

Practical Aspects in Designing Process Scale-Up – A Workshop

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A decorative graphic consisting of several overlapping, wavy, curved bands in shades of orange and yellow, extending from the bottom left towards the top right of the slide.

Workshop Agenda

Introduction & Overview of Scaling	15 minutes
Divide into Groups – Make, Purify, FF	30 minutes
Collect scaling experiences	
Identify scaling challenges & solutions	
Summary presentation to whole workshop (5 minutes per group)	15 minutes

Scale-Up Goals

Develop a robust set of **Process & Operation Parameters** (from smaller scale testing) that defines **Process Performance** under **Manufacturing Scale Conditions** to ensure that the product produced in large scale is the same as was produced in smaller scale

Scaling Mindset

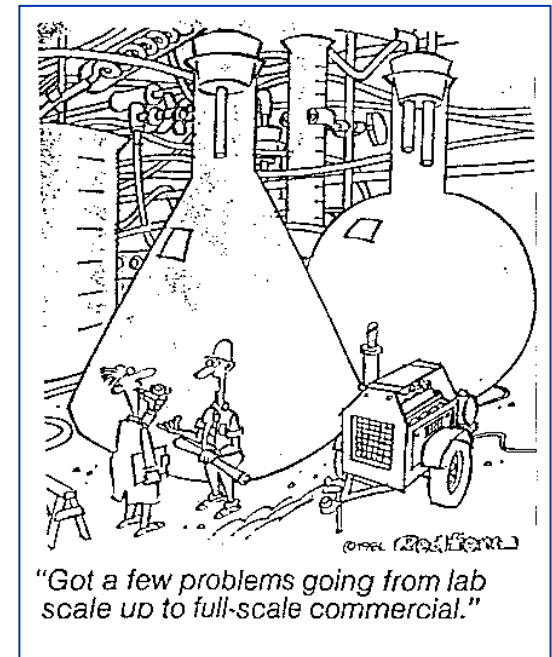
Don't disregard scaling just because you never have had to scale up – key message for R&D

- Eventually, successful processes are scaled up
- Usually little to no time to re-develop process later
- If a process works, there is resistance to change

“Most often the large-scale process is developed by making small changes in the method used to generate research material. The research process is used "because it works".

A more cost effective method is to consider each possible alternative before deciding on the final process”

- *Protein Purification - Design & Scale up of Downstream Processing*
S.M.Wheelwright pg. 7



Importance of Robust Scale-up

Faster robust scaleup has a tremendous payback

- \$20 million/year in sales = \$55K/day revenue and \$33K/day in earnings
- 80% market shared for First to Market

Risk of delay or non-approval because drug product changes during scale-up or data package not complete

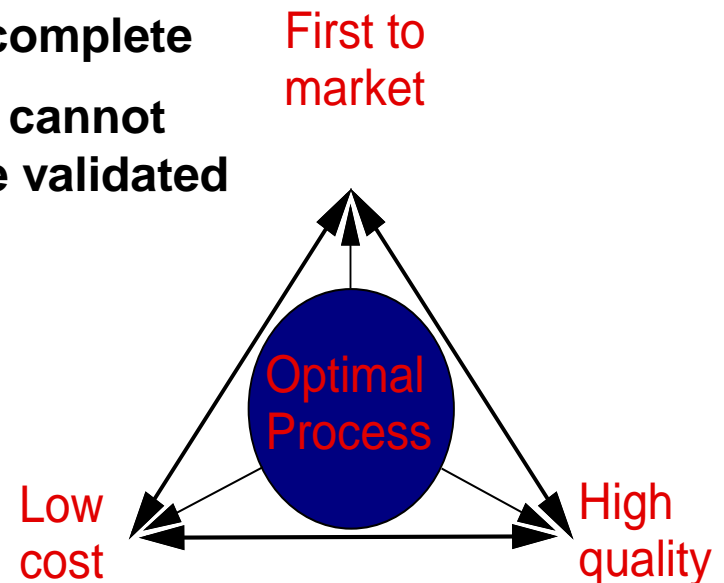
Risk of delay or non-approval because system cannot meet specifications or takes much longer to be validated

Risk That System is Too Big :

- High Product Recovery Losses
- High Capital & Operating Costs

Risk That System is Too Small :

- Low Volumes Cannot Satisfy Market Demand
- High Operating Costs at Full Capacity



i.e. “Begin with the End in Mind”

Industry Comments on Scaling Vaccine Processes

Wyeth Biotech, USA

"You want to be certain that throughout the development, scale-up, and product-manufacture phase that you have similar and consistent product characteristics. This is absolutely critical"

Sanofi Pasteur USA

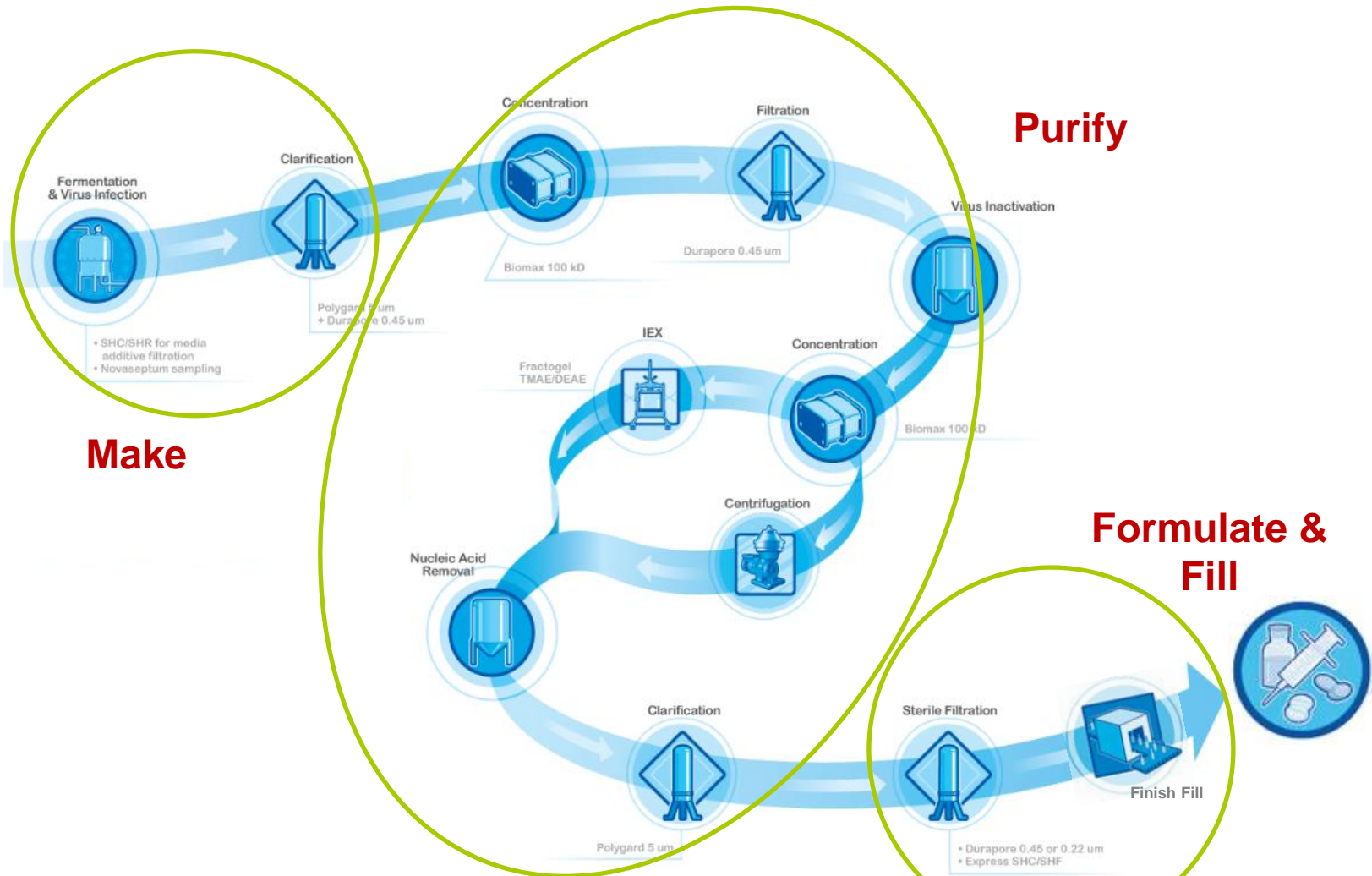
"Vaccine manufacturing is challenging; and the larger the scale, the greater the challenge"

Vaccines "are biological processes that are very difficult to characterize and control."

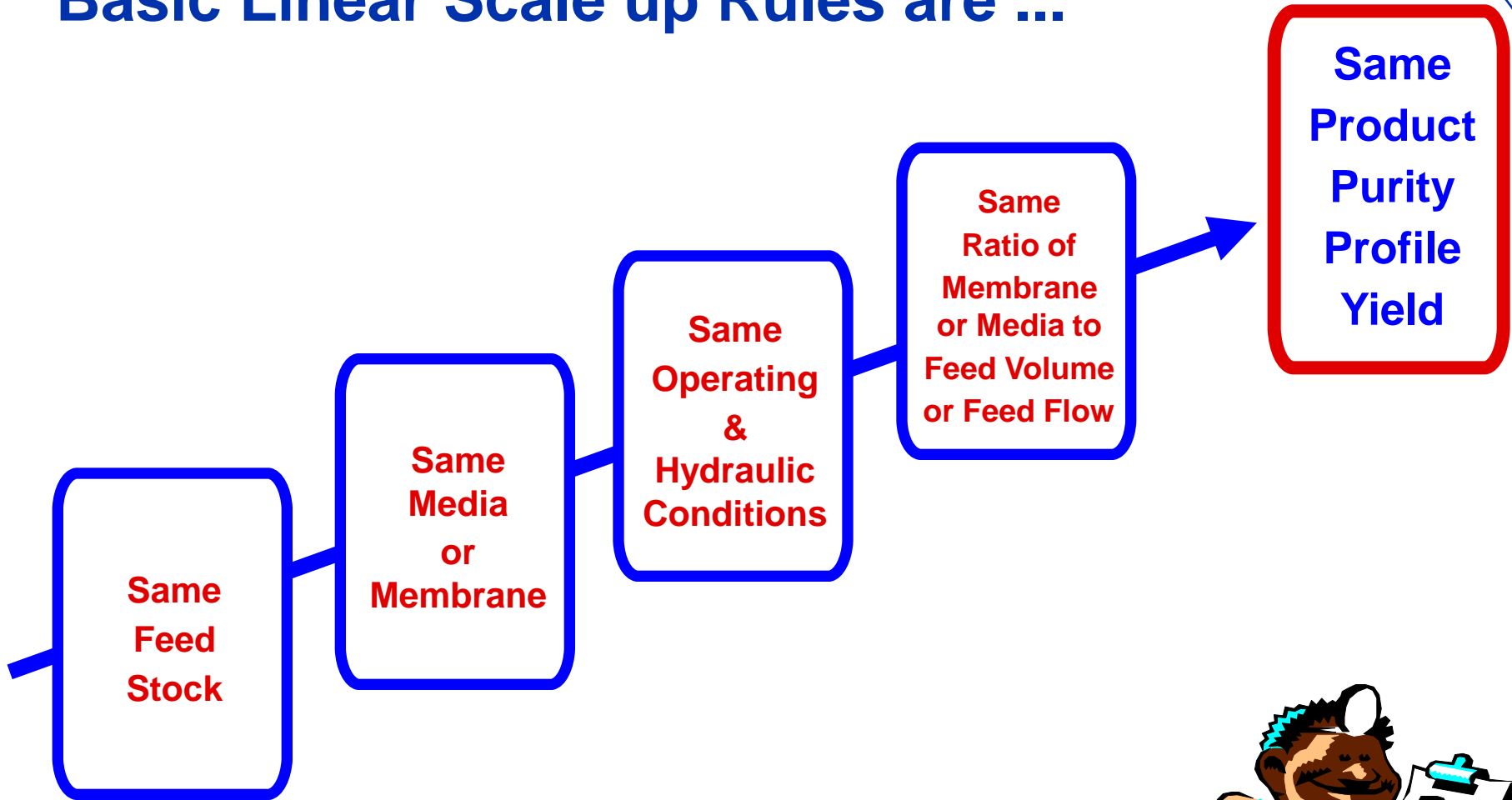
GlaxoSmithKline Biologicals Canada

"We multiplied the pieces of equipment, keeping the scale the same. We already understand the process, which limits the likelihood of changes in the vaccine and makes for an easier regulatory pathway."

Generic Vaccine Process:



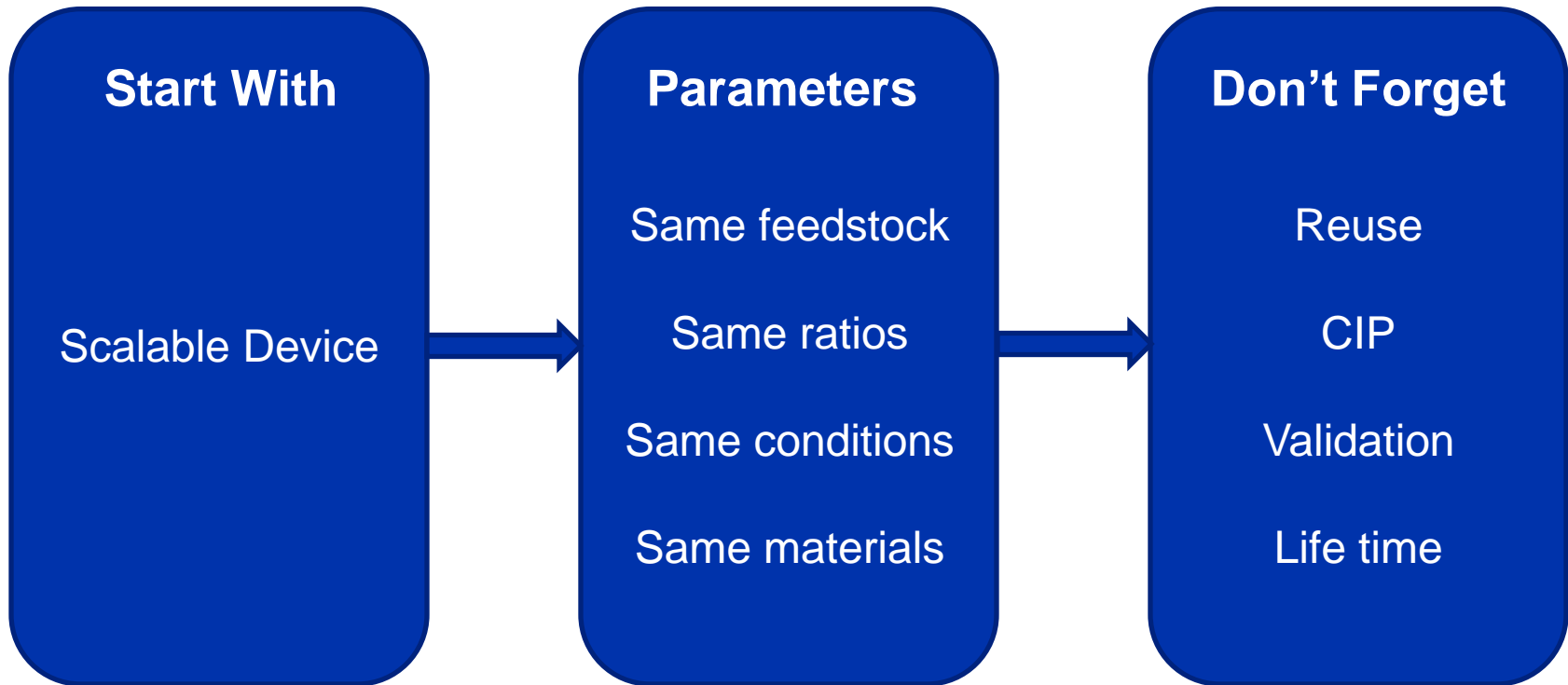
Basic Linear Scale up Rules are ...



Linear scaling is the easiest & most robust method
Useful for filtration and chrom unit operations

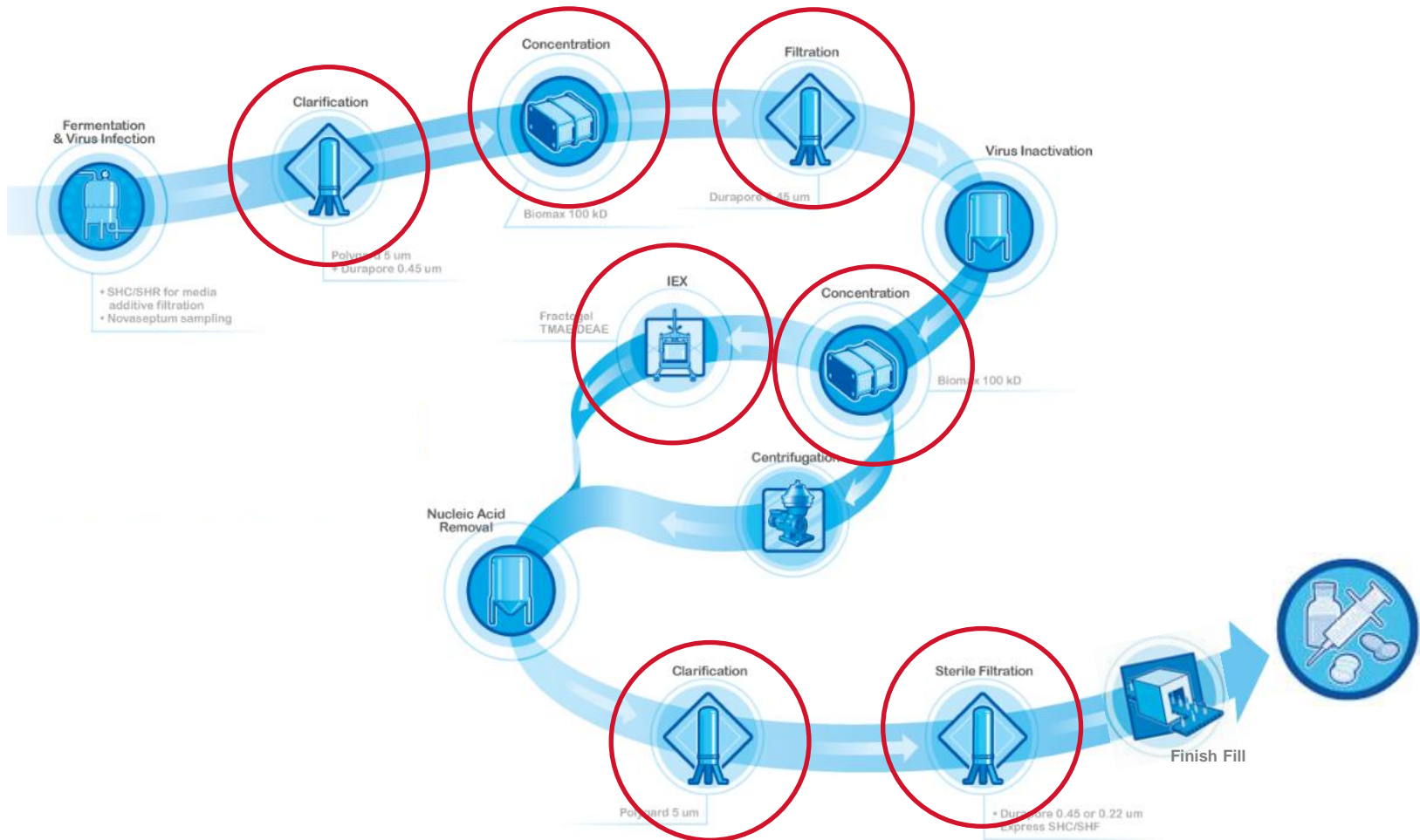


Good Linear Scaling Practice



Key word is “same”.
As many parameters as possible need to be kept constant during scaling

Unit Operations – Linear Scaling



Example of Simple Scale-Up Tasks from R&D to Production

R&D / Process Development

————— to ~20x —————>

- Media Selection
- Methods Optimization
- Loading Studies
- Purity / Impurity Identification



Pilot Plant

————— ~ 5 - 20x —————>

- Process Optimization
- Scaling strategy
- Column selection
- System selection
- Hygienic operation
- Validation



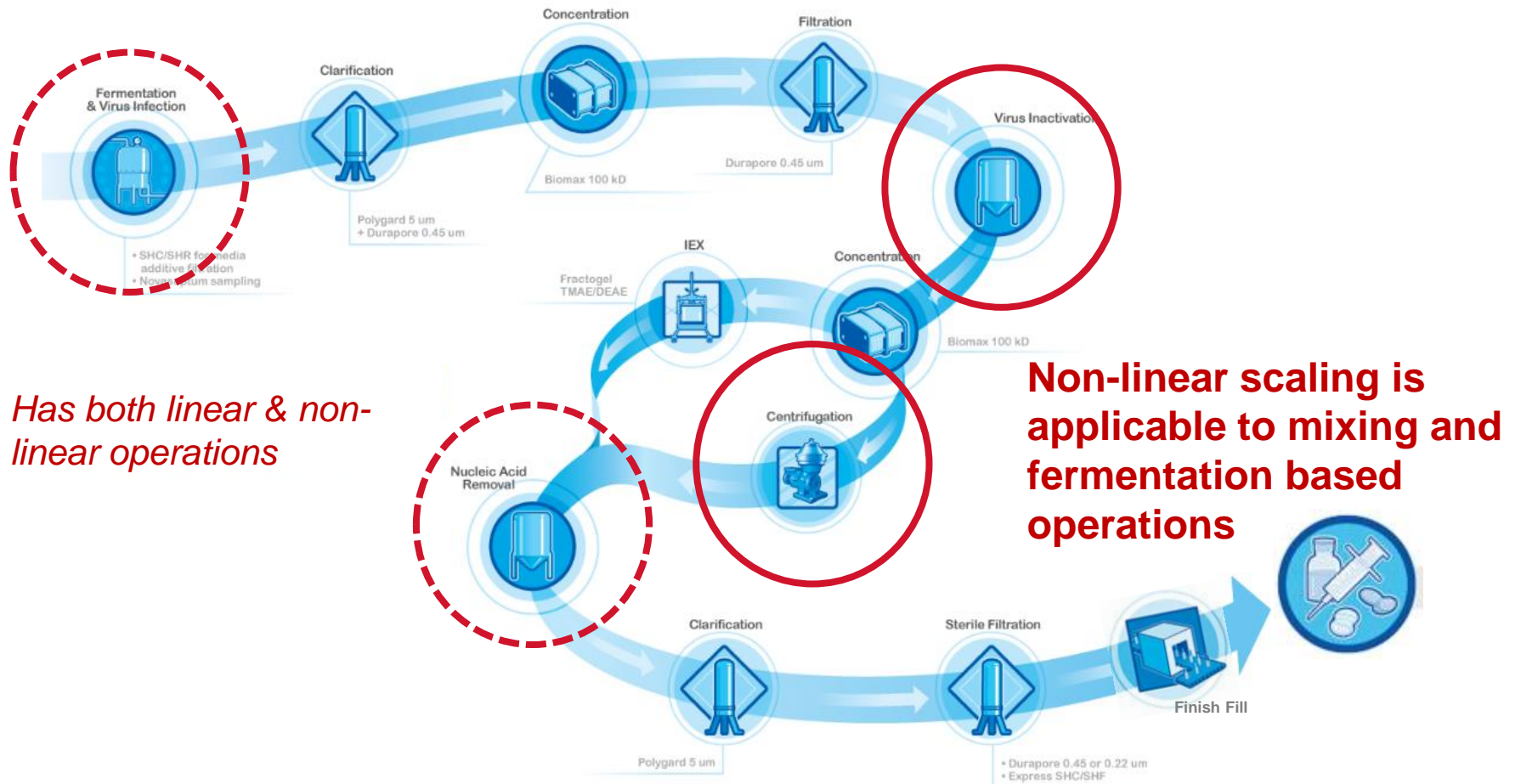
Manufacturing

————— ~ 3 - 10x —————>

- Production planning
- Column design & specification
- System design & specification
- Hygienic operation
- Validation



Unit Operations – Non-Linear Scaling



Workshop Plan

Divide into 3 groups – Upstream (make), Downstream (Purify), FF (Formulation & Filling)

Step 1 – Collect Group's Scaling Experiences on a Flipchart
R&D to Pilot OR Pilot to Production

Step 2 – Brainstorm Challenges & Solutions on a Flipchart

- Key Unit Operations in the group's Area
- Focus Unit Operations of Greatest Risk
- Scaling Challenges & Solutions for 1 or 2 of the chosen unit operations