CMC Overview for Biologics

Gayle Derfus, PhD

Executive Director, Biologics Drug Substance Process Development
Gilead Sciences

Learning Objectives

- Role of CMC teams in biologics drug development
- Describe biologics and their manufacturing processes
- Understand phase-appropriate product/process development and scale-up
- Describe challenges for biologics supply chain management

CERSI
UCSF-Stanford

Introduction

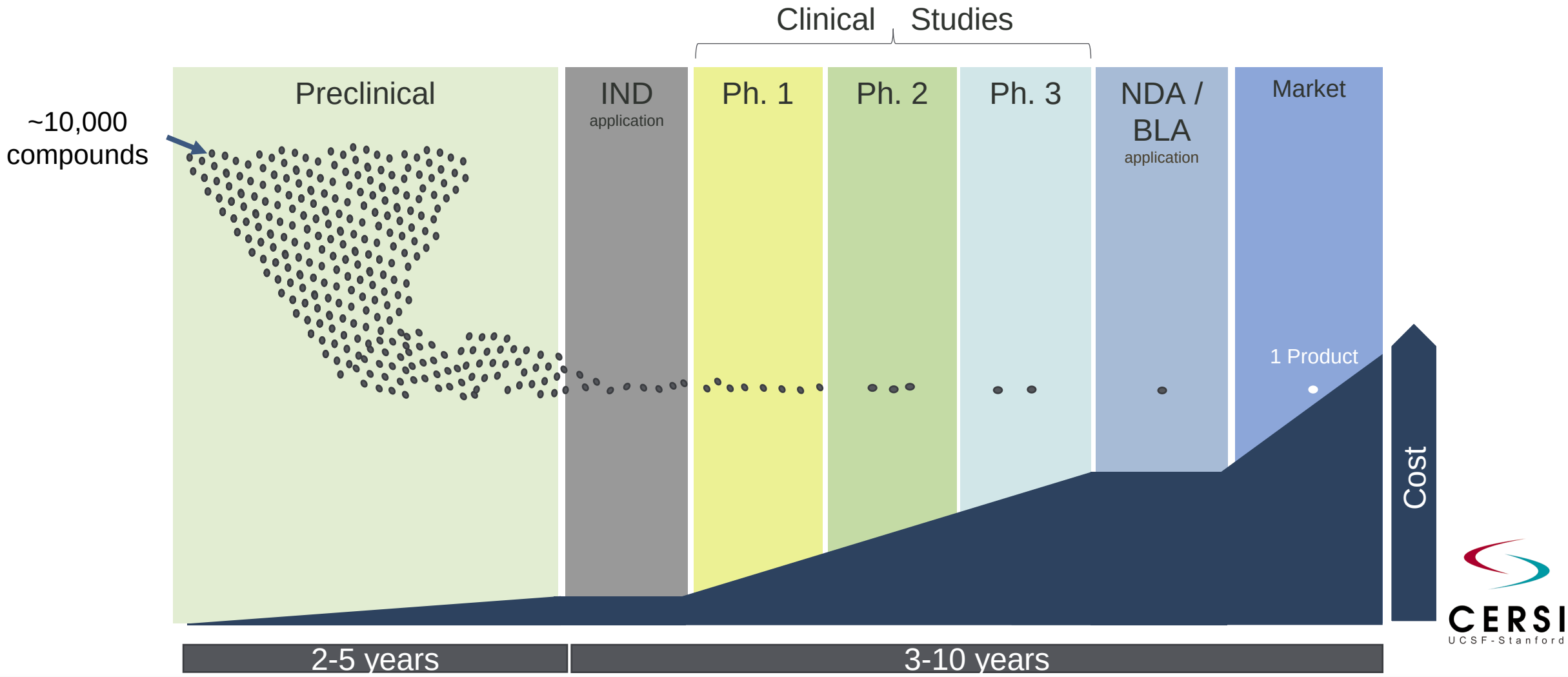
CERSI
UCSF-Stanford

Drug Development: From Idea to Product

- CMC teams must develop drugs that are
  - Safe and effective
  - Consistent from clinical trials to marketed product
  - Consistent across all batches/lots produced

CERSI
UCSF-Stanford

Drug Development is a Long & Rewarding Road



Clinical (Human) Study Phases have Different Purposes – CMC Team Must Plan Accordingly

Phase 1

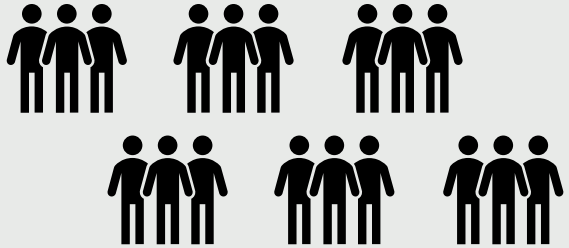
Is it safe?

What is the right dose?

Phase 2

Does it work?

Phase 3



Is it better than existing treatment?

- Increasing quantity of drug required
- Increasing product and manufacturing process understanding

CERSI
UCSF-Stanford

Target Product Profile (TPP) Outlines the Desired Characteristics of a Proposed Product for a Specific Indication

- The CMC team helps to define the target product profile and develops product to meet requirements

Example CMC-relevant elements of a TPP for HIV Cure[1]

Product Characteristic	Minimum Requirement	Ideal Requirement
Target patient population	Subset of people with HIV	All people with HIV
Administration route	Parenteral acceptable	Single dose oral preferred
Regimen duration	12 months	3 months
Storage	Cold storage acceptable	Stable at ambient temperature

1. Lewin et al, on behalf of Sunnylands working group

CERSI
UCSF-Stanford

CMC Team Contributes to Regulatory Filings to Enable Drug Approval

CMC information is provided to regulatory agencies at two key milestones: prior to starting human studies, and prior to selling the product

- Manufacturing process
- Product testing methods and results

In response to these applications, agencies request more CMC information as well

CERSI
UCSF-Stanford

CMC Activities Require Collaboration Across Many Functions

Drug Substance (DS)
- Develops a scalable DS manufacturing process

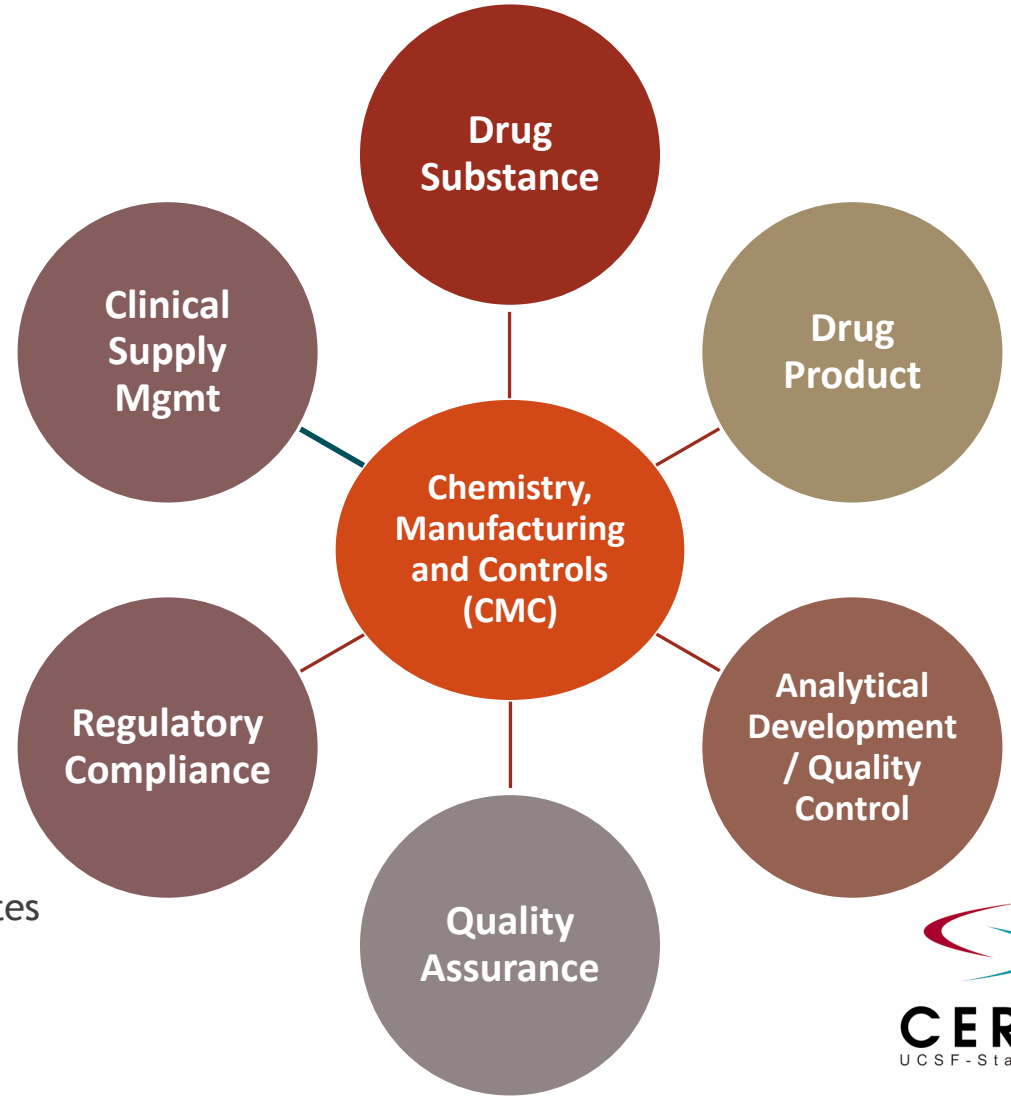
Drug product (DP)
- Develops a formulation and DP configuration

Analytical Development / Quality Control
- Develops methods and generates data that support the manufacturing and regulatory strategy for DS and DP

Quality Assurance
- Applies quality standards to DS and DP manufacturing and testing

Regulatory Compliance
- Oversees regulatory requirements to ensure patient safety

Clinical Supply Management
- Labels drug product and manages storage and shipment to clinical sites



CERSI
UCSF-Stanford

Biologics

Defining Biologics

One key feature that defines biologics and distinguishes them from small molecule therapeutics is how they're made:

- Small molecule: *chemical synthesis*
- Biologics: consist of or produced by *living organisms*

CERSI
UCSF-Stanford

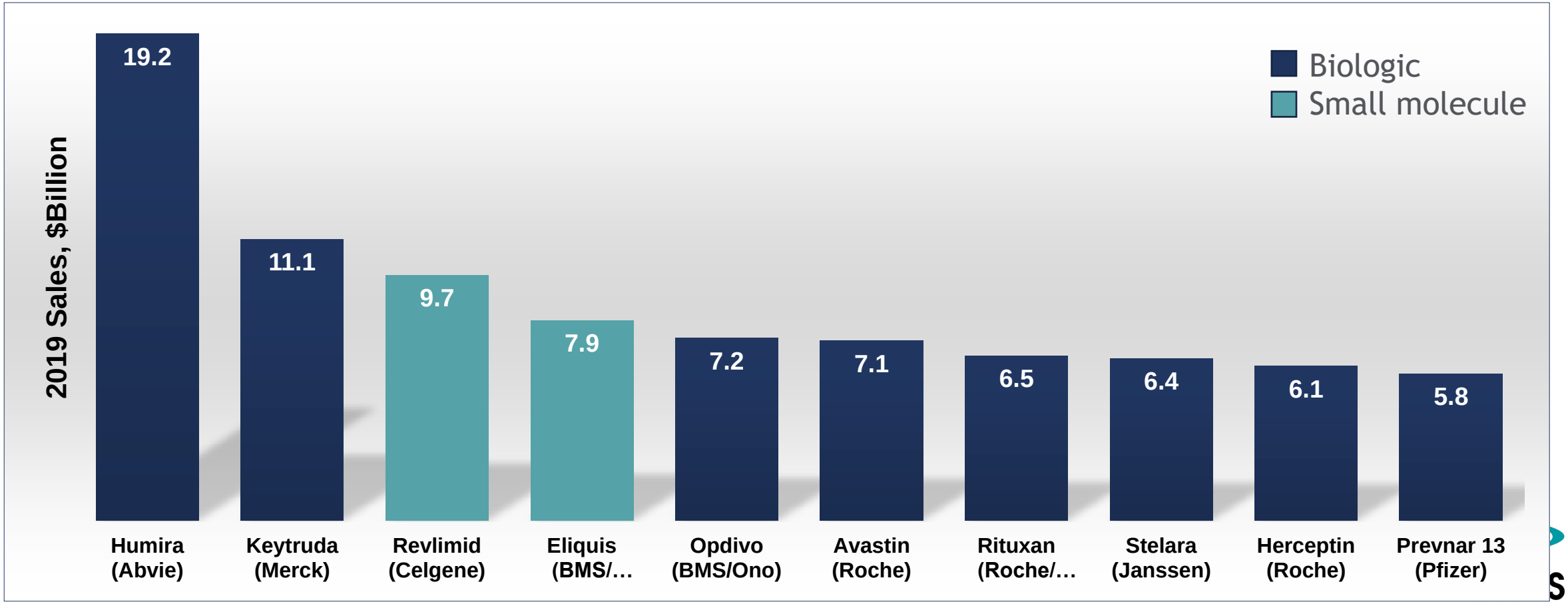
Biologics vs. Small Molecules

- Biologics are, in some ways, more complex to develop than small molecules

Feature	Small molecule	Biologics
Molecule size	≤1,000 Da	>2,500 Da
Uniform product	Yes	No – heterogeneous mixture
Production time	+	+++
Manufacturing cost	$	$$$

CERSI
UCSF-Stanford

Examples of Top-Selling Biologics



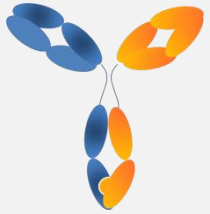
www.statista.com (2019)

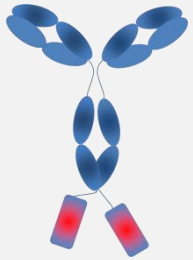
Biologics Modalities

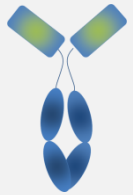
Recombinant protein formats

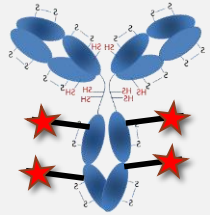

Monoclonal antibody


Bispecific, asymmetric

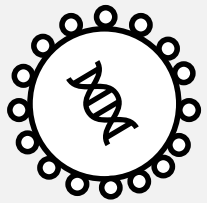

Bispecific, symmetric

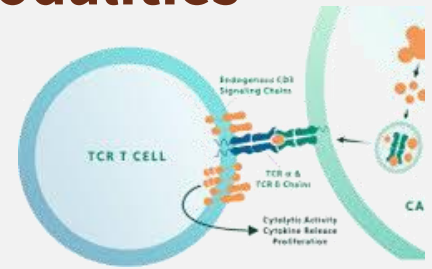

Bi-functional


Fc-fusion


Antibody-drug conjugate

Non-protein modalities


Viral vaccine



Cell therapy
www.kitepharma.com

- Modality or molecule type is selected based on desired mechanism of action (MOA)

CERSI
UCSF-Stanford

Molecule Assessment

Purification

- Assess low pH stability
- Purify transient material for stability and analytical evaluations

Analytical

- Identify unique molecular features
- Assess suitability of available methods
- Generate/assess PQ data for stability studies

Drug Product

- Evaluate stability in platform formulation
- Determine melting temperature
- Assess solubility and viscosity if high dose or SC TPP

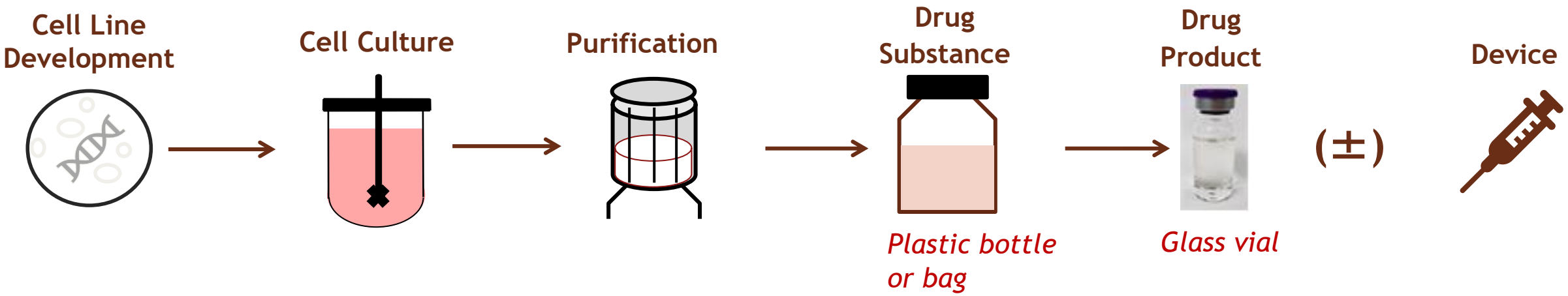
Cell Line

- Establish cloning, transfection, and host cell requirements
- Evaluate expression level

- CMC team can collaborate with research/discovery team to ensure developability of the molecule

CERSI
UCSF-Stanford

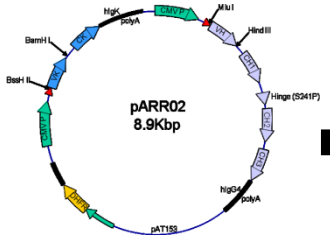
Biologics (Recombinant Protein) Manufacturing Process



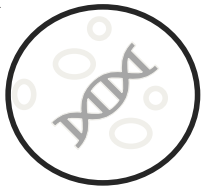
CERSI
UCSF-Stanford

Cell Line Development Process Overview

Prepare recombinant DNA

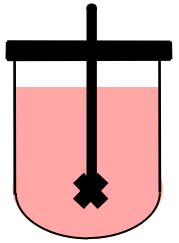


Construct recombinant vector

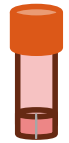


Transfect host cell with recombinant vector

Evaluate candidate clones



Select final clone



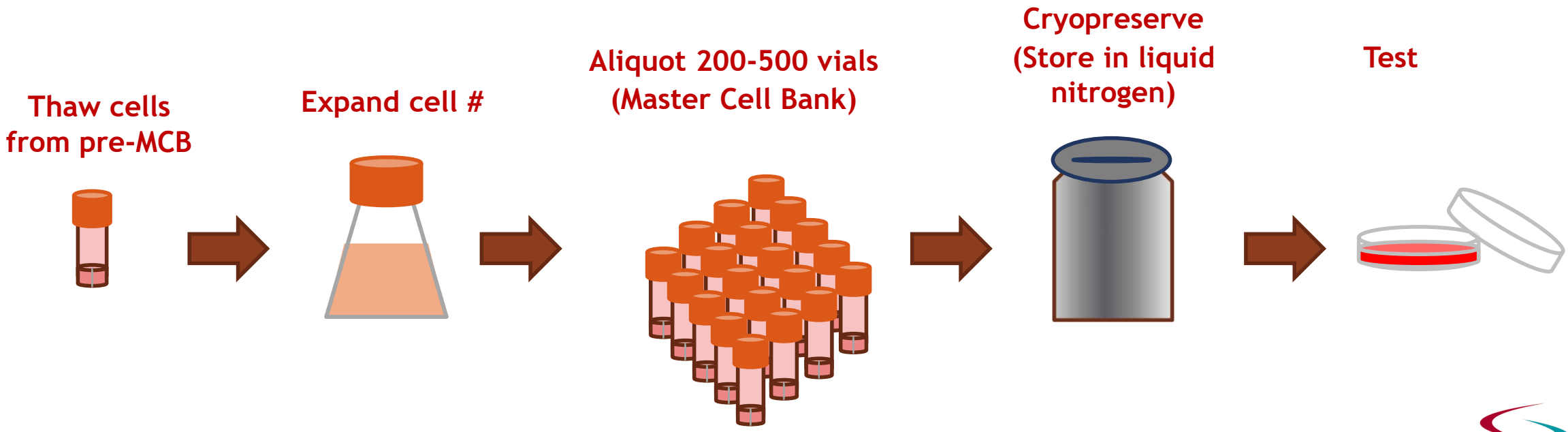
Cryopreserve cell bank (pre-MCB)

MCB: Master Cell Bank

CERSI
UCSF-Stanford

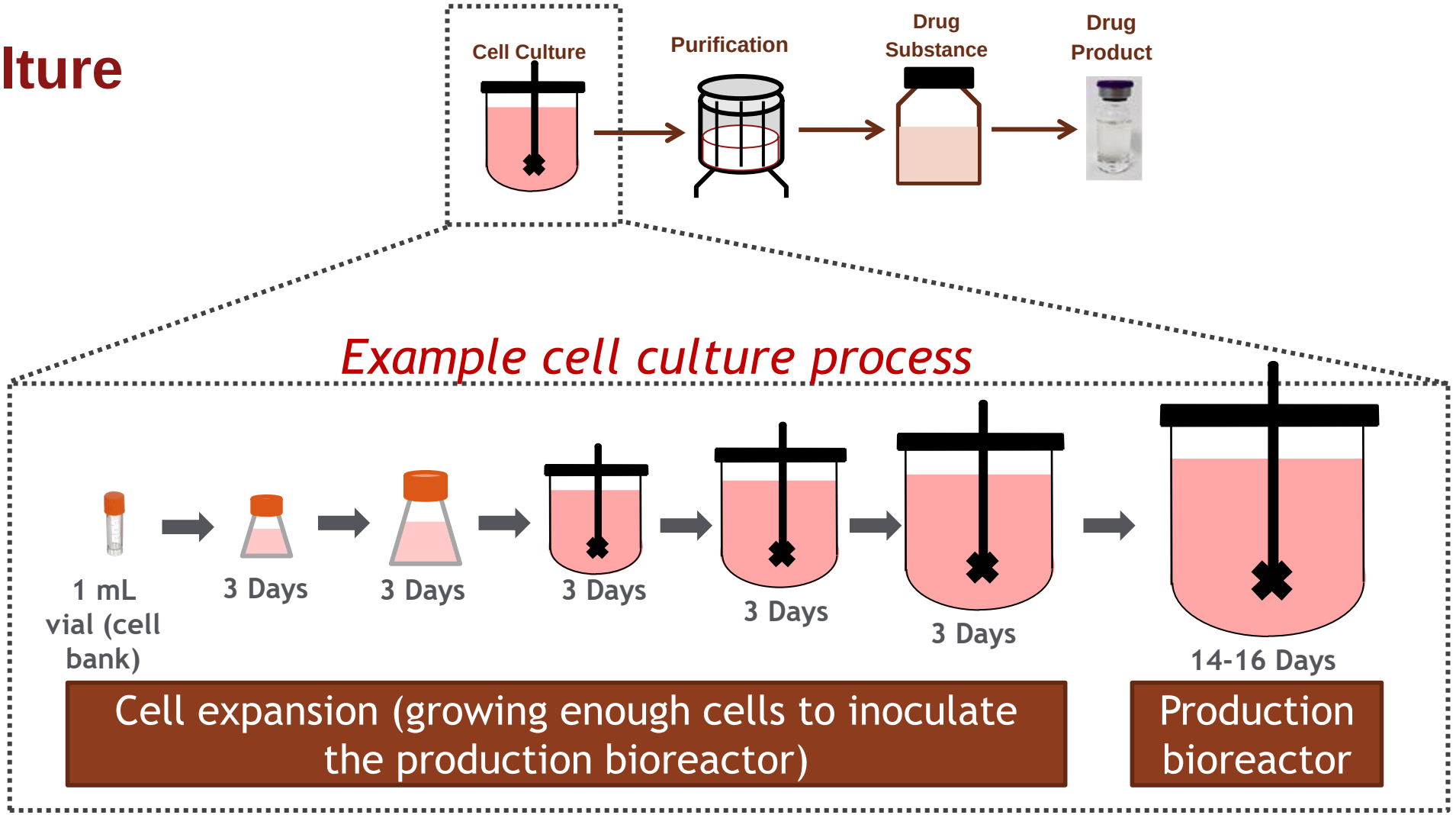
Cell Banking

- The cell bank is a critical raw material that defines the product



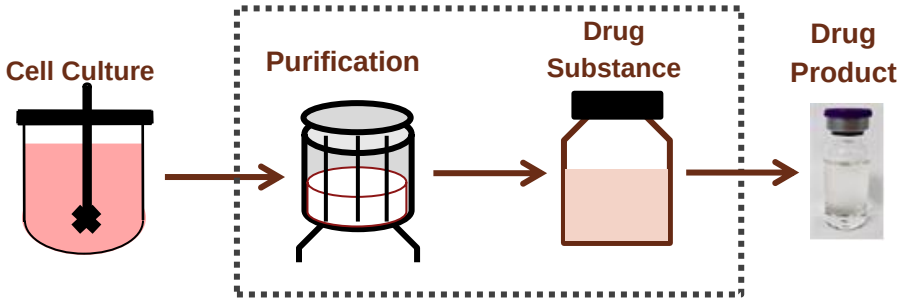
CERSI
UCSF-Stanford

Cell Culture



CERSI
UCSF-Stanford

Recovery & Purification



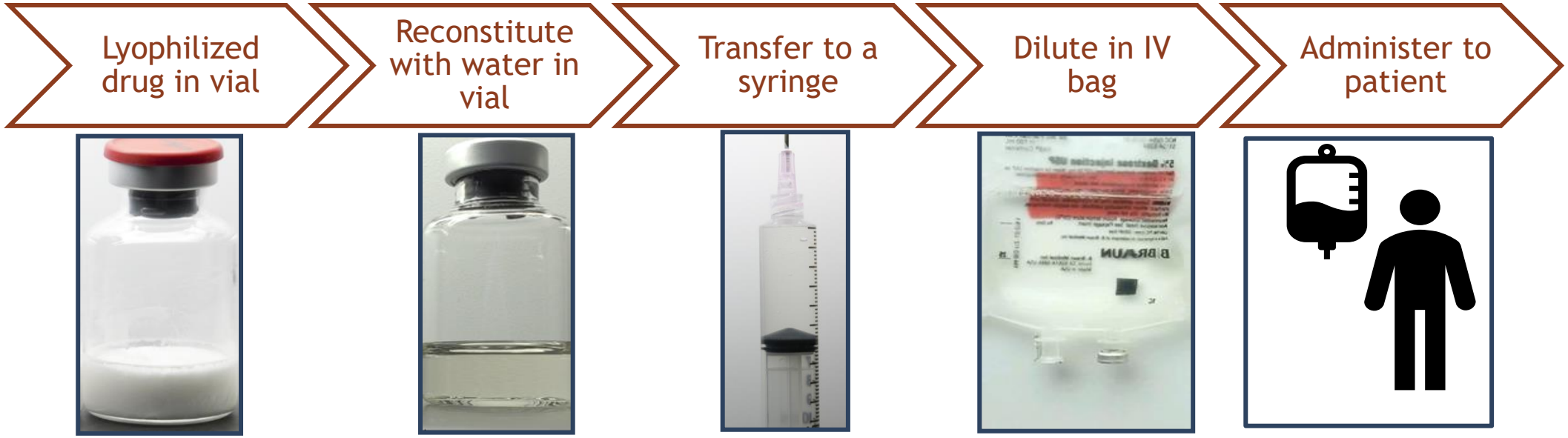
- Purification steps employ various separation techniques to isolate the recombinant protein and ensure removal of any contaminants

Example step for mAb	Primary Purpose
Harvest	Removes cells and debris while recovering product
Protein A affinity chromatography	Concentrates the mAb, removes host cell proteins (HCP) & DNA, and culture media components
Low pH Hold	Inactivates viruses
Polishing Chromatography	Further reduce HCP, DNA, aggregated mAb, mAb variants, or viruses
Virus Filtration	Removes viruses
Ultra filtration / diafiltration	Concentration and buffer exchange in final formulation (generate the drug substance)

CERSI
CSF-Stanford

Formulation / Drug Product Development

- Drug product scientists must prepare for all the steps in the process to get from stored drug product to patient



- *Choose formulation, configuration, storage conditions; ensure stability*
- *Manage drug product fill*

- ***Author pharmacy manual to ensure accurate dosing***
- ***Ensure in-use compatibility***

CERSI
UCSF-Stanford

Choosing a Formulation & Drug Product Configuration

- Formulation scientists select formulation and configuration based on TPP, planned dose, molecule characteristics, and stability
  - Intravenous vs sub-cutaneous delivery
  - Drug concentration
  - Excipients in the formulation (other components added as buffers and stabilizers)
    - Excipient selection is critical as there is no additional purification following final formulation
    - Aim to use excipients that are generally recognized as safe (see FDA GRAS designation)
  - Liquid or lyophilized
  - Storage temperature
  - Vial size and fill volume
  - Device needed?

Liquid

Lyophilized

CERSI
UCSF-Stanford

Drug Product Manufacturing (Fill / Finish)

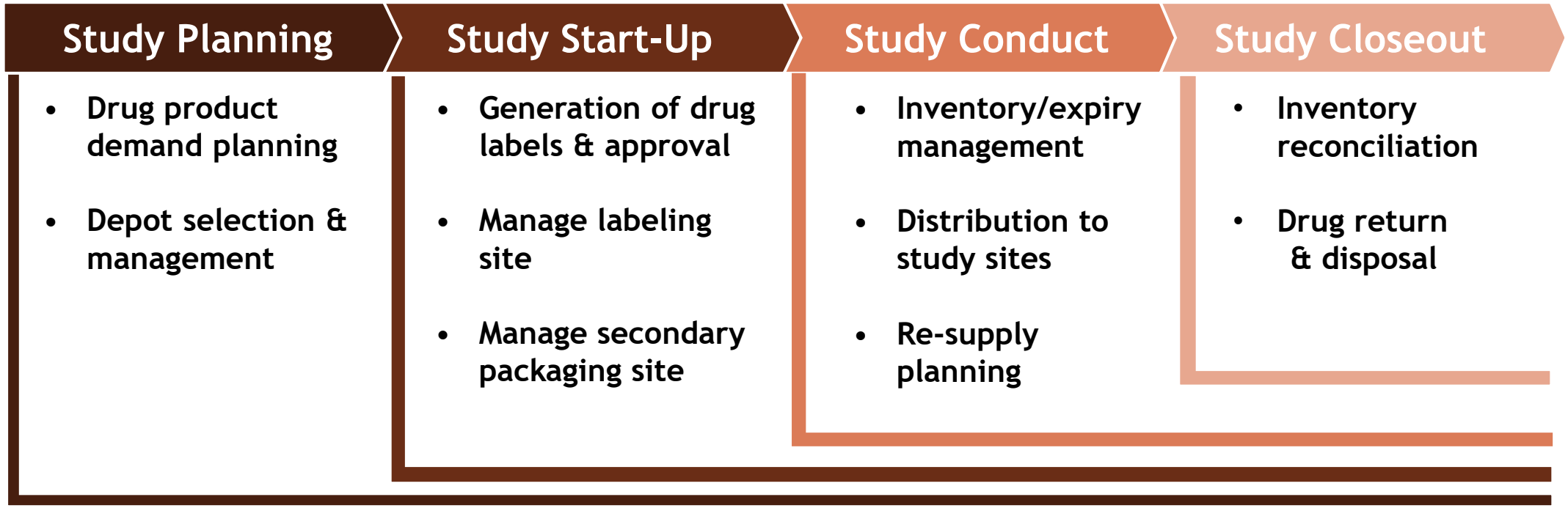
- Aseptic processing is used to produce the final drug product vials that will be shipped to the clinic or to market

Thaw Drug Substance (DS)	Filtration	Fill	Finish
• Pool and mix DS batches as needed • Dilute if needed	• Bioburden reduction • Sterile • Filter integrity test	• Fill vials • Fill weight check • Stopper and cap • Overseal	• Visual inspection • Packaging

CERSI
UCSF-Stanford

Packaging, Labeling, and Distribution

- CMC team directly supports the clinical study management team to ensure properly labeled drug is safely transported to clinical study site on time for planned dosing



CERSI
UCSF-Stanford

Assay Development / QC Testing: What are we Looking For?

Identity – must verify that intended product was manufactured

Product related species – molecular variants with comparable potency and immunogenicity to the intended product

Product related impurities – molecular variants with differing potency or immunogenicity to the intended product

Potency – heterogeneous nature of biologics drives need for potency test linked to mechanism of action (MOA) of the drug

Process Impurities – impurities derived from the manufacturing process

- Host cell substrates (host cell proteins, host cell DNA)
- Cell culture process (media components)
- Purification process (leached resin)

CERSI
UCSF-Stanford

Phase Appropriate Development Strategies

Early vs. Late Stage Drivers

Early-stage development

- **Speed to clinic**
  - Platform processes and test methods
  - Molecule selection to IND in 12-18 months
- Produce clinical supplies for Phase 1/2 trials

Late-stage development for commercialization

- **Molecule-specific**
  - Optimized processes
  - Maintain product consistency
- Produce biologics for pivotal trials and commercial supply

- Processes changes may be desired for commercialization to *increase yield* or *improve consistency* of product quality or process performance
  - Must assess changes for potential impact to product comparability
- Method changes may be driven by increased product understanding

CERSI
UCSF-Stanford

Phase-Appropriate Development: Cell Culture

- Develop cell line
- Create and test master cell bank
- Define Phase 1 process

- Optimize and scale up process as needed
- Create working cell bank
- Define and transfer commercial process to a CMO to make drug for pivotal studies
- Characterize process using qualified scale-down models and define control strategy
- Conduct process performance qualification (PPQ)
- Conduct genetic characterization and adventitious virus evaluation of cell line
- Generate process development history reports

- Life-cycle management
- Continued process verification

CERSI
UCSF-Stanford

Phase-Appropriate Development: Purification

- Support cell line selection
- Test virus clearance capacity of the process
- Define Phase 1 process

- Optimize and scale up process as needed
- Define and transfer process to a CMO to make drug for pivotal studies
- Characterize process using qualified scale-down models and define control strategy
- Conduct resin re-use studies
- Complete virus clearance capacity assessment
- Conduct process performance qualification (PPQ)
- Conduct genetic characterization and adventitious virus evaluation of cell line
- Generate process development history reports

- Life-cycle management
- Continued process verification

CERSI
UCSF-Stanford

Phase-Appropriate Development: Formulation & Drug Product

Pre-Clinical

- Assess degradation pathways
- Select Ph1 formulation
- Stability studies to support shelf-life
- In-use compatibility studies
- Pharmacy manual
- Define Ph1 DP fill process
- Transfer process to fill site

Phase 1

- **Define commercial formulation and drug product configuration**
- **Container compatibility assessments**
- Characterize formulation
- Characterize DP fill process and define control strategy
- **Characterize subvisible particles**
- **Global in-use compatibility studies**
- Extractables & leachables assessment
- Primary stability studies
- Scale-up drug product manufacturing as needed
- Conduct process performance qualification (PPQ) for DP fill process

Phase 2

Phase 3

Post-BLA

- Life-cycle management
- Continued process verification

CERSI
UCSF-Stanford

Phase-Appropriate Development: Analytical

- Identify molecule liabilities
- Reference standard strategy and qualification
- Develop Ph1 test methods
- Ph1 assay qualification
- Define DS & DP specifications
- Transfer methods to QC labs

- Identify and characterize variants impacting function and degradation pathways
- Identify and assess critical quality attributes (CQA)
- Develop commercial test methods
- Support process development
- Optimize test methods as needed
- Validate and transfer methods
- Develop and optimize residual process impurity methods
- Revise specifications as needed
- Define stability master plan to support shelf life
- Define reference standard strategy
- Define comparability strategy and execute evaluation for any manufacturing changes

- Assay life-cycle management
- Critical reagent management

CERSI
UCSF-Stanford

Comparability Evaluation

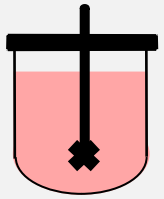
- When processes changes are made during development and post-approval, a comparability exercise is conducted to demonstrate there was no adverse impact to product quality, safety, and efficacy of the product

- A risk-based approach is used to determine the extent of the comparability exercise, which may include
  - Analytical testing: release testing, extended characterization, and stability
  - Non-clinical or clinical studies with post-change drug product

CERSI
UCSF-Stanford

Why Scale-Up? Scale-Up of Drug Substance Manufacturing Process is One of Two Key Strategies to Ensure Sufficient Commercial Supply

Strategy 1: Process Improvements



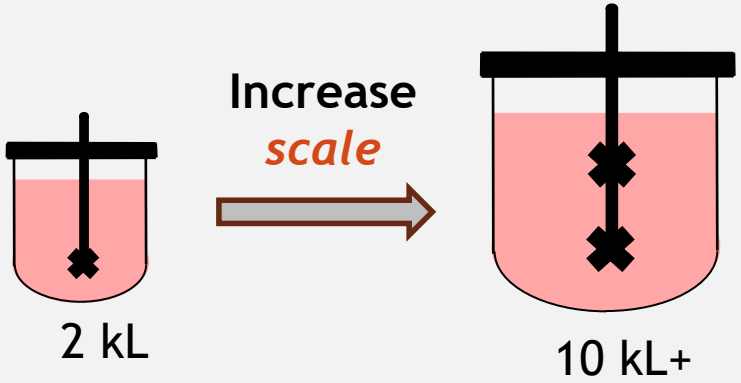
Cell Culture

→ Increase *titer*
(g protein per liter)

Purification

→ Increase *yield*
(% of protein recovered)

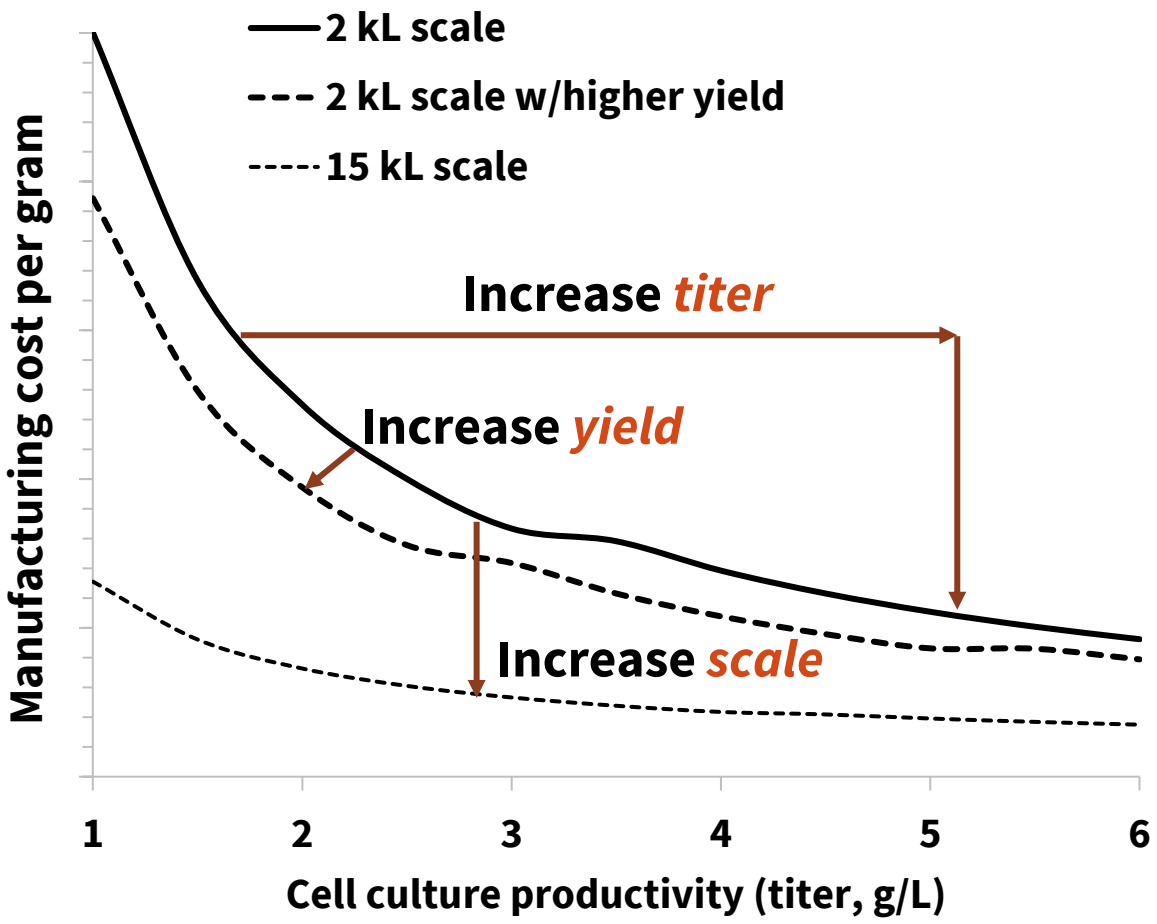
Strategy 2: Scale-Up



- Number of batches required per year is reduced with higher titer, higher yield, and larger scale

CERSI
UCSF-Stanford

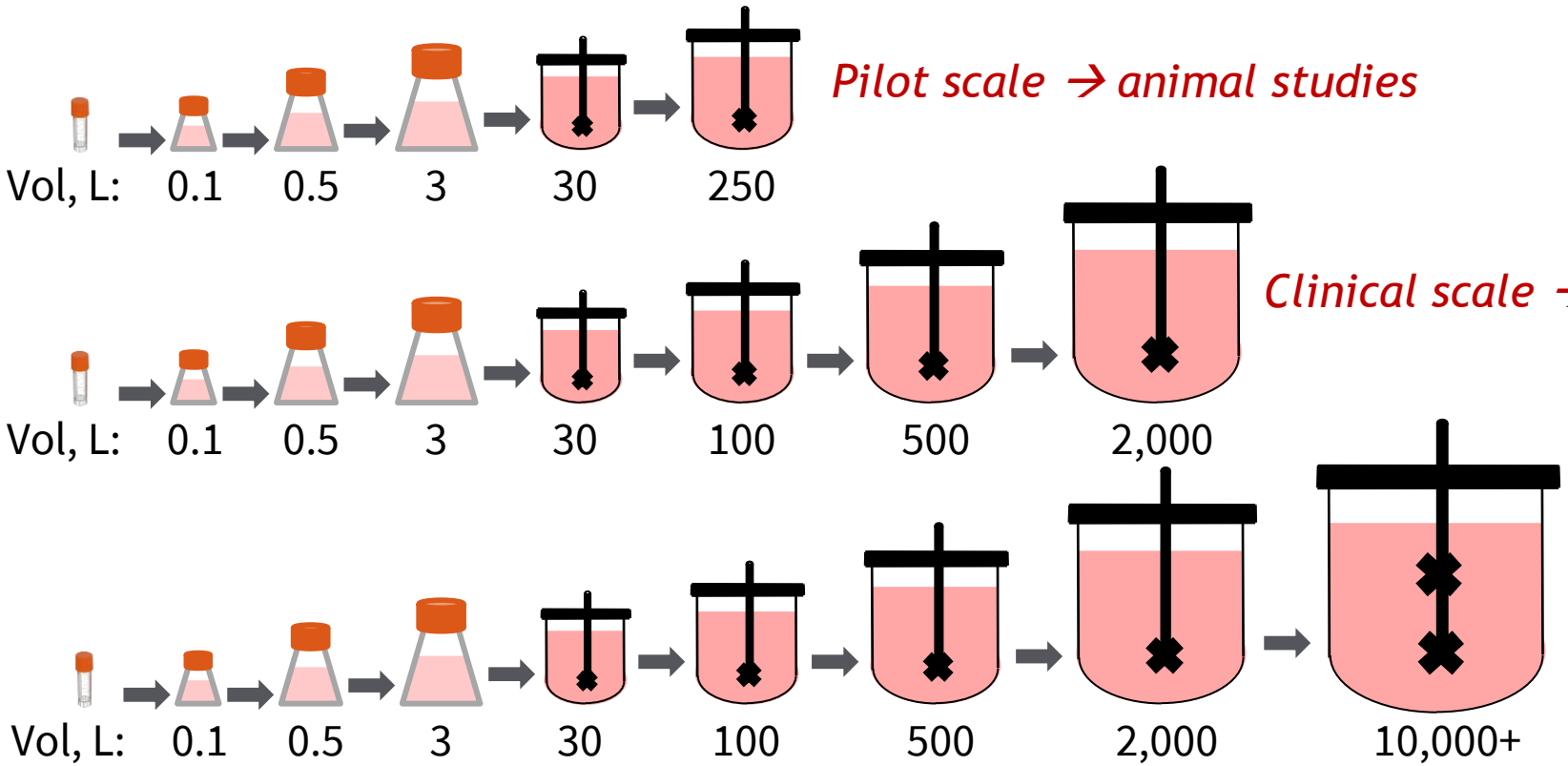
Scale-Up Also Provides Manufacturing Cost Savings



CERSI
UCSF-Stanford

Scale-Up for Commercialization – Drug Substance Manufacturing Scale is Defined by Volume of the Production Bioreactor

- Actual scale required depends on the anticipated demand for the molecule, and productivity of the process, but typical scales are shown here



CERSI
UCSF-Stanford

Scale-Up Considerations: Cell Culture

Operating conditions are selected to ensure consistent performance at all scales

- *Direct* vs *indirect* control:
  - Some operational parameters are controlled *directly* by the bioreactor control system – e.g. temperature, pH, dissolved oxygen, agitation (mixing) rate
  - Others are controlled *indirectly* – e.g. cell growth, titer, CO_2 accumulation
- *Scale-dependent* vs *scale-independent* parameters
  - *Scale-independent* parameters have identical set-points at all scales
    - Temperature, dissolved oxygen, and pH set-points
  - For *scale-dependent* parameters, set-points are different at different scales
    - Feed volumes – scaled linearly
    - Gas flow and agitation (mixing) rates – scaled non-linearly

CERSI
UCSF-Stanford

Scale-Up Considerations: Purification

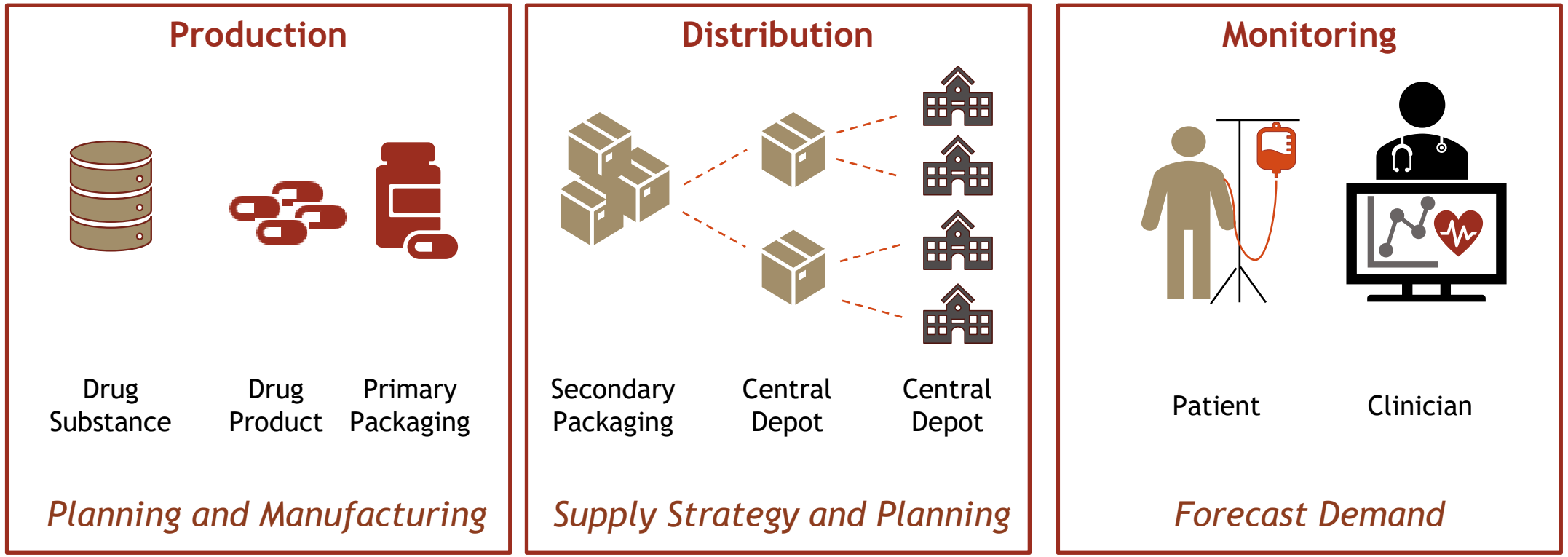
Operating conditions are selected to ensure consistent performance at all scales

- Solid removal
  - Facility capability (centrifuge, depth filter)
  - Shear stress on cells can lead to reduction of product upon harvest
- Liquid handling
  - Solution and intermediate product pools: pool volume constraints, hold time, agitation speed and mixing time
- Chromatography
  - Keep constant across scales: bed height, product concentration, residence time
  - Scale up linearly: total load, volumetric flow rate, cross-sectional area
- Membrane filtration
  - Safety factors are used to ensure successful at-scale operation despite variability in in-process fluid and membrane variability

CERSI
UCSF-Stanford

Supply Chain Management

Supply Chain: CMC Team Ensures Alignment of Production and Distribution Schedules with Clinical or Commercial Demand



- For biologics, must ensure cold storage and transportation conditions, and integrity of drug product container closure (glass vials) during shipping

CERSI
UCSF-Stanford

Questions?

CERSI

UCSF-Stanford