

# ASGCT Translational Science Training Course: Bench to Bedside Facilitating First in Human Trials

## Introduction

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## ASGCT Translational Science and Product Development Committee

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## Goals of Today's Course

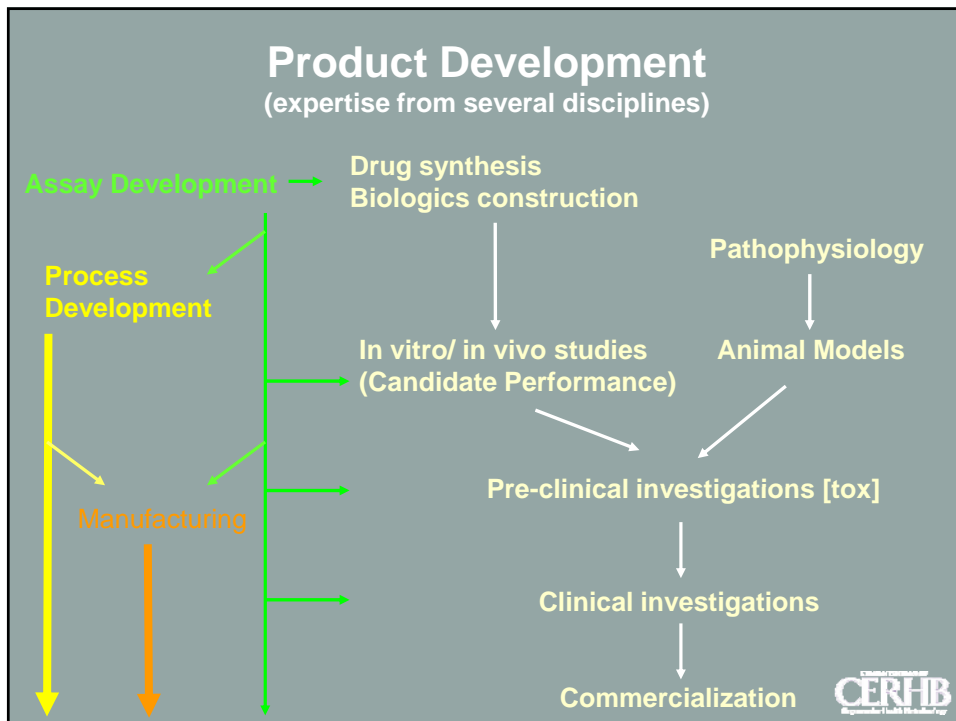
- Develop an understanding of
  - Translational Research
  - Product development
  - Regulatory landscape and process
  - Project team roles
  - Resource requirements and availability
- Different product classes have unique considerations
  - Common themes
- There is more than one way to do things



## Translational research (Bench to Bedside)



Translational research activities are foundational for companies, and are increasingly gaining importance in the academic setting where new technologies are being tested in humans prior to entering the commercial sector



# Product Development



## Perspective

- Expensive
  - Toxicology: \$250K – 500K
  - Phase I: \$1M - 3M
- Lengthy
  - Toxicology: 6-12 months
  - Phase I: 1-2 years
- Locked-in
  - Cost and time invested
- Takes many people
  - Amount of work
  - Different expertise



# Perspective

Bedside  $\longleftrightarrow$  Bench



Know where project is going to achieve success, reduce errors, and reduce cost

- Clinical Trial Design (doses, pts/cohort, #cohorts)
- Toxicology Study Design
- Regulations



# Regulations



- Code of Federal Regulations (CFR)
  - General and permanent rules of the Federal government
  - Contains the official text of regulations enforced by federal agencies



## US Federal Regulatory Agencies

- **FDA/Center for Biologics Evaluation and Research (CBER) Office of Cellular, Tissue and Gene Therapies (OCTGT)**
  - Safeguard Public health
  - ensure the safety, efficacy, potency and purity of biological and related products
  - review pre-clinical and clinical research
  - regulatory authority overseeing the development and licensing of products

DHHS  
↔

- **NIH/Office of Biotechnology Activities (OBA) / Recombinant DNA Advisory Committee (RAC)**
  - GT, Genetic Testing, Xenotransplantation
  - public review of protocols with novel scientific, safety, ethical, legal and/or social issues
  - public awareness and debate of public policy (GTPC)
  - monitor compliance with NIH Guidelines (funding)



## On-site Review

- **Investigational Review Board**
  - scientific and non-scientific members
- Review proposed clinical research
  - risk/benefit
  - study design
  - Protect subjects
    - informed consent

- **Institutional Biosafety Committee**
  - scientific and non-scientific members
- Review proposed research involving biological agents
  - Bacteria
  - Viruses
  - Animals
  - rDNA

## External Review

- Data Safety Monitoring Board
  - experts in the fields of medicine and science that are applicable to the study, statistical experts, lay representatives
  - independent committee set up specifically to monitor data throughout the duration of a study to determine if continuation of the study is appropriate scientifically and ethically



## Guidelines (open to interpretation)

Guidance documents do not confer rights for or on any person, and are not in place to bind the FDA or the public. Alternative approaches may be used if they satisfy the requirements of the applicable statute, regulations, or both. Guidance documents represent the FDA's current thinking on a particular subject

### ICH Tripartite Harmonized Guidelines



## Investigational New Drug Application

- **Investigator-sponsored IND**
  - submitted by a physician who both initiates and conducts a clinical investigation, and under whose immediate direction the investigational drug is administered or dispensed
- **Company-sponsored IND**
  - If a pharmaceutical company will be supplying the drug, but will not itself be submitting the IND, the company is not the sponsor



## Interactions

- The “Agency” does not tell you how to comply with the regulations or how to conduct studies
- You are responsible for interpreting the regulations and implementing systems that establish compliance
- Some things are negotiable



## Pre IND Meeting

Propose the plan outline, ask questions, get feedback

- Study objectives and design (scientific rationale)
- Toxicology study design
- Previous human experience
- Intended patient population (risk/benefit, defined disease)
- Patient accrual (inclusion/exclusion, numbers needed)
- Proposed dose and escalation plan (pre-clinical data)
- Patient monitoring, safety evaluations, AE's
- Potential efficacy endpoints
- Schedule of protocol events
- Manufacturing/characterization summary
- Stopping rules (germline trans, severe immune rxn)



## IND content

- General investigational plan
- Clinical Protocol
- Chemistry, Manufacturing, and Control Information (CMC)
- Pharmacology and toxicology
- Investigator brochure
- IRB approved consent form
- Previous human experience



## Nonclinical (Animal) Safety and Toxicity Studies

- Distribution
  - organ (blood, brain, liver, lung, kidney, heart, LN)
  - Gonads
- Toxicity
  - Liver enzymes (AST, GGT, ALT)
  - Muscle enzymes (CPK)
- Immune Response
  - Humoral (neutralization, ELISA)
  - Cellular (CTL assays)
- Histology
- Genotoxicity/mutagenicity/tumorigenicity
- No Effect Dose
- Minimum Effective Dose
- Maximum Tolerated Dose
- Lethal Dose



## Toxicology Study Material

- Tox conducted with material manufactured and formulated like the clinical material
  - Does not need to be manufactured under GMP, but process and materials must be well documented
  - Characterized
  - Stability tested



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## cGLP Practices

- Non-clinical laboratory (animal) research to support licensure 21CFR58
  - validity and accuracy of data
  - consistency of research and quality of study article

**ICH S1-S8**

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## Phase I Clinical Trial

- Initial Study
- Product safety evaluation
- Side effects associated with increasing doses
- Gain early evidence of effectiveness
- May include healthy participants and/or patients
- Dose evaluations



## Phase II Clinical Trial

- Controlled clinical study
  - placebo
  - Phase IIA: dosing
  - Phase IIB: efficacy
- Product safety evaluation
  - Determine the common long and short-term side effects and risks
- Evaluate the effectiveness of the drug for a particular indication in patients with the disease
  - Dose ranging
  - Potential efficacy endpoints



# Good Clinical Practices

- GCP is a standard for the design, conduct, performance monitoring auditing, recording, analysis, and reporting of clinical trials.
  - 21 CFR 50
    - Protection of Human Subjects
    - Informed Consent
    - Safeguards for Children
  - 21 CFR Part 56
    - Institutional Review Boards
  - 21 CFR Part 11
    - Electronic Records; Electronic Signatures



ICH E6

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# Clinical Trial Material

- Manufactured and tested under GMP
  - Process defined
  - Single use aliquot
  - Extensively characterized product
  - Stability tested



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## Lead Identification



- Discovery
- Efficacy
- Reporting
- Documentation

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## Biopharmaceutical Manufacturing (Protect the Product)

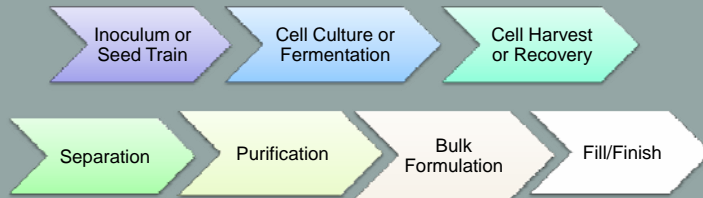
- **Controlled Processes**
  - Reproducible
  - Consistent
  - Robust
  - Aseptic
- **Product**
  - Safe
  - Pure
  - Potent
  - Stable



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# Processing Steps

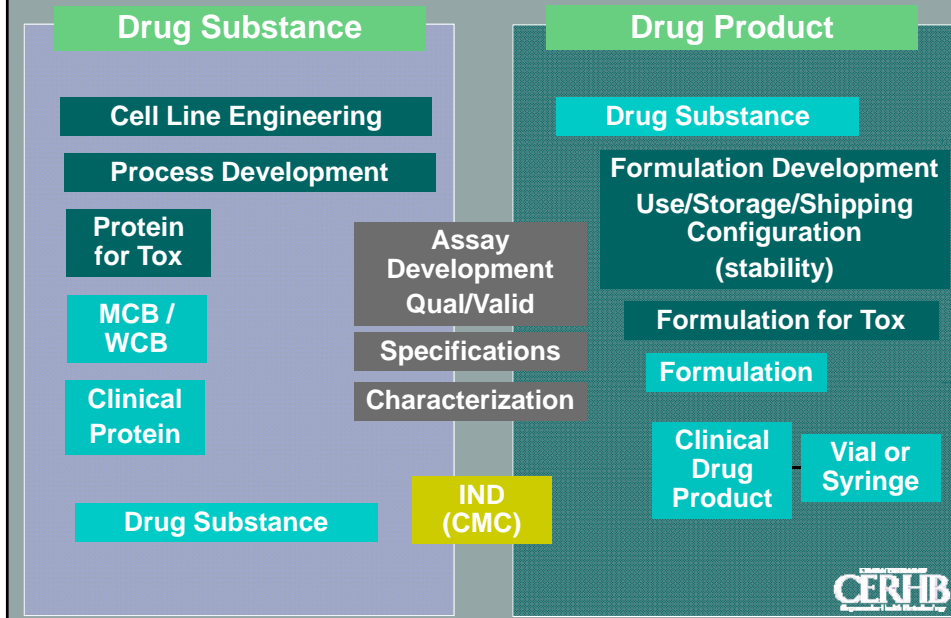
## Upstream Processing



## Downstream Processing



# cDNA to Phase I Clinical Trial



## Fill and Finish



Single use aliquots

- Formulation
- Filtering
- Filling
  - Vials
  - Bags
  - Bottles
  - Tubes
  - Syringes
- Labeling
- Packaging



## QC Testing

Product Characterization and Safety Testing

- **Titer**
  - Infectious center Assay (ICA)
  - Real-time PCR
  - CAP ELISA
- **Potency**
  - Transgene protein activity
- **Purity**
  - PAGE and silver stain for protein
  - rcAAV (ICA)
  - 293 Ch. DNA
  - Benzonase residual
- **Identity**
  - Plasmid RFLP
  - Viral DNA seq
- **Appearance**
  - Visual inspection
- **pH**
- **Osmolality**
- **Safety**
  - Adventitious agents
  - Sterility, B&F
  - Mycoplasma
  - Endotoxin
- **Stability**
  - Infectious titer
  - Sterility
  - Degradation

## cGMP Practices

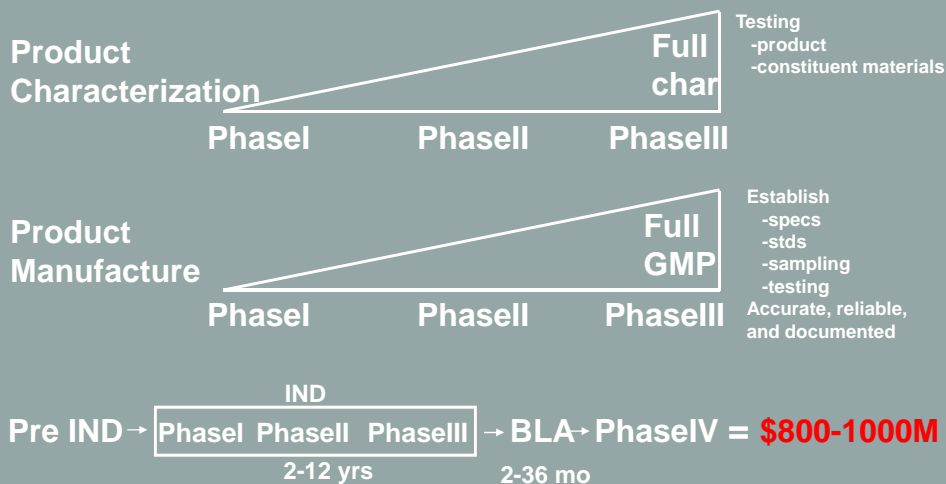
Regulations that describe the methods, equipment, facilities, and controls required for producing human products, medical devices and processed food. Current scientifically sound practices and principles that are implemented and documented during product development and production to ensure consistent manufacture of safe, pure, and potent products  
21CFR210,211,610



ICH Q7

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## Product Development Continuum



Source: FDA

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## Project Team Roles, Organization & Communication



## The Main Players

- **Clinical team**
- **Research & Development**
  - Discovery
  - Process Development (PD)
  - Assay Development (AD)
- **Manufacturing**
  - Production/Purification
  - Facilities
- **Quality Control (QC)**
- **Quality Assurance (QA)**
- **Regulatory Affairs**
- **Business**
  - Market analysis, Sales, Advertising, Bus. Development



## Clinical Team

- Develop clinical protocol
  - Identify patient population
    - Inclusion/exclusion criteria
  - Delivery route and method
- Design toxicology study
- Identify clinical trial locations
- Assemble Statisticians, Nurses, etc
- Establish DSMB
- Obtain IRB and IBC approvals
- Write investigator's brochure
- IND



## Research & Development

Discovery: Finding (in-house or in-license) a potential product

Process Development:

- Design and develop processes to make the product
- Work with Clinicians for product configuration
- Develop plan for manufacturing the product



## Process Development

### Drug Substance

- Maximize
  - Yield (COG)
  - Purity
  - Potency
  - Stability (in-process hold steps)
- Raw materials sourcing and specifications
  - In-house manufacture
- Closed systems, Automated
- Scale-up
- Sampling points (stability: different matrices)
- Production Batch Record Development
- Tech transfer to cGMP environment
  - Training of personnel



## Process Development

### Drug Product

- Number of vials, syringes, or bags
- Fill volume (fill tolerance depends on pump accuracy)
- Delivered volume (recovered from vial and injected)
- Formulation
  - Product stability
  - Compatibility with use
- Storage temperature
- Labeling and Packaging
- Shipping conditions and validation



# Quality Control

- Demonstrate Product Safety
- Characterize product
  - Test samples of the product and materials used to make product
- Demonstrate product lot consistency
- Demonstrate product stability
  - Historical
  - Concurrent with clinical trial
- Environmental and Personnel Monitoring
- Assay Development & Validation



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# Testing

- In-house assay development
  - Specificity
  - LOD/LOQ
  - Linearity and Range
  - Reagent sourcing
  - Test Record Development
  - Assay Qualification / Validation
  - Generating cell substrates, standards, controls
  - Maximizing throughput and turnaround
  - Sample tracking procedures
- Outsourced testing
- Review results

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## United States Pharmacopeia (USP)

- A compilation of officially recognized standard testing methods and reference standards relating to medicine and other health care technologies
- Validation Categories for analytical methods
- European: Eur. Ph.



## Specifications

- Establish the specifications of the raw materials and product - CFR 211.165
  - Composition, physical & chemical properties
  - Strength, potency
  - Identity
  - Purity
  - Safety
  - Stability & shelf life



## Manufacturing/Production Unit

- Responsible for making the product under control
  - Operate process equipment
  - Manufacture ancillary materials
  - Routine production environment control
    - Maintaining proper temperatures, cleanliness, etc..
  - Monitor processes associated with making the product
  - Implement corrective actions in the event of a problem
  - Drafting & Following written procedures



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## Facilities Department

- Engineering (Facilities Management)
  - Proper operation of building systems
  - Proper installation/operation of equipment and IOPQ
- Facility Maintenance & Housekeeping
  - Maintenance & repair of equipment & facility
  - Metrology (calibrations)
  - Routine cleaning
- Receiving and Shipping
  - Insure proper routing of incoming raw materials
  - Inventory control
  - Finished products go to proper destination

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## Quality Assurance

- Oversight responsibilities – ensure compliance with GMPs, GLPs, GCPs
  - Independent
  - Review and Approve all Records, Reports, written procedures, specifications
  - Audit methods, results, systems and processes
    - Data trending
    - Compare data to established standards
  - Prepare and issue documents
  - Document control

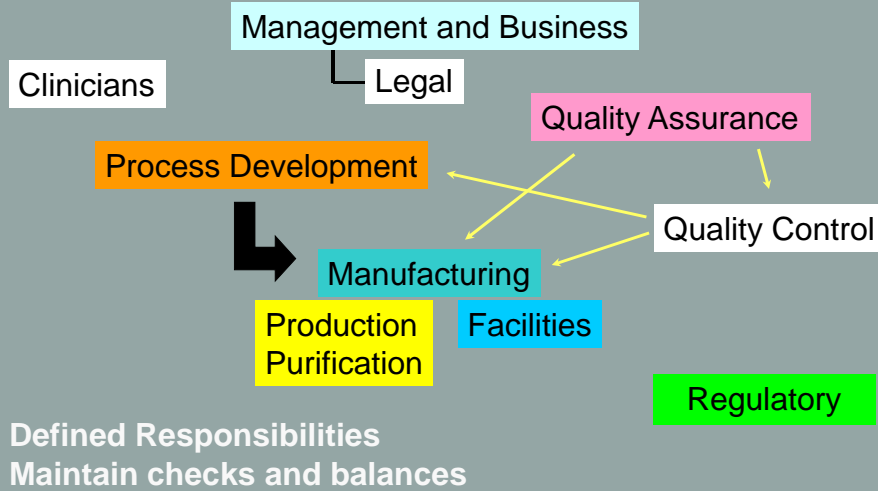


## Quality Assurance Cont'

- Investigations
  - Out-of-Specification occurrences
  - Deviations
- Change Control
- Training oversight
- Vendor Qualification
- Validation plans
- Inspections
- Review customer complaints
- Ultimate authority to release/reject raw materials and product lots
  - According to pre-set specifications



# Organization



# Delivery to the Investigational Pharmacy



## Product Quality

- The team is responsible for ensuring the quality of the product and conduct of the trial



**Patient Protection!**

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## Project Management

- Form a Project Team
- Develop project plan & timeline
- Allocate resources
- Execute project plan
- Monitor progress according to timeline

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## Project Manager

- Key person to coordinate team & monitor progress
  - Develops the Project Plan & Master Schedule/Timeline
  - Identifies skills/personnel needed to complete project
  - Resource Acquisition/Budget
  - Tracks and communicates status of project



## Project Manager cont'

- Facilitates meetings & documents minutes
- Discusses and documents barriers, opportunities and solutions
- Updates the Project Plan (delays are inevitable and must be managed)
- Reallocates resources within & between projects
- Evaluates risk/benefit and gets team buy-in for action



# Product Cost Drivers

- Amount of product needed: driven by doses
  - Clinical
  - QC testing
  - Stability
- Manufacturing process
  - Reagents (cell banking, buffers)
  - Duration
  - Manpower and facility space requirements
- Analytical methods
  - Reagents (cell banking, controls, standards)
  - Qualification/validation
- Early choices have high impact
  - Tagged protein
  - Expression cassette
    - Cell line
    - Vector
  - Intellectual Property



Fast/easy = slow

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# Timeline and Budget

- When does product need to be delivered?
  - Target Start of Clinical Trial?
  - Work backwards to develop timeline
- Budget
  - Manufacturing Costs
    - Pre-clinical
    - Clinical
  - Additional Personnel
  - Pre-clinical study costs
    - Animal models, analyses
  - Clinical Costs
    - Doctors, Nurses, Statisticians, Patients...

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## The Next Sessions

In-depth presentations covering:

Regulatory Considerations

Design of Preclinical Efficacy and Safety Studies

Manufacturing and Quality Systems/Quality Management

Analytical Development

Resources

Thank you