Product Development
Moving from the Bench to Clinic
Introduction to the Principles and Practice of Clinical Research

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Product Development

Overview of Product Development

Costs of Product Development

Product Development, Manufacture and Testing of Clinical Materials

GMP Facility and Environmental Monitoring

Example: H5 Influenza Vaccine from Bench to Clinic
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An Example of Product Development

1958 – A pandemic caused by H2N2 flu results in more than 69,000 deaths in the U.S.
1967 – Dr. Hunein Massab of the University of Michigan develops a live, cold-adapted flu virus for use in a vaccine
1976-91-NIAID sponsors series of clinical trials to evacuate safety and efficacy to live, attenuated flu vaccine.
2000 – Initial submission to the FDA for licensure in adults and children age 1 to 64
2003 – FluMist is available for use for the first time to healthy adults and children ages 5 through 49
2007 – FluMist approved for healthy adults and children ages 2 through 49
Source: NIAID website
How are Products Selected for Development?

Graphics showing financial value of the product if successful
Future revenue = cost of development
Probability of success
Scientific
Legal
Engineering
Business
Steps in Biological Product Development

Discovery -> Pre-clinical -> PoC in Humans -> Ph.III -> Registration

IND = Individual New Drug Application
BLA = Biologics License Application
Product Development Teams

Product Development team formed to direct development of clinical candidates
Includes members of all required functions: R, D, Reg, Clin, Manuf, PM
Responsible for developing
  Target product profile
  Overall development timelines
  Budgets
Product Development

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Drug Development Costs

Data difficult to obtain
Measurement of total cost
  Out of pocket expenses
  Risk adjusted cost of capital
Basic Research Costs are NOT included
Drug Development Costs

Chart:

Exhibit 3
Capitalized Preclinical, Clinical, And Total Cost Per New Drug in Millions of 2000

Health Affairs, 25, no. 2(2006): 420-428
Doi” 10.377/hlthaff.25/2.420
Probability of Success
Exhibit 2
Average Phase Time And Clinical Capitalized Costs for Investigational Compounds
Health Affairs, 25, no. 3 (2006): 420-428
Doi: 10.1377/hlthaff.25.2.420
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Product Development: Why So Long and Expensive?
Development Process
Production Facility
Pre-Clinical Safety Testing
Clinical Trials
Vaccine Production Program
Development Cycle at the VRC
Research and Development
cGMP Production
Clinical Trials
Immune Assessment
Keys to Process Development

Consistency

Scalability

Safety
  Raw materials
  Cell lines
  Excipients

Analytical methods
Biological Products

Biological Products – Cell Substrates
  Antibiotics – Mycelial (fungal)
  Vaccines – Bacterial & Viral
  Recombinant Proteins – Bacterial & Mammalian
    Growth factors
    Monoclonal antibodies
  Vaccines
Adventitious Agent Safety Concerns

Fungal/bacterial << mammalian cell derived

Safety – Lessons From Our Past

Biological Product Cell Substrates

Polio - Primary monkey kidney cells

Yellow Fever - Embryonated chicken eggs

Small Pox – Calf skin

Monoclonals/proteins – Rodent Cells
Solutions to Some Product Safety Concerns
Use of highly characterized cell lines rather than primary cells
Validated manufacturing process
Validated adventitious agent (bacterial and viral) clearance in the manufacturing process (where possible)
Highly controlled raw materials
Move to animal component-free raw materials
DNA Vaccine Bulk Manufacturing Process – A VRC Example
DNA Plasmid Fermentation

Photo of someone working in a lab
Can You Manufacture Enough Product? Chart showing Plasmid DNA
DNA Plasmid Fermentation

Graph
100L Fermentation - OD Profile
Graph showing 100L Fermentation
100 L Fermentation – Feed Profile

Graph
100L Fermentation - Acetate Profile

Graph
100L Fermentation - pDNA Productivity
Graph
Is the Process Consistent?  
Graph
Is the Process Scalable?
Graph
DNA Plasmid Purification
Photo showing someone at a computer
Size Exclusion Chromatography Graph
Affinity Chromatography
Graph
Ion Exchange Chromatography Graph
DNA Plasmid Assay
Development
Photo of someone in the lab
Product Consistency: DNA

Plasmid Bulk Testing

Chart: Plasmid DNA Bulk Drug Substance Test Results
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Manufacture of Products for Clinical Trials

Good Manufacturing Practices (GMPs)
FDA Regulations – apply to process and facility
Philosophy of cGMP

• Document/approve exactly what you’re going to do
• Document/approve exactly what you did
• Review all work to ensure that what you did is exactly what you said you would do

Paramount concern is safety of clinical subject
Facility Design and GMP
Environmental Considerations
Engineering Controls

HVAC Design
Air handlers
Airlock setup and room pressurization
Room classifications
Heap filtered air

WFI system

Disposable or cleanable fluid path solution preparation
Liquid and solid biowaste systems
Unidirectional clow building layout
Airlock Setup and Room Pressurizations

Separate air handlers for each area
Separation between production areas is maintained by a system of negative pressure airlocks protecting both entry and return corridors
All airlock functions and room pressure differentials are individually monitored and alarmed
GMP – Protect Product from Contamination Solution: Undirectional Flow/Segregated Manufacturing Areas

Chart
Chart
Utilities

Photo of utility system

Flexible delivery of 19 utility systems
Approximately 9 miles of pipe
Over 180 miles of cable
How Clean is a GMP Cleanroom and How Do We Keep it That Way?

Environmental Monitoring

(or should the 5 second rule apply?)
Purpose of Environmental Monitoring
Monitor critical processes within the pharmaceutical and biotechnology industries. Determine the microbial and particulate content of cleanroom air and surfaces. Highlight conditions contributing to excessive microbial & particulate levels due to ineffective cleaning, or personnel/equipment issues (trending). Alert to conditions exceeding classifications
Pro-active tool for Quality Assurance
To be monitored
Non-viable airborne particulates
Viable airborne particulates
Viable surface bound particulates on cleanroom surfaces and personnel

Contamination Sources:
People ~ 75%
Ventilation ~ 15%
Room Structure ~ 5%
Equipment ~ 5%
Classifications Table
Counting Particles

Particle Counter (for measurement of non-viable airborne particles)
Uses a calibrated laser particle counter

Settling Plates (for measurement of viable airborne particulates)
   Uses active settle plates and/or air sampler

RODAC Plates (for measurement of viable, surface-bound particles)
   Uses agar plates with agar above the edge of the plate
A Real Life Example
Comparison of GMP and non-GMP Areas
Table
The Personnel Gowning Process
Sterile gloves
Mask
Hood
Gown
Boots
Second pair of sterile gloves
(IPA used between each step)

Photos showing the different steps
cGMP Compliance

Over 1 million pages of QA documentation to date in validated electronic document control system
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Product Development Activities

Manufacture of Clinical Trial Materials

Example: Influenza Vaccine from Bench to Clinic
Indonesia Strain-Influenza DNA Vaccine Development
Flow chart
Swine-Origin Influenza A
(A/California/04/2009 (H1N1))
DNA Vaccine Development
Timeline
Chart of timeline
Conclusions
Product Development is multi-disciplinary

Industry estimates average drug development requires 8-10 years and $800 million (year 2000 dollars)

Economics drive the selection of drug candidates

FDA establishes strict rules for the manufacture (cGMP), animal testing (GLP) and clinical evaluation (GCP) of new drug products