview of Drug Development



Review Process - IND



- IND Arrives at FDA
- Review Team selected
- Data evaluated
- Safety Review Meeting
- Reasonably Safe?
  Yes/No

30 Calendar Days

Goals of Nonclinical Testing: FDA Perspective

- To recommend an initial clinical safe start dose and appropriate dose escalation
- Identify targets
- Inform patient inclusion/exclusion criteria
- Determine if toxicities can be clinically monitored
- Inform the risk-benefit decision making
- Support labeling claims

Key Questions for Non-Clinical Studies to Answer

- What is the physiologic/pharmacology profile?
- Are the mechanisms of action known?
- What is the relevance of the toxicities to humans?
- Are the effects dose-responsive?
- Does the route of administration/dosing regimen/dose level affect the activity/toxicity in relevant species?
- What risks can be identified for the clinical trial?

Reference: Serabian and Pilaro, Toxicologic Pathology, 27, p 27-31, 1999

Resources to get you started

ICH Guidances:

- **ICH S6: Safety Studies for Biotechnological Products**
- **ICH M3: Timing of Pre-clinical Studies in Relation to Clinical Trials**
- **ICH S7A: Safety Pharmacology Studies for Human Pharmaceuticals**
- **ICH S7B: Safety studies for QT prolongation**
- **ICH S1: Carcinogenicity Studies**

ICH= International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Resources to get you started Conti...

- **ICH S2: Genotoxicity Testing**
- **ICH S9: (Under Development) Nonclinical Evaluation for Anticancer Pharmaceuticals**
- **Complete list available at :**
  http://www.ich.org/cache/compo/276-254-1.html

- Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use
  http://www.fda.gov/cber/gdlns/ptc_mab.pdf

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Nonclinical Tools

- **Key Point:** Need to conduct toxicity testing in pharmacologically relevant species for biologics
- Pharmacology studies (*In vitro* and *In vivo*)
- Pharmacokinetic studies
- Toxicology Studies
  - General
    - ✓ Single dose studies (PK)
    - ✓ Repeat dosing studies (Pivotal toxicology studies)
  - Specialized Studies

Nonclinical Tools: Biologics

- Key supporting information needed for study interpretation and determination of the validity of findings
  - Tissue-cross reactivity studies in panels of normal tissues in species of interest

    (Monoclonal antibody products only)
  - Immunogenicity Assays

Nonclinical Tools: Biologics Conti.

- Key support information needed for study interpretation and determination of the validity of findings
  - Pharmacokinetic (PK)/ Pharmacodynamic (PD) information
    - Was exposure maintained for the duration of the study?
    - Did PK parameters such as clearance change due to increase in anti-drug antibody production?
    - Was the PD effect observed based on the pharmacology?

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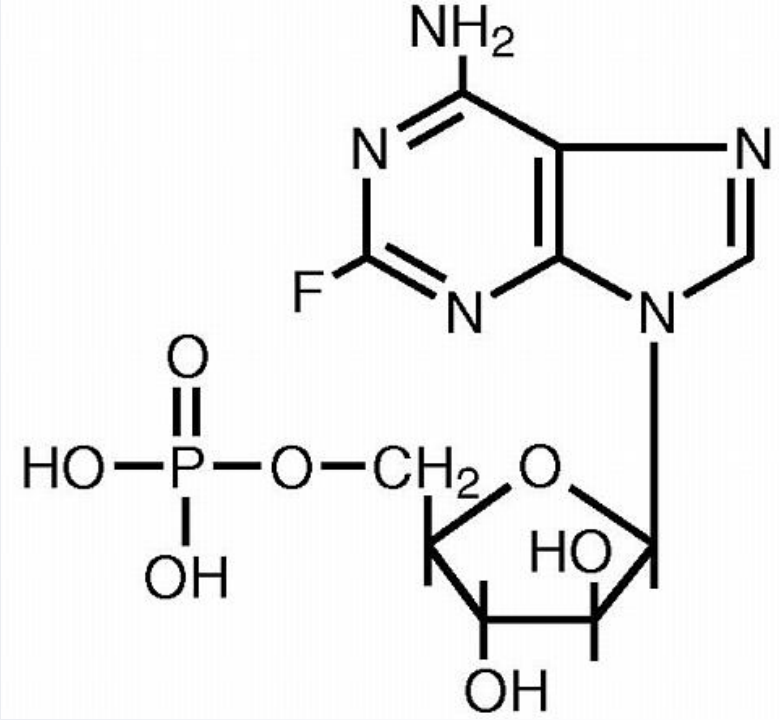
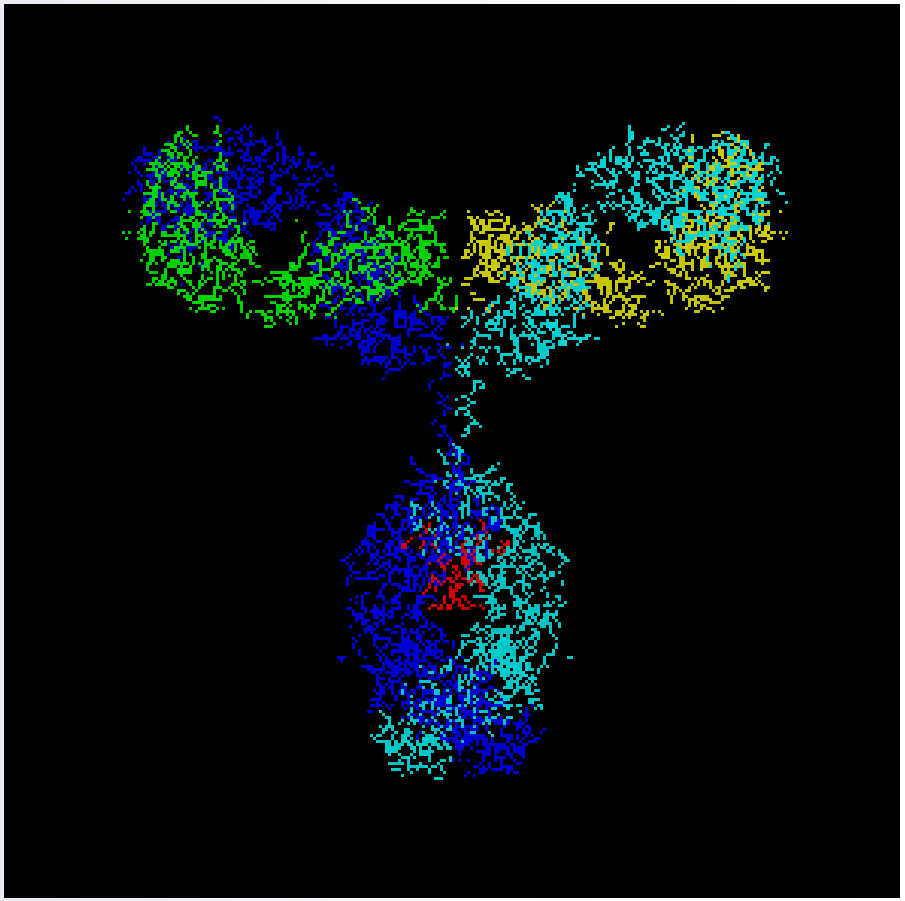
Traditional Drugs are small…

- **FLUDARA® (fludarabine phosphate)**
- **Indication: B-cell chronic leukemia (CLL)**
- **Molecular weight 365.2 Daltons**
- **Antimetabolite that inhibits DNA synthesis**



Biotherapeutic Drugs are BIG!

- **RITUXAN® (rituximab)**
- **Target: CD20**
- **Destroys normal and malignant B cells**
- **Molecular weight ~145,000 Daltons**
- **Chemical formula (non-glycosylated IgG1κ)**



Some Basic Differences Between Drugs and Biologics

Traditional Drugs	**Biologic Therapies**
Low molecular weight	High molecular weight
Previous examples	Unique
Historical data base	Concurrent controls
Maximal tolerated dose	Optimal biologic dose
Species-independent	Species-specific
Metabolized	Degraded
Standard approaches	Flexible approaches
Short half-life	Often long half-life

Examples of Biopharmaceuticals

- Proteins
  - Growth factors
    - Somatropin (human growth hormone)
    - Human G-CSF
  - Cytokines
    - IFN-alpha
- Antibodies
  - Block receptors: anti-EGFR and anti-HER2
  - Neutralize ligands: anti-VEGF
  - Most therapeutic antibodies on the market are the IgG subtype
- Immunoconjugates
  - i.e. antibody linked with a radiolabel or antibody linked to a toxin

Biologics versus small molecules

- The need to conduct toxicology studies for biologics in a pharmacologically relevant model can result in toxicology studies being conducted in a single species
  - Toxicity studies in a single species are acceptable if no other relevant species is available
  - Guidance documents (ICH S6, ICHS 5A, and ICH M3) allow for this type of a testing strategy
  - Studies in non-relevant models can be misleading and are discouraged

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- **Safety pharmacology, Reproductive, Carcinogenicity studies**
  - **Challenges**

ICH S7A 2.9 and Biologics

- 2.9 Conditions Under Which Studies Are Not Necessary
  - "For biotechnology-derived products that achieve highly specific receptor targeting, it is often sufficient to evaluate safety pharmacology endpoints as a part of toxicology and/or pharmacodynamic studies, and therefore safety pharmacology studies can be reduced or eliminated for these products."

ICH S7A 2.9 and Biologics

- 2.9 Conditions Under Which Studies Are Not Necessary
  - "For biotechnology-derived products that represent a novel therapeutic class and/or those products that do not achieve highly specific receptor targeting, a more extensive evaluation by safety pharmacology studies should be considered."

- So, now what do you do???

- **Key point:** The general pharmacology/toxicology studies can be used to assist in the development of a safety pharmacology program or determine if one is needed.

Safety Pharmacology:
Regulatory Reality Today for Biologics

- For the original IND, the pivotal toxicology study has the core battery (vital functions of safety pharmacology parameters) integrated in the study design
  - Cardiovascular system: e.g. HR, blood pressure, ECG
  - Respiratory system: e.g. Respiratory rate,
  - Central Nervous system: e.g. functional observation battery (Please note that FOB is not always requested)

- Basically, integration of the "core battery" into the pivotal toxicology study is the majority of the safety pharmacology data that we reviewed at the early stages of IND submission.
  - i.e. Cynomologus monkey 4 week or 13-week study

Safety Pharmacology:
Regulatory Reality Today for Biologics

- Good scientific justification for integration into the pivotal toxicology study
  - Complete study design allows reasonable interpretation of the information in context of the PK/PD, immunogenicity, clin chem, hematology histopathology, recovery groups
- Totality of information acquired during a pivotal toxicology needed for interpretation of the study
  - Pharmacologically relevant species
  - Repeat dosing
  - More time-points

Safety Pharmacology: Regulatory Reality for Biologics

- Specialized safety pharmacology studies may still be required if particular adverse effects are of concern based on the pharmacology studies or toxicology data
  - GI, Kidney, Immunotoxicity etc.
  - Chronic use indications (Optimistic that cancers may have better long-term outcomes in the future)

- **Challenge:**
  - Balancing the principles of the 3R's (replacement, refinement and reduction of animals) while still reducing uncertainty in defining a safe first in human clinical dose
    - Especially important when non-human primates are the only pharmacologically relevant species

Potential Issues: Biologics and Safety Pharmacology

- Nonclinical studies may only be performed in one pharmacologically relevant species
  - Issues with certain species:
    - i.e. cynomologus monkey: reduced n and reduced statistical power to detect differences in any pharmacology or toxicological endpoint
    - Larger sample sizes are often feasible in mice and rats but not in monkeys
    - Assay may provide statistically significant results with a reasonable N
    - A negative result from a standardized assay may underestimate the potential liability of the biotherapeutic
    - Techniques to obtain some of the safety pharmacology data may not be available at this time

Potential Issues: Biologics and Safety Pharmacology Conti…

Some of the challenges of trying to do traditional safety pharmacology studies with biologic drugs:

- Exaggerated pharmacology can be observed after repeat dosing and tissue/receptor saturation, which can may require greater than 4 weeks of repeat administration for products with long half-lives
  - ICH S7A "Safety pharmacology studies generally performed by **single dose** administration"

- Due to large size of biotherapeutics, *in vitro* assays may not be feasible or scientifically justified
  - i.e. *In vitro* hERG assays

Bottom line

- Overall, safety pharmacology testing should be decided based on:
  - Prior or current knowledge of the class of biologic
  - Effects of similar product/target
  - Consider the patient population under study
    - i.e. life threatening or not
- Implement careful design based on information available and pay attention to the type of error for assay of interest (false positive or negative)

Bottom line Conti…

- Overall, the need for safety pharmacology testing should be conducted based on:
  - Question to be answered
  - Duration of exposure versus time to effect
  - Practical use of animals
    - Feasibility of animal model to provide predictive information
    - Apply best technologies at the time to address particular question of interest

Overview Reproductive Toxicology

- Fertility and early embryonic development (Segment I)
- Embryofetal development (Segment II)
- Prenatal and postnatal development (Segment III)
- Still determining the most appropriate strategy for testing biotherapeutics, especially when nonhuman primates are used
  - Often a case-by-case approach and for hazard characterization

Reproductive Toxicology: Challenges

- ICH S5 and ICH S6 provide for flexibility in reproductive toxicity testing strategies

- At least for male fertility, older male cynomolgus monkeys can be evaluated during a repeat dose toxicology study
  - However, it is often difficult to obtain sexually mature males

Reproductive Toxicology: Challenges Conti…

- Small molecular weight (< 1Kda) are generally not species specific and can be tested in standard well validated studies in rodents and rabbits
  - Extensive databases available
- Biopharmaceuticals that are non-species specific can be tested similar to a small molecule
  - Still need to consider route of administration and potentially long half-life of the biopharmaceutical
  - Can still have issues with immunogenicity in rodents and rabbits (Humanized monoclonal antibodies)
  - Exaggerated pharmacology effects of the biopharmaceutical in the normal animals; secondary effects (i.e. insulin)
  - Unlike small molecular weight drugs, the large molecular weight pharmaceuticals have a limited capacity to diffuse across membranes and cross the placenta
- If biopharmaceutical limited to a single species non-human primates, well-validated species such as rabbits and rodents can **not** be used.

Bottom line Conti…

- The timing of the reproductive toxicology studies during biotherapeutic development is currently being debated in the ICH S6 guidance.
  - Life-threatening versus non-life threatening will be a consideration
- In patients with late stage or advanced cancer, embryofetal toxicology studies are conducted in two species when feasible.
- Fertility and peri and postnatal toxicology studies are often **not** needed to support treatment in advanced or late stage cancer.
  - Could be utilized if particular scientifically justified concerns need to be addressed

Carcinogenicity Studies: Challenges

- "Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals." (ICH S6)

- Bottom-line, the vast majority of biologics developed in the oncology area lack standard carcinogenicity testing
  - Life-threatening disease
  - Benefit risk ratio support use

- **Challenges:**
  - As more and more cancers become curable, can new approaches need to be devised for identifying carcinogenicity risk for new oncology biotherapeutics?

  - How will the field of toxicology develop more informative assays that can predict carcinogenicity in humans in the future?

Summary

- Toxicology programs for oncology biotherapeutics require novel approaches for nonclinical safety assessment
  - no “one size fits all” paradigm for oncology biologics
    - Different indications with different benefit/risk ratios: Late versus early stage cancer
    - Different pharmacological classes with unique issues
  - traditional animal toxicology models may not be appropriate or feasible
  - studies may have to be “individualized” to address specific safety concerns
  - Animal models are not always concordant predictors for human adverse events
    - Cross-species extrapolation is difficult
    - We have made substantial progress in our understanding of biological systems but there still is a lot more to learn!

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