Professional Development Program

Biotechnology Entrepreneurship Boot Camp

Presented by:

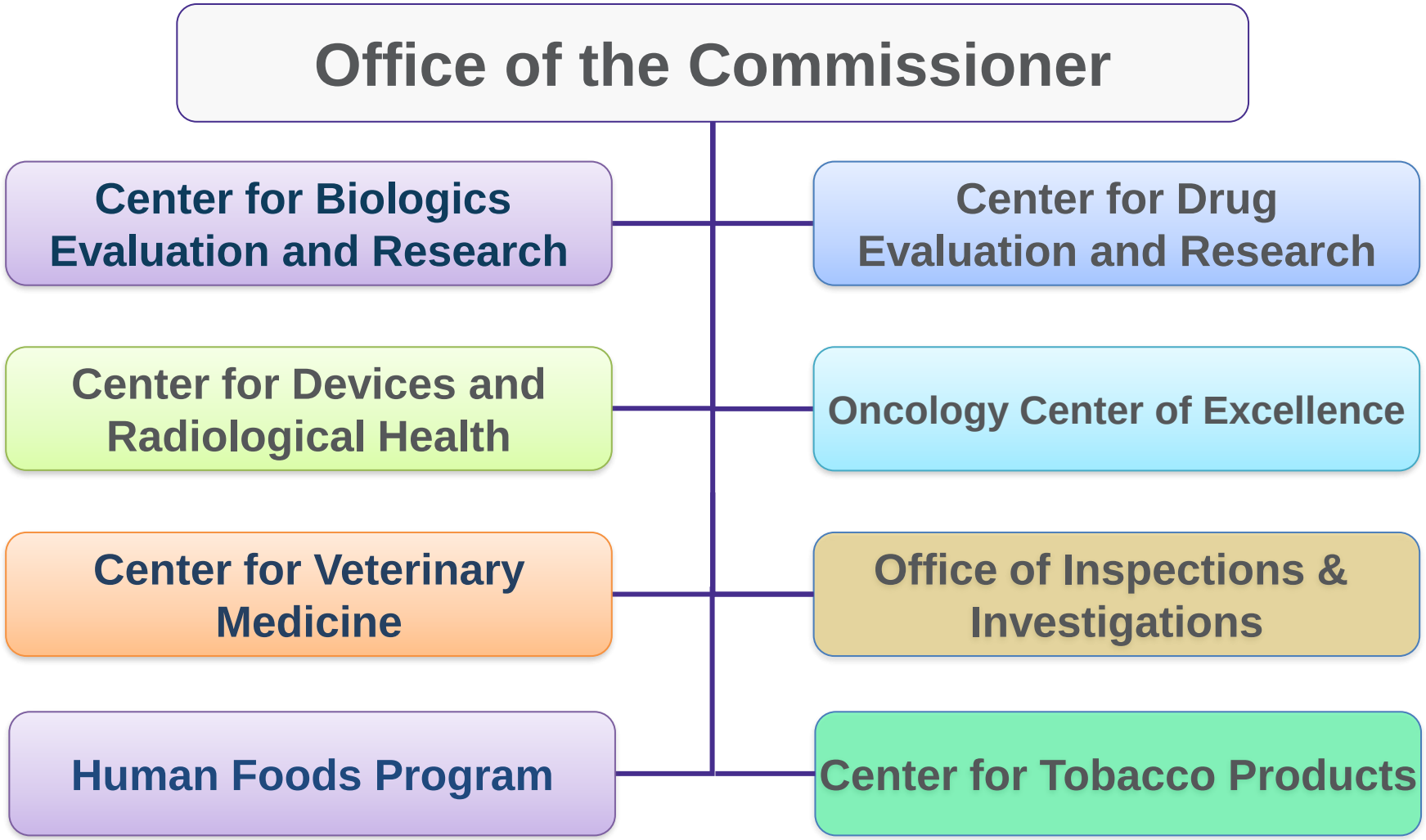
David T. Lin, PhD, MBA

June 14–15, 2025

Session 7: Demystifying Regulatory Pathways for Market Entry

Professional Development Program

FDA Organization



Current as of January 3, 2025

Acts & Regulations Pertinent to Biological Product Development

- PHS Act (42 USC 262-63) Section 351
- FD&C Act (21 USC 301-392)
- Prescription Drug User Fee Act (PDUFA), 1992
  - User fees (application fee, establishment fee, product fee)
- FDAMA, 1997
  - Risk-based review of medical devices
  - Exemption for pharmacy compounding
- Public Health Security and Bioterrorism Preparedness and Response Act (“PDUFA III”), 2002
  - User fees for medical devices
  - Best Pharmaceuticals for Children Act
  - Pediatric Research Equity Act

Acts & Regulations Pertinent to Biological Product Development

- FDA Amendments Act (“PDUFA IV”), 2007
  - Tropical disease priority review voucher program
- Biologics Price Competition and Innovation Act, 2009
  - Created path for approval of biosimilars and interchangeable biological products
  - Exclusivity of 12 years for original biological product
  - Exclusivity of 1 year for first interchangeable biosimilar product
  - On March 23, 2020, all biological products approved under a NDA are “deemed” to be a BLA

Acts & Regulations Pertinent to Biological Product Development

- FDA Safety and Innovation Act (“PDUFA V”), 2012
  - User fee for generic drugs, biosimilar drugs
  - Rare pediatric disease priority review voucher program
- FDA Reauthorization Act (“PDUFA VI”), 2017
- FDA User Fee Reauthorization Act (“PDUFA VII”), 2022
  - INTERACT meeting (“Pre-Pre-IND”) and Type D meeting in CBER and CDER
  - New allergenics products
  - Use-Related Risk Analysis (URRA) for drug-device and biologics-device combination products

Acts & Regulations Pertinent to Biological Product Development

- 21 CFR Regulations
  - 600-680 Biological Product Standards
  - 314.126 Adequate and well-controlled trials
  - 312 Investigational New Drug Application
  - 210-211 Good Manufacturing Practices
  - 1271 Human Cells, Tissues, and Cellular and Tissue-Based Products
  - 812 Investigational Device Exemptions
  - 820 Quality System Regulations
  - 4 Regulation of Combination Products
  - 58 Good Laboratory Practices
  - 56 Institutional Review Boards
  - 50 Protection of Human Subjects

Current Regulatory Pathways

- Biologic Products:
  - IND – Investigational New Drug Application (21 CFR 312)
  - BLA – Biologics License Application (21 CFR 600-680)
- Drugs:
  - IND - Investigational New Drug Application (21 CFR 312)
  - NDA – New Drug Application (21 CFR 314)
- Medical Devices:
  - 510(k) – (21 CFR 807)
  - IDE – Investigational Device Exemption (21 CFR 812)
  - PMA – Pre-Market Application (21 CFR 814)

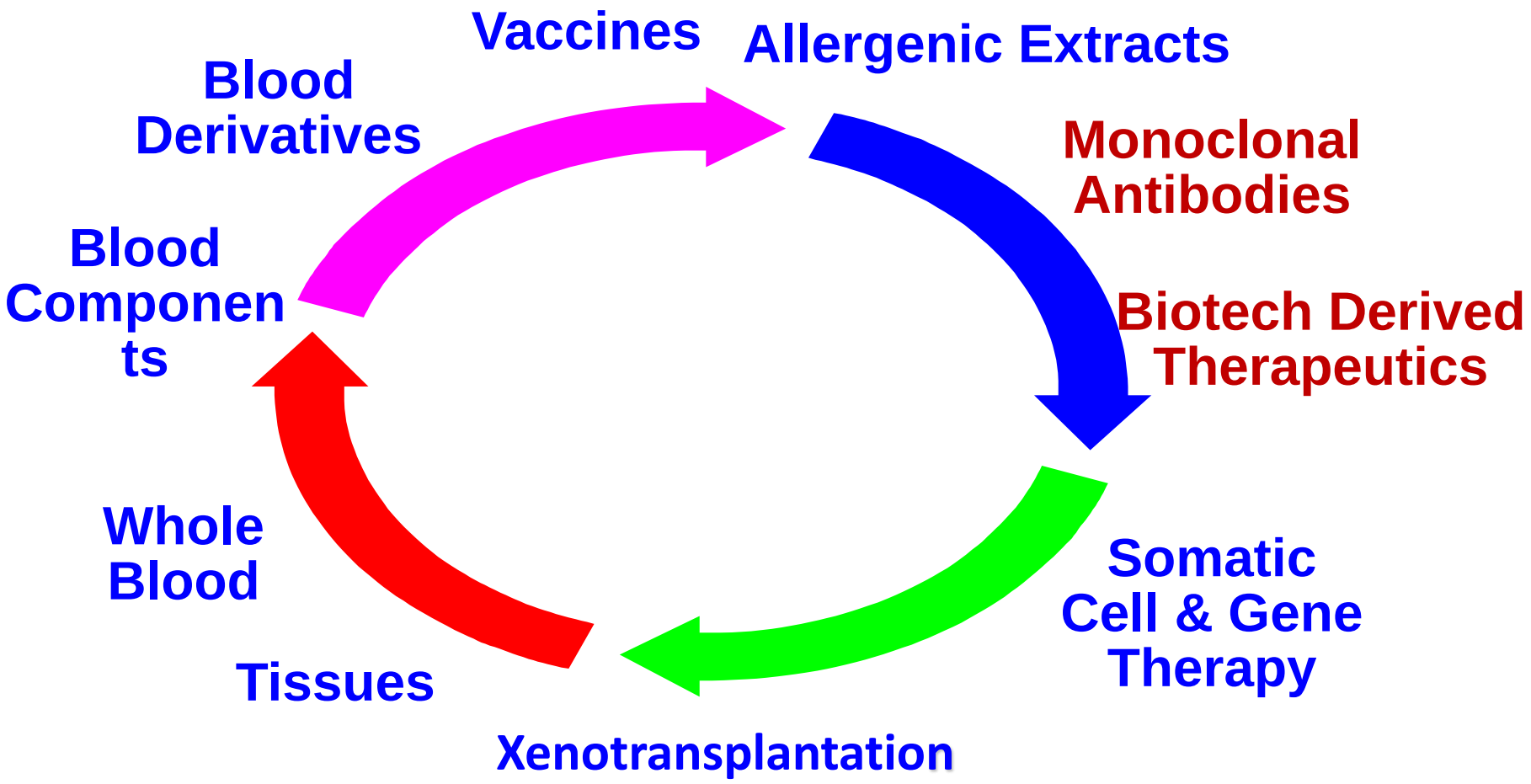
Drug or Biologic - Regulatory Differences

- IND PHASE
  - Identical Regulations for Drugs and Biologics - 21 CFR 312
  - Differences in emphasis and expectations of review divisions
- APPLICATION PHASE
  - DRUGS: New Drug Application (NDA) Regulations - 21 CFR 314
  - BIOLOGICS: Biologics Licensing Regulations - 21 CFR 601
  - Harmonized Application Form - Form 356h; Drugs - NDA; Biologics-BLA
- POST APPROVAL PHASE
  - DRUGS: Inspections, Annual Reports, Manufacturing changes (§314.70)
  - BIOLOGICS: Inspections, Lot release, Manufacturing changes (§601.12)

Laws, Regulations, Guidance

- LAWS:
  - Public Health Services Act (Biologics)
  - Food, Drug and Cosmetic Act (Drugs)
- REGULATIONS:
  - Code of Federal Regulations (CFR)
  - Proposed rule – Comments – Final rule
  - Title 21 – Food and Drug Administration Regulations
  - 21 CFR 600 – Biological Products : General
- GUIDANCE:
  - Represents FDA current thinking on a specific topic. Does not confer any rights and does not bind the FDA or the company

BIOLOGICAL PRODUCTS REGULATED BY CBER or CDER



Therapeutic Biological Products: CDER

- Monoclonal antibodies for in vivo use
- Proteins intended for therapeutic use, including cytokines (e.g. interferons), enzymes (e.g. thrombolytics), and other novel proteins, except for those assigned to CBER (e.g., vaccines and blood products). This category includes therapeutic proteins derived from plants, animals, microorganisms, and recombinant versions of these products
- Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or modifying a pre-existing immune response)
- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo

Therapeutic Biological Products: CBER

- Cellular Products, including products composed of human, bacterial or animal cells …. or from physical parts of those cells
- Gene Therapy Products
- Vaccines
- Allergenic Extracts
- Antitoxins, antivenins, and venoms
- Blood, blood components, plasma derived products including recombinant and transgenic versions of plasma derivatives, blood substitutes, plasma volume expanders, human or animal polyclonal antibody preparations, and certain fibrinolytics such as plasma-derived plasmin, and red cell reagents

Translational Development

Discovery
Research

Regulated Product
Development

Empirical, trial & error,
unregulated environment

Structured, highly
regulated environment

How to Get Product into Clinical Development

- Demonstrate potential clinical usefulness (**early efficacy**)
  - In vitro and / or in vivo (animal) models of disease
- Demonstrate adequate **quality** of product
  - Reproducibly manufacture product
  - Demonstrate purity
  - Formulate into “medicine” – solution, tablet, capsule
- Demonstrate adequate **safety**
  - In vitro and in vivo safety studies
  - Characterize toxicity
  - Justify starting dose and proposed maximum dose

Planning

- Start with an end in mind
  - Product for marketing or
  - Proof of concept

- Develop a basic Target Product Profile
  - Indication
  - Target population
  - Dosage
  - Presentation

Product Development Regulatory Goals

- Develop a reproducible process that can yield a consistent product and that can be run under GMPs
- Develop analytical procedures that can reliably measure product parameters, that are stability indicating, and can demonstrate product comparability following manufacturing/facility/equipment changes
- Develop animal models that can demonstrate proof-of concept and safety
- Demonstrate safety and efficacy in clinical trials

Translational Development – Regulatory Challenges

- GLP
- Choice of animal model/ species

- GMP

- GCP

- INDs, BLAs, NDAs

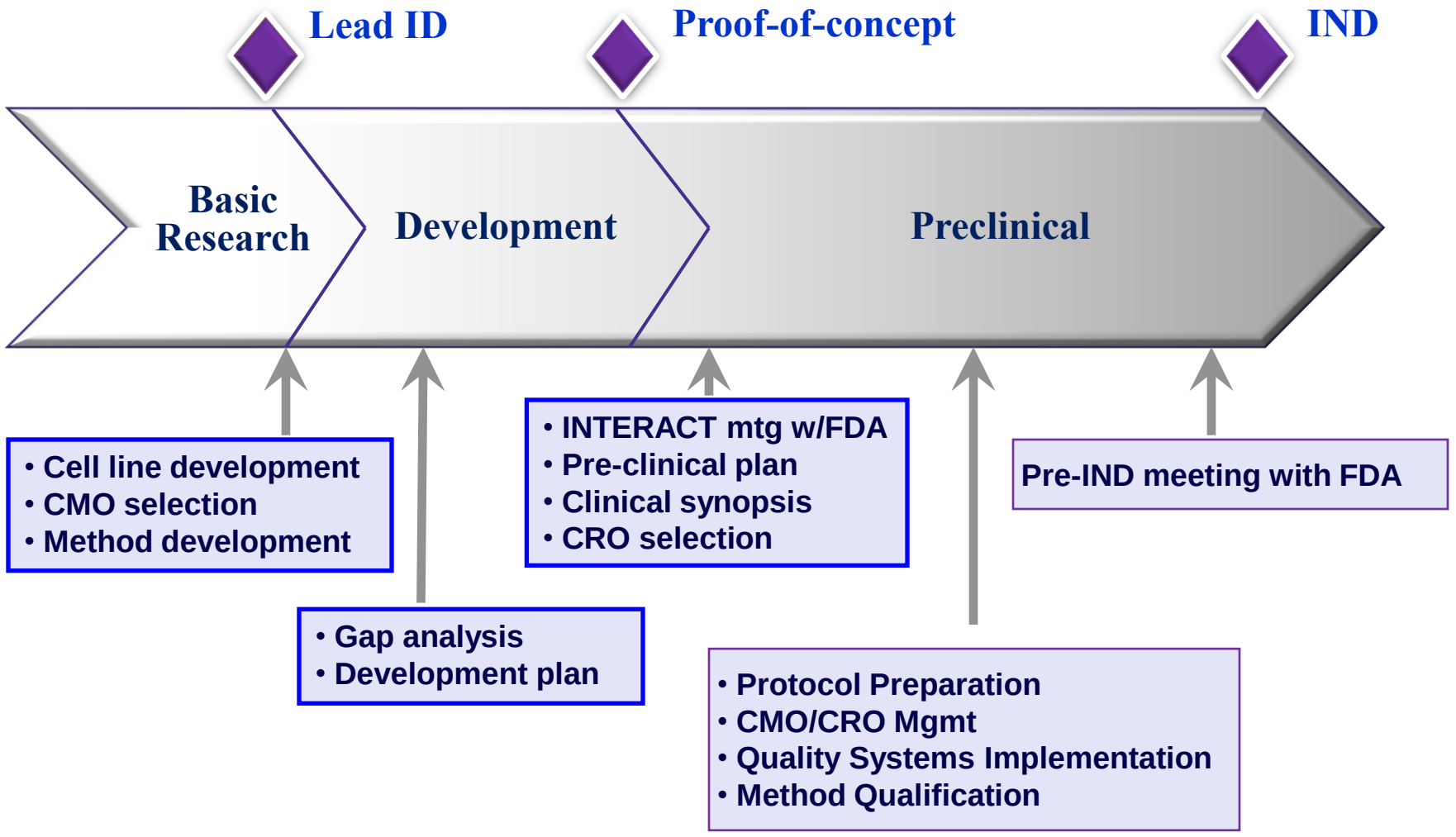
Comprehensive Product Development Planning and Management

- Gap Analysis of all development areas
- Team approach to development management
  - Preclinical, CMC, clinical, project management

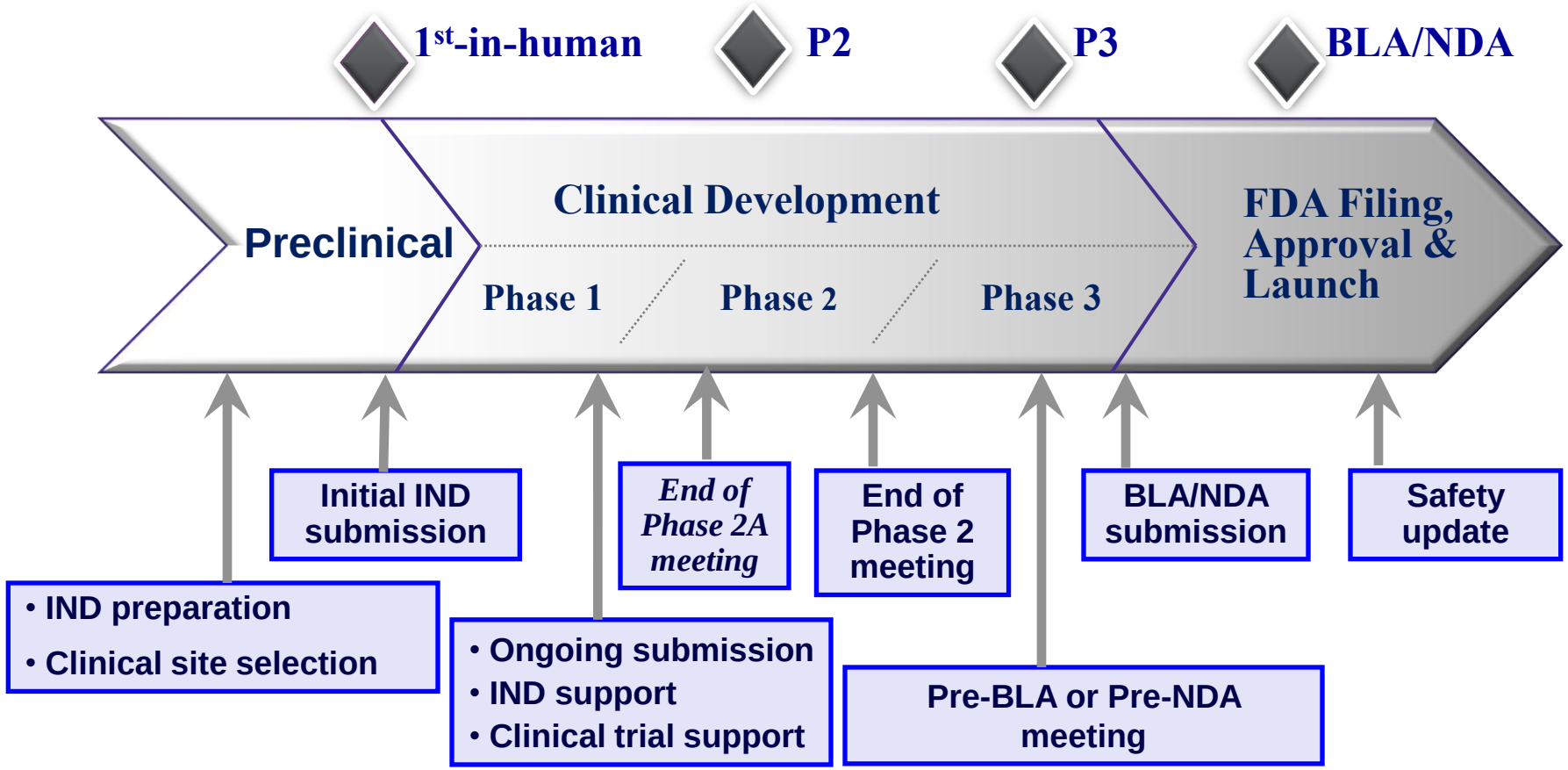
Product Development Phases

- Preclinical Animal Studies (pre-IND)
  - Proof-of-Concept
  - Toxicology
  - Safety Pharmacology
- IND Submission
- Clinical Trials
  - Phase 0, 1, 2 & 3
- Product Approval/Licensure
- Post-Marketing Studies (Phase 4)

Key Early Development Milestones



Key Clinical Development Milestones



FDA Expedited Review Pathways

Accelerated Approval

- Approval of drugs/biologics for serious conditions that fill an unmet medical need based on a surrogate endpoint.

Fast Track

- Review process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.

Breakthrough Therapy

- A designation designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy.

Priority Review

- A review designation whereby FDA's goal is to take action on an application within 6 months.

Good Regulatory Planning

- Understand your product
- Understand the regulatory expectations
- Develop the Product Development Plan with regulatory expectations in mind

- Check everything and everyone
- Get advice from independent experienced people early and often!

What is a Product Development Plan?

- A “roadmap” for your product’s development
- A concise, product-focused strategic document laying out the path to licensure/approval
- A detailed analysis of your product status and developmental requirements, including the four primary aspects of product development: Manufacturing, Preclinical, Regulatory and Clinical Development
- An integrated stand-alone document tying the four main areas of product development with budgets, tasks and timelines through Phase 1 or beyond

Typical PDP Content

- Background and Product Assessment
- Manufacturing Development Plan
- Preclinical Development Plan
- Clinical Development Plan
- Regulatory Development
- Project Management
- Budget
- Timelines

Manufacturing

- GMP
  - Some concessions for early clinical trials
  - Need a qualified experienced person to assess compliance requirements
- Manufacturing contractors
  - Compliance with GMP
  - Qualify contractors by audit
  - Monitor activities
- Examples of horror stories
  - Sterility tests on Master and Working Cell banks
  - Use of animal products
  - Poor documentation
  - Data integrity

Preclinical Safety

- Contractors
- Compliance with GLP
- Need for monitoring
- Examples of what can go wrong
  - For cause audit
  - Poor sample handling
  - Contractor retested at their expense

Clinical

- Clinical Research Organizations (CROs)
- De-barred Investigators
- FDA audits
  - Falsification of qualifications
  - Source data verification
  - Not following inclusion/exclusion criteria
  - Adequate oversight of CRO by Sponsor
- Post hoc analysis of results

Summary

- Regulatory Compliance is Critical to Success
  - If the FDA does not approve it you cannot test it in humans and you cannot sell it
- Achieving Regulatory Compliance is not simple
  - It requires a significant dedication of resources by product development specialists who have expertise with your product type
- A Rigorous PDP will provide a roadmap to efficient development and speedy approval

Thank You

David Lin, PhD, MBA
President & Principal Consultant
TS Pharma Experts LLC