Key Areas for Strategic Drug Development Planning

Process Development for Future Scale-up and Commercial Viability

PDA Israel Chapter
Key areas for Strategic Drug Development Planning
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Presentation Overview

Topics for discussion:

- Scale Up: Definition and Objective
- Key factors to consider for Scale Up
- Case Studies
- Summary

Scale-Up Definition

Scale-Up is the process of increasing the batch size of a process from a smaller scale to a larger scale.

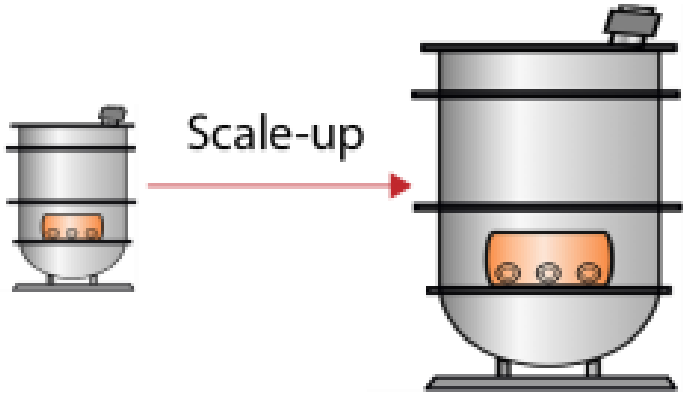


Image Courtesy: https://www.wuxibiologics.com/scale-out-vs-scale-up-biomanufacturing/

Scale-Up Objectives

Smooth transition to pilot and full-scale production

Development of a well defined process

Solving all quality issues

Increasing production process efficiency

Production of high quality products with minimal CAPEX and OPEX

Scale-Up Phases

- Process Development Phase

- R&D scale set-up
- Product Quality determination

- Process development and Optimization stage.

- GMP Production (facility)

- Clinical Trial Phase

- Toxicity (safety) in animals and humans

- Efficacy and dosing

- Comparison of treatment methods

Scale-Up Ratios

- Recommended scale up ratio is 1:5
- Lab scale should be determined by expected full scale – a small increase in lab scale will enable a large increase in full scale
- If larger scale-up is required, gradual scale-up is preferable to large scale-up ratios

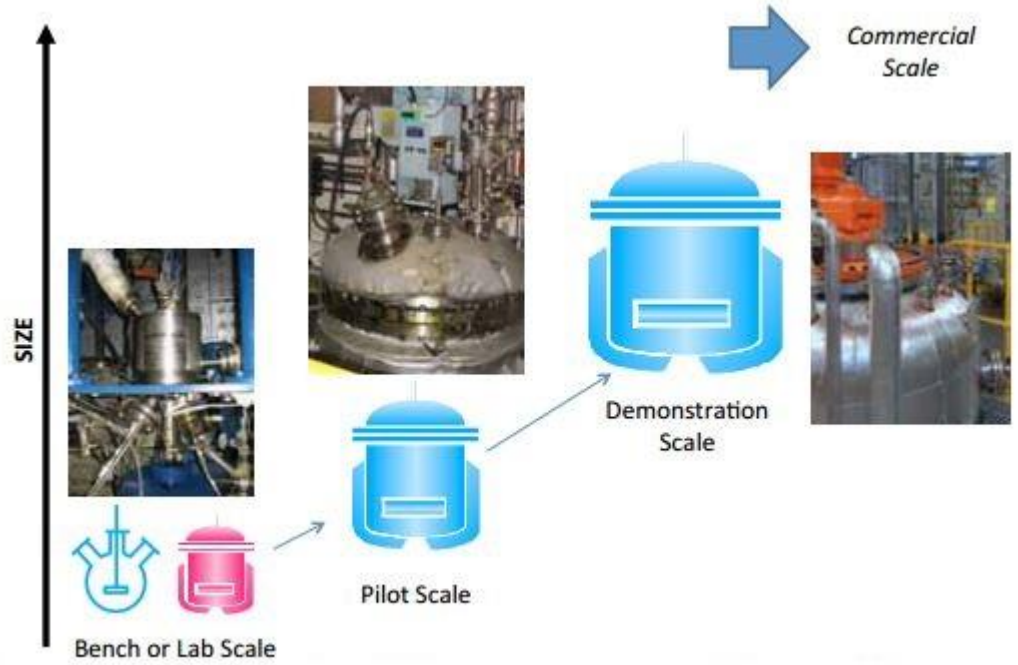


Image Reference: http://www.allfordrugs.com/scaleup

Key factors to consider for Scale-Up

Product Economics

- Market Study
  - Check market requirement of product
  - Standard packaging type available in market (bottles, vials, PFS) – Area wise evaluation
  - Standard product volumes available in market – Area wise evaluation
- Possibility of sellable By-products

Key Factors To Consider For Scale-Up : Process Economics

Process Economics:

- Factors to consider for determination of Batch size:
  - Planned Annual Production Capacity (according to product economics)
  - CAPEX (Design, Construction, Procurement, Commissioning and Validation)
  - OPEX (Electricity, utilities, maintenance and man power)

Key Factors To Consider For Scale-Up : Stage

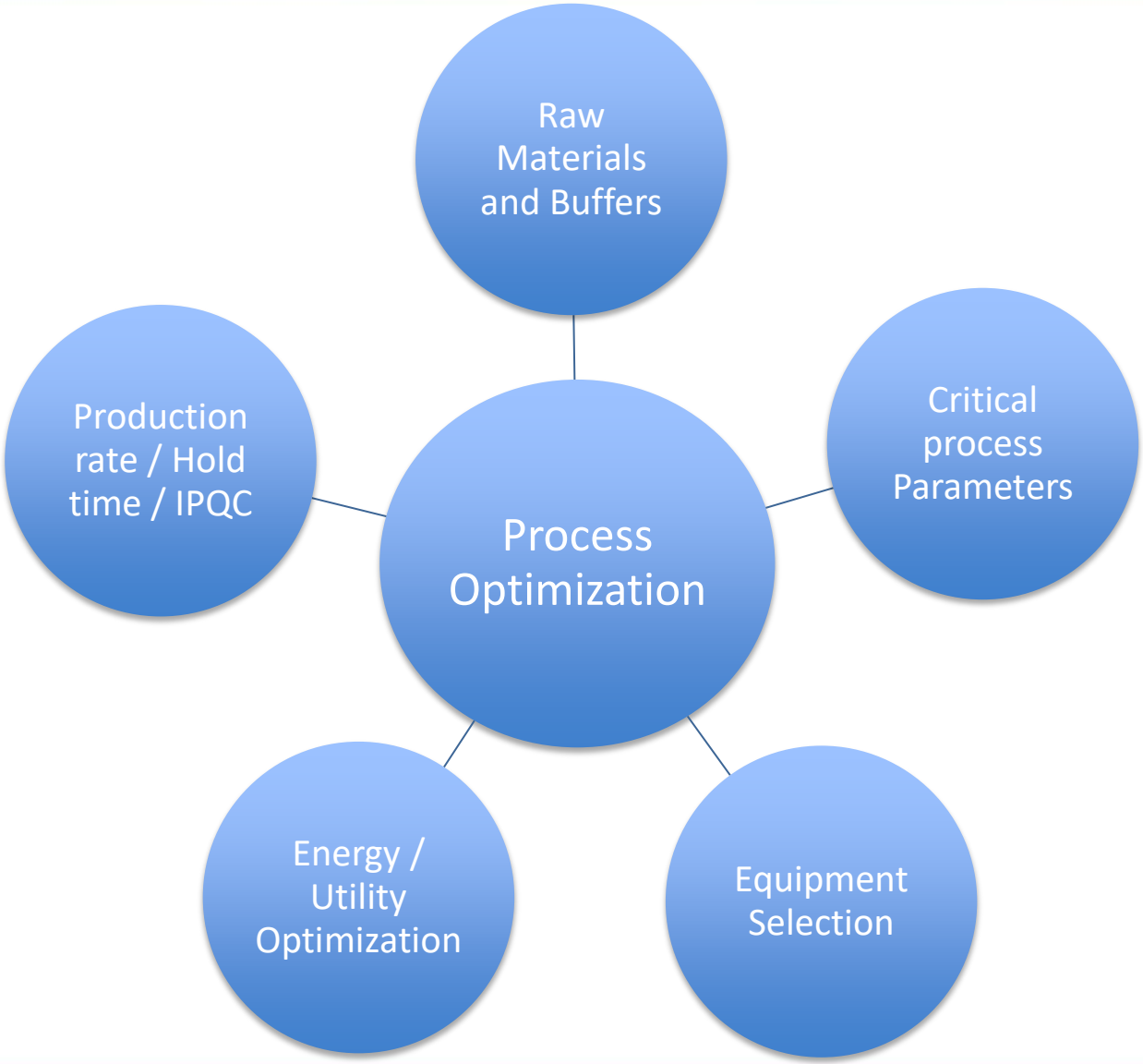
Lab Scale ⟹ Pilot Scale

- Evaluation of lab data and improving/optimizing the process
- Evaluation of the physical, chemical, biological or microbiological properties of the product
- Defining critical process parameters and ranges
- Performing stability studies

Pilot Scale ⟹ Commercial Scale

- Identifying problem/critical areas
- Checking operational and commercial feasibility of scale up to full scale production

Key factors to consider for Scale – Up: Process Optimization



Raw Materials

- Consider the same grade raw materials as Approved and Validated during pilot scale
- Identify economical packages suitable for the batch size
- Plan storage of raw materials according to lead time

Critical Process Parameters

- Identification of critical process parameters in order to assure consistent product quality
  - Example: Agitation profile can affect chemical reaction

- Optimization of Process parameters for efficient energy use
  - Example: Cascade control or simple heating/cooling according to required temp. range

Key Factors To Consider For Scale Up: Process Optimization

Equipment Selection:

- During Scale-up it is recommended to maintain equipment type and geometry
- H/D ratio shall be maintained during scale up
- Sometimes, scaling down is also required for better process understanding and data collection

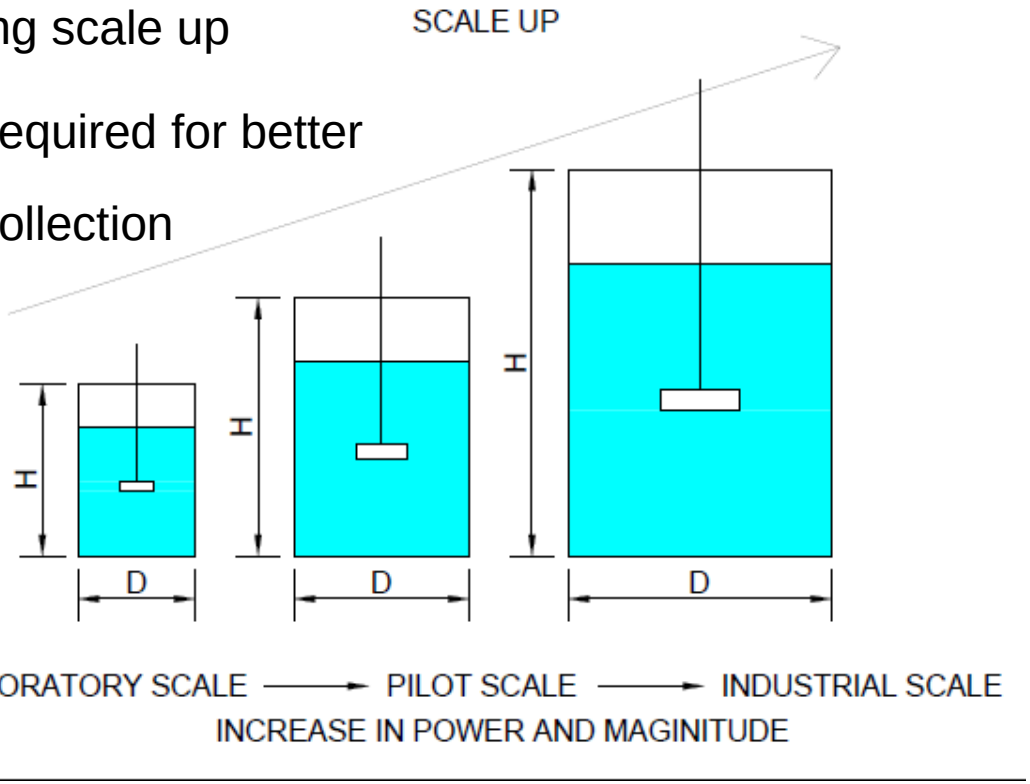


Image Courtesy: http://fermentationtechnology.blogspot.com/2008/01/scale-down-in-fermentation-technology.html

Key factors to consider for Scale-up: Process Optimization

Production Rate is affected by:

- Product losses and process yield
- Equipment cleaning times
- Hold times during IPQC
  - Determination of hold times is critical for batch planning
- Equipment Performance, product quality & production rate shall be validated

Buffers / Solutions

- The number and amount of buffers required affects:
  - raw material requirement
  - water requirement
  - utilities requirement
  - equipment utilization
  - area utilization
- Optimizing process to reduce the number of buffers or solutions required will consequently reduce all the above requirements.
- Recommended to replace hazardous solvents with other buffers

Energy / Utility Optimization

- Optimization of energy consumption by defining critical process parameters
- Cleaning protocol needs to be set up and water requirement for cleaning should be optimized
- Feasibility of solvent recovery, waste water treatment and recycling needs to be checked

In line testing and IPQC

- Defining sampling and testing points where corrective actions can be taken if out of spec results are produced.
- Plan ahead what corrective actions can be implemented and make the necessary provisions for implementation

CASE STUDIES

Case Study -1

Case Study:

Gradual freezing of proteins with validated cooling curve, 4 hours to reach -30˚C and 12 hours to reach -80˚C

- **During Lab production:**
  - Freezing was carried in -80^{0}C blast freezer (Make-Revco)
- **During Scale-up:**
  - 3X Scale up: The largest available blast freezer in the world was purchased with double cooling systems working in parallel
  - 9X Scale up: Two more were purchased batch was divided to sub lots - increasing the QC cost three times
- **Scale-up was carried after phase II trial – process changes were not possible**

Discussion with VP R&D:

- Why wasn‘t liquid nitrogen (known to have better impact due to fast crystallization) used in the first place?
- Answer: At the time of lab trial liquid nitrogen utility was not avilable at the lab

Recommendation:

- Experienced production and engineering personnel should monitor R&D stage to ensure process scalability

Case Study:- Sterile filling of vaccine in vial

- Product Media Volume :- 0.4 ml/vial
- Overfill :- 20 % - due to surface tension during transfer from vile to syringe

20 % overfill will increase the batch size to generate same production capacity

Case Study -2

Recommendation:

- Change from vial to pre-filled syringe (PFS) reducing overfill to 5%. 15% increase in production capacity with same batch size.

Was implemented before phase II trials – <u>therefore change was possible</u>

Labeled Size	Recommended Excess Volume (UPS<115>)
0.5 ml	~ 20%
1.0 ml	~ 10%
2.0 ml	~ 7.5%
5.0 ml	~ 6%
10.0 ml	~ 5%
20.0 ml	~ 3%
30.0 ml	~ 2.5%
50.0 ml or over	~ 2%

6-20% OVERFILL ==> 4-18% EXTRA PRODUCT PER BATCH

PFS

Vial

* Prefilled syringes: An innovation in parenteral packaging; Int J Pharm Investing. 2011 Oct-Dec; 1(4): 200-206.

Summary

Accurate planning of scale-up from R&D stage will lead to huge financial savings during commercial production

THINK ABOUT THE FUTURE

THINK BIG

GOD FORBID YOU MAY SUCCEED

Thank You!

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