NCI Drug Development Workshop: How to Advance A Therapeutic Candidate from Bench to Bedside



Session V. Development of Biological Products

# PROCESS DEVELOPMENT: Navigating the UP/DOWNstreams

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# **Process Development for Biologics**

- Manufacturing a biologic product involves a process that uses living cells or their components.
- The process is typically carried out in a bioreactor which allows for the highest control of the environment.
- This presentation will cover:
  - Goals of Process Development (PD)
  - How cell line selection drives the PD
  - Considerations for Upstream PD
  - Navigating Downstream PD



# Drug development requires paradigm shift to advance drug from bench to clinic



Hypothesis-driven paradigm 'expand knowledge'

Engineering paradigm 'keep the <u>END</u> in mind'

# **Process Development**

- The sequence of operations and parameters required to ensure that manufacturing process produces a product within specification.
- The objective of process development is to develop a robust, scalable, reproducible, and cost-effective process that results in safe and efficacious biopharmaceuticals.
- Process development is the means to the <u>END</u>.



### **Phases of Process Development**



# Process Development Links Tech Transfer & cGMP Manufacturing





Often may be used to perform IND enabling Toxicology and Safety Studies

# **Early Process Development**



- The early phase of process development involves selection of the cells or components that will produce the biologic.
- Highly characterized cells are required to ensure quality and safety of biologics.
- Regulatory authorities require information about the cells including:

### **Derivation**

- Characteristics species, strain, genotype, phenotype, generation, pathogenicity, toxins, purity, ect.
- Data published, historical, and experimental
- Procedures used to generate the cells e.g. media requirements

### **Stability**

- Consistent production and recovery of product
- Stability during storage and cultivation

### Testing

- Consistency of the coding sequence
- Other traits (e.g growth characteristics, biochemical/immunological markers, productivity)



Remember that the sequence, vector & cell line used at the research bench may not be the same as those used in cGMP PD

# **Choosing An Expression System**

System	Advantages	Challenges	Examples
Mammalian	<ul><li>Highest-level protein processing</li><li>Transient or stable</li></ul>	<ul> <li>High yields (grams/liter) may require suspension cultures</li> <li>Complex culture conditions</li> </ul>	<ul> <li>Human Embryonic Kidney 293 (HEK293)</li> <li>Chinese hamster ovary (CHO) cells</li> </ul>
Bacterial	<ul><li>Scalable</li><li>Low cost</li><li>Simple culture conditions</li></ul>	<ul> <li>Protein solubility</li> <li>May require protein specific optimization</li> </ul>	<ul> <li>Escherichia coli (<i>E. coli</i>)</li> </ul>
Yeast	<ul> <li>Eukaryotic protein processing</li> <li>Scalable</li> <li>Simple media</li> </ul>	<ul> <li>Fermentation required</li> <li>Growth conditions may require optimization</li> </ul>	<ul> <li>Saccharomyces cerevisiae (S. <i>cerevisiae</i>)</li> <li>Pichia pastoris (<i>P. pastoris</i>)</li> </ul>
Insect	<ul> <li>Protein processing like to mammalian</li> </ul>	<ul> <li>Culture conditions more complex than prokaryotics</li> <li>Production of recombinant baculovirus vectors are time consuming</li> </ul>	<ul> <li>Baculovirus expression vector system (BEVS)</li> </ul>

# **Establishing a Cell Bank System**

- Establishing a cGMP cell bank system is early development step for biopharmaceutical production.
- Cell bank systems decrease risks of maintaining a cell line (e.g. microbial contamination, loss of desired characteristics, and genetic drift).
- A master cell bank (MCB) aliquots of a uniform cells derived from a single source – are used to manufacture a working cell bank (WCB). The WCB is used for production.
- The source and process for generating MCBs and WCBs must be documented and traceable.
  Cell Banking Math:



# **Upstream Process Development**



- Upstream processes are the steps in which cells are grown in bioreactors.
- Key upstream processes include:
  - Inoculum development
  - Culture medium generation
  - Optimization of growth kinetics



Remember that the conditions and processes used at the research bench may not be the same as those used in cGMP PD

# **ICH for Biologics**

- The International Council for Harmonization (ICH) documents technical requirements for pharmaceuticals for human use.
- Joint initiative involving both regulatory authorities and pharmaceutical industry representatives of the US, EU, and Japan.



# **Downstream Process Development**



- Downstream processes are the steps to recover and purify the biologic product.
- Key downstream processes include:
  - Cell disruption if the biologic product is intracellular
  - Separation of the biomass/cells from product
  - Concentration of medium if the product is extracellular
  - Purification of the product
  - Impurities Removal viral inactivation, endotoxin & host cell impurities removal
  - Protein modification refolding, PEGylation, bioconjugation, enzymatic processing
  - Formulation & Fill/Finish
  - Quality Analytics acceptance criteria

### **Downstream PD Considerations**

What's the best process?

# Precipitation and centrifugation methods

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- Salting out
- Isoelectric point precipitation
- Precipitation with miscible solvents
- Non-ionic hydrophilic polymers
- Polyvalent metallic ions
- Centrifugation
- Gradient centrifugation

### **Filtration Processes**

- Microfiltration
- Depth filtration
- DF (diafiltration)
- UF (ultrafiltration)
- TFF (tangential flow filtration)
- CFF (crossflow filtration)

### Viral Inactivation & Impurity Removal Processes

- Low/High pH
- Solvent/Detergent
- Heat/Pasteurization/Irradiation/Sterilization
- High-energy light
- Chemical inactivation
- Chromatography
- Filtration

### **Chromatography Processes**

- Column chromatography
  - Ion exchange
  - HIC (Hydrophobic interaction)
  - Anion and cation exchange
  - Size exclusion
  - Immunoaffinity chromatography
  - Normal phase chromatography
  - Reverse phase chromatography
  - Expanded bed absorption
- Membrane chromatography
- HPLC (High performance liquid chromatography)

# **Comprehensive Product Development Team Is Essential To Navigate PD**



- For biologics the Product is the Process effective process development for manufacturing is central to product quality and the path to clinical trials.
- Drug development paradigm shift requires comprehensive development team to guide process with END in mind.
- Cell line selection defines the upstream & downstream process.

# **Let's Talk About Developing Your Biologic**

### **Biological Resources Branch (BRB)**

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#### https://dtp.cancer.gov/organization/brb/default.htm



### **DCTD** Consultation

DCTD Div CCR Cer	ision of Cancer Treatment & Diagnosis ter for Cancer Research Search this ste
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Development Consultation	A focused consultation service provided by staff from the DCTD Developmental Therapeutics Program and Cancer Imaging Program
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