Technology Transfer: A Development Perspective

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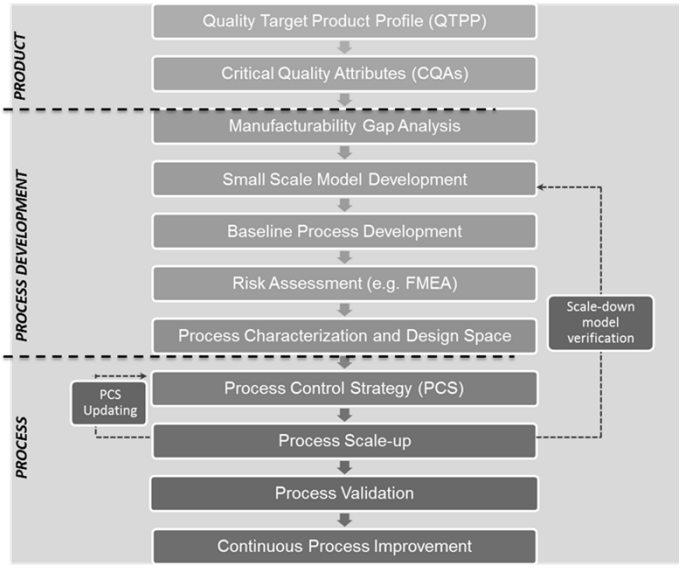
Connecting a World of Pharmaceutical Knowledge

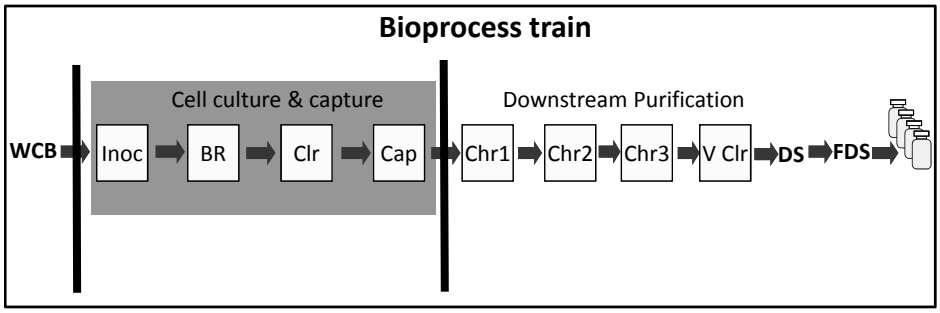
Outline

- Process Development
  - QbD Approach
  - Small scale model development
- Tech transfer
  - Governance
  - Approach
  - Troubleshooting examples
  - Keys to success

QbD Approach for Phase III Development



Small Scale Model Development



- **Cell culture**
  - Scale-dependent parameters same as proposed commercial scale
  - Scale independent parameters: choose based on modeling, experiments, SME knowledge
- **Purification**
  - Temp, buffers, loading, flow rates, column heights, and collection criteria based on proposed commercial scale
- **Other**
  - Hold steps, process times, linkage

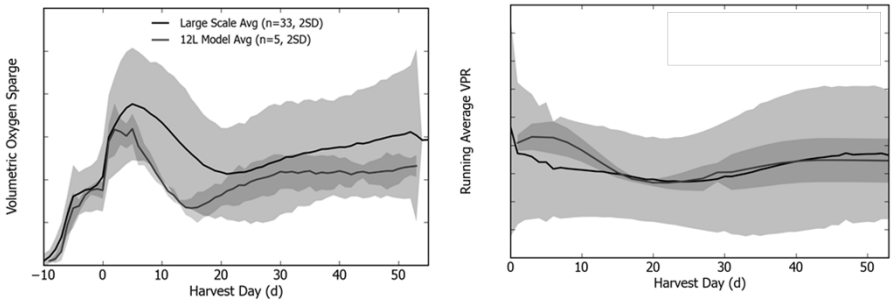
Small Scale Model Development

- Scaleable to intended commercial scale
- Experience with similar processes
- Similar control (pH, DO, automation) to commercial scale

Small Scale Model Development

Scale Independent Parameters	Scale Dependent Parameters/Factors
Seed Train	-
Media formulation	Bioreactor pressure
Temp	Working volume
pH	Impeller agitation rate
pCO2	Overlay flow rate
DO	O_2 sparge rate
Duration	O_2 sparge pore size
N-1 Temp	Need for antifoam
BR Seeding density	Shear / mixing

Scale Down Model Qualification



- Choose suitable parameters for statistical comparison
  - Cell growth / viability
  - Metabolic parameters
  - Productivity
  - Product quality (CQAs)

Process Characterization

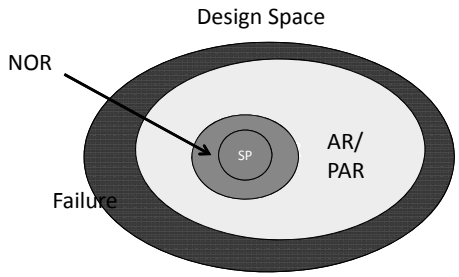
- Identify potential (p) CPPs & pKPPs
  - Well-controlled but critical, or difficult to control or detect
  - Prior knowledge
    - Ph I/II process
    - Similar processes in-house
    - Published papers & industry experience
    - Theoretical understanding
  - Risk Assessment (FMEA)
    - Severity x Occurrence x Detectability = Risk Priority Number (RPN)

FMEA Risk Analysis Matrix

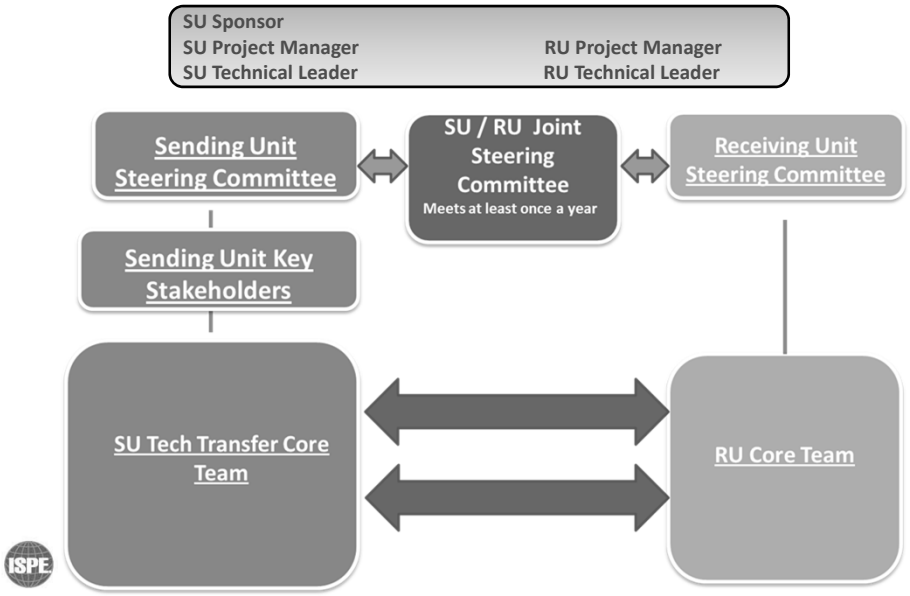
RPN	Detectability				
S×O	2	4	6	8	10
100	200	400	600	800	1000
80	160	320	480	640	800
64	128	256	384	512	640
60	120	240	360	480	600
48	96	192	288	384	480
40	80	160	240	320	400
36	72	144	216	288	360
32	64	128	192	256	320
24	48	96	144	192	240
20	40	80	120	160	200
16	32	64	96	128	160
12	24	48	72	96	120
8	16	32	48	64	80
4	8	16	24	32	40

Process Characterization

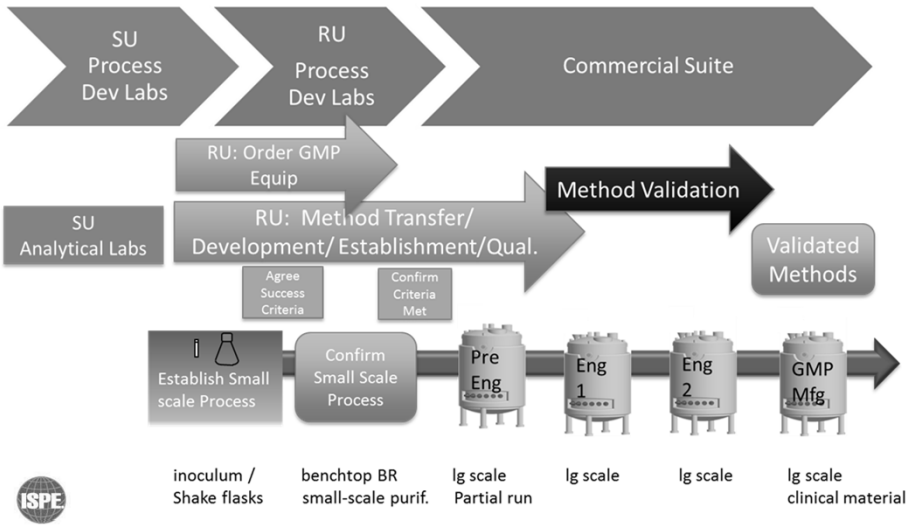
- Experimental results used to refine critical parameter designations



Technology Transfer Team Governance Example



Tech Transfer Strategy



Troubleshooting Examples

- pH control at scale not adequate based on on-line data
- Depth filter capacity lower than anticipated based on small-scale data
- At-scale recovery over chromatography steps less than anticipated
- Offline pO2 values offset at large scale (same DO setpoint)

Elements for Successful Technology Transfer

- Appropriate approach & strategy
- Robust process
- Definition of roles and responsibilities during transfer
  - "Engineering run guidelines" document
  - Clear delineation of decision-making process
- Attention to all process & logistical details
  - New and modified batch records & assoc. documents carefully reviewed by both development & mfg
  - Transfer of new *process-specific* protocols & training

Elements for Successful Technology Transfer

- On-floor presence of development representatives from cell culture & purification development during engineering /clinical runs
  - Daily run monitoring
  - Decision-making follow-up
  - Information flow – "Daily Run Updates"
  - Coordination of extra sampling

Lessons Learned

- Gap / Risk analyses only as good as SME assessment
- Communication between multidisciplinary teams key
- Planned experiments can address known equipment differences
- Consider all possibilities when scale-up differences are observed
- Development people tend to underestimate likelihood of operational issues

Thank you!

Questions?

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