Biopharmaceutical Development:

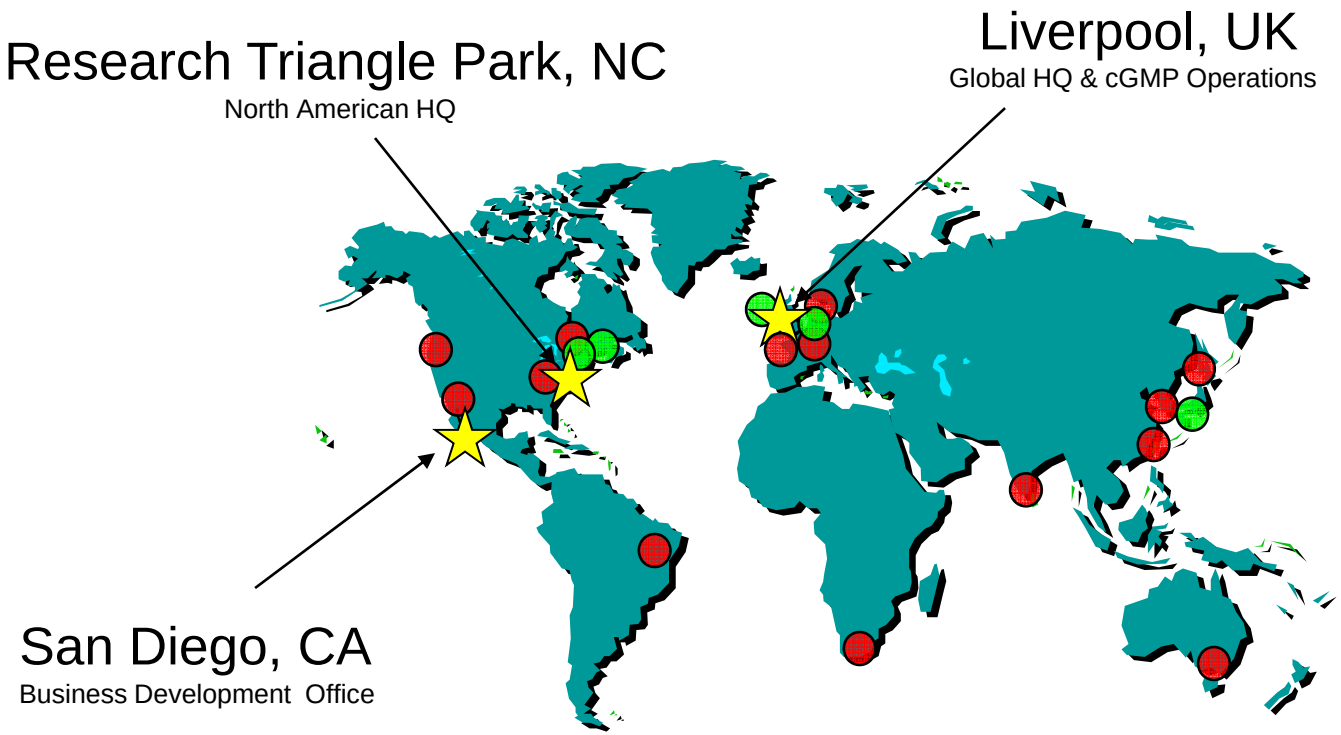
Creating and maintaining commercial value during outsourcing and technology transfer from research to the market

Crawford Brown PhD
Chief Executive Officer
Eden Biodesign Ltd

Any questions are welcome and encouraged, they can be asked by e-mailing:

eden.biodesign@propelmg.com

Eden Biodesign Maintains a Globally Integrated Biopharmaceutical Network

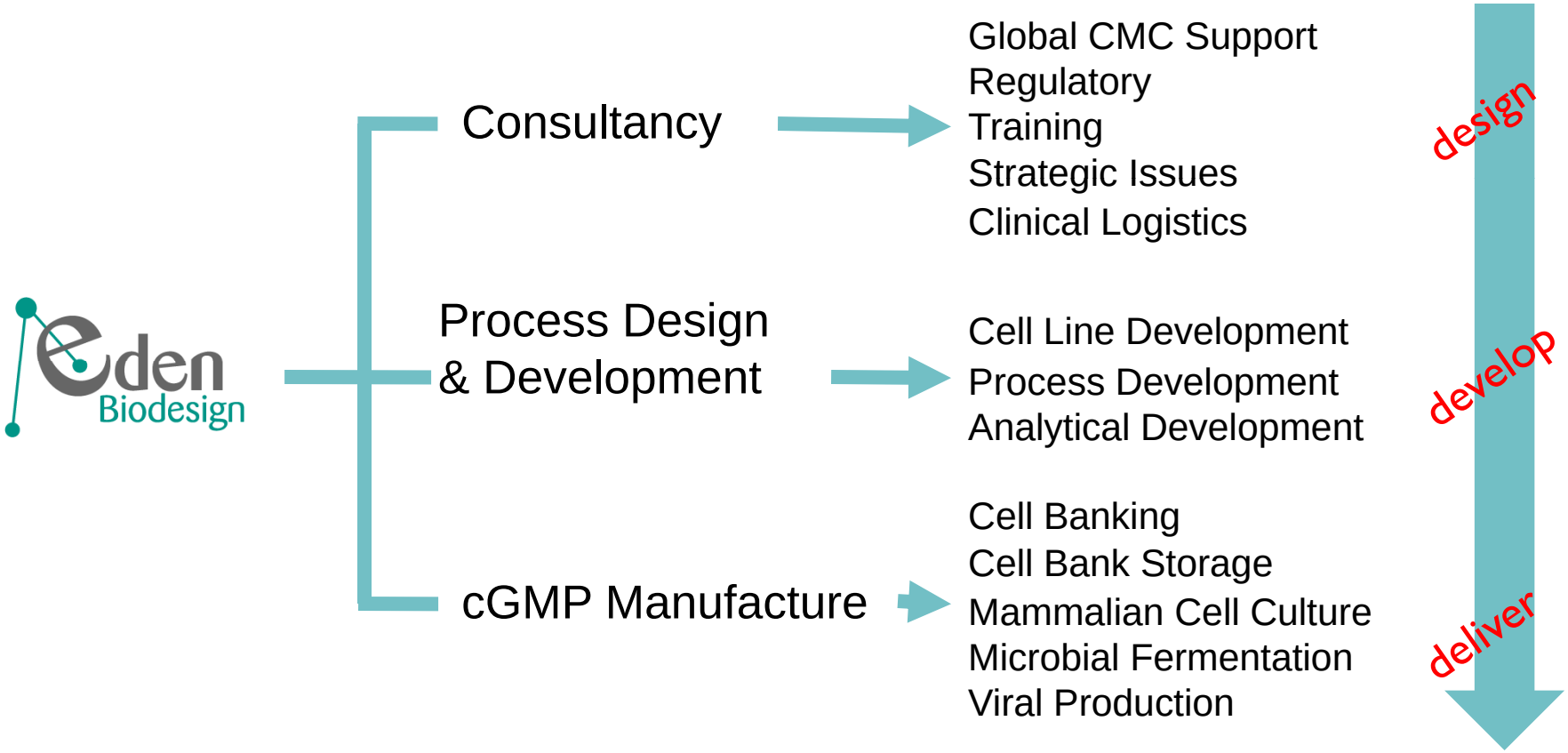


Clients on six of seven continents

● ***Client Assignments*** ★ ***Eden Presence*** ● ***Strategic Partners***

Eden Biodesign

An unusual breadth and depth of services supported by considerable drug development experience and expertise



Eden Biodesign

"Designing and developing valuable new medicines by the application of good science from day one"

Biopharmaceutical Development - Overview

Creating and maintaining commercial value during outsourcing and technology transfer

Part 1 - The ideal scenario

Part 2 - The ‘real world’ scenario

Part 3 - Analysis of the most common problems & some solutions

Part 1 The Ideal Scenario:
Product Development Plan

Product Profile
Target Indication
Target Dosing Regimen (dose/route/freq)
Efficacy Claims
Pharmacoeconomic Rationale

Profits

Development Costs

+ve NPV

Today

Launch Year **1 2 3 4**

Part 1 The Ideal Scenario: *Regulatory Approval*

Proven quality of the biotechnological product

- ✓ a validated and reproducible PROCESS
- ✓ a characterised and consistent PRODUCT

⬇

pre-determined acceptance criteria

and specifications

Part 1 The Ideal Scenario:
Regulatory Approval

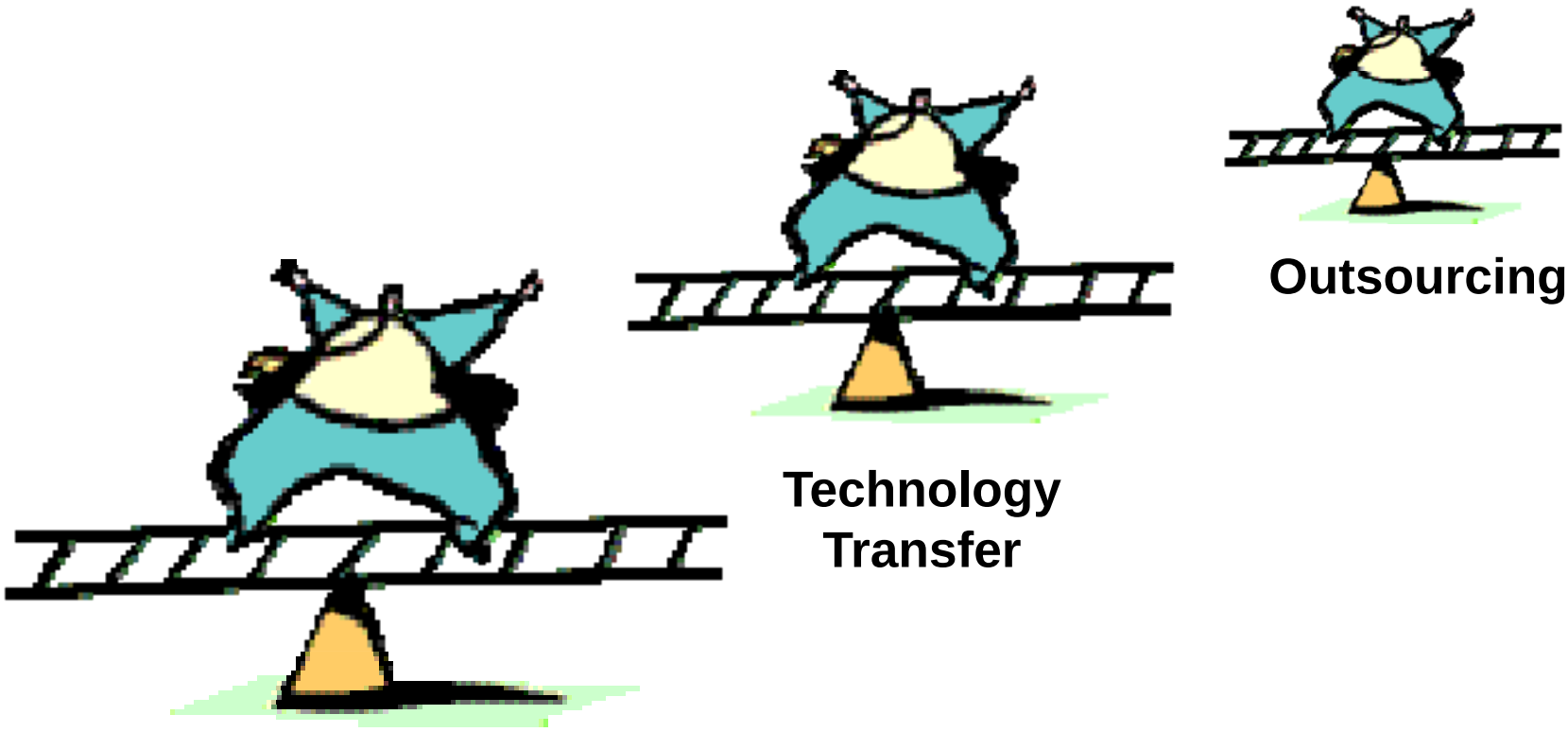
BATCH	1	2	3	4	5
LAL (EU/mg)	< 0.04	< 0.02	< 0.02	< 0.02	< 0.02
pH	7.1	7.2	7.1	7.1	7.2
Protein (mg/ml)	20	42	45	48	45
Bioassay	89%	89%	92%	99%	97%
SDS-PAGE					
- Purity	98.6%	97.3%	98.0%	98.6%	98.1%
- New Bands	None > 0.1%	None > 0.1%	None > 0.1%	None > 0.1%	None > 0.1%
- Profile	CFS	CFS	CFS	CFS	CFS
GF-HPLC					
- Purity	99.6%	>99.9%	>99.9%	>99.9%	>99.9%
- Identity	0.0	0.0	0.0	0.0	0.0
Bioburden	0 cfu/ml	0 cfu/ml	0 cfu/ml	0 cfu/ml	0 cfu/ml

*** MAB data, CBER, obtained through FOI conformance series**

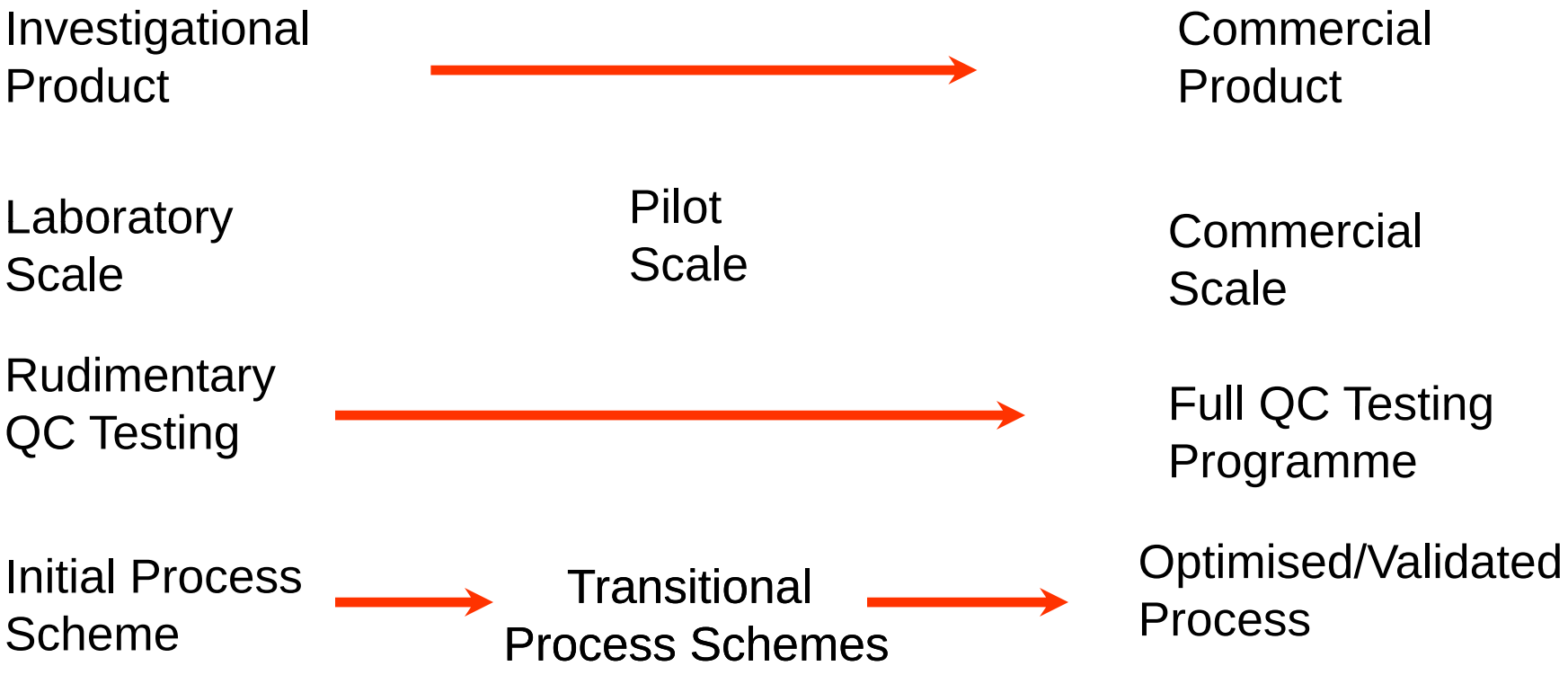
Part 1 The Ideal Scenario: Clinical Trial Supply

- Clinical supplies packaging and labelling completed in compliance with GCP.
- Distribution to clinical centres completed in a timely fashion.
- Shelf-live as declared in label brackets to completion of clinical studies including follow-up.

Biopharmaceutical Development: Part 2 The 'Real World' Scenario



Part 2 The 'Real World' Scenario: *Biopharmaceutical Development*



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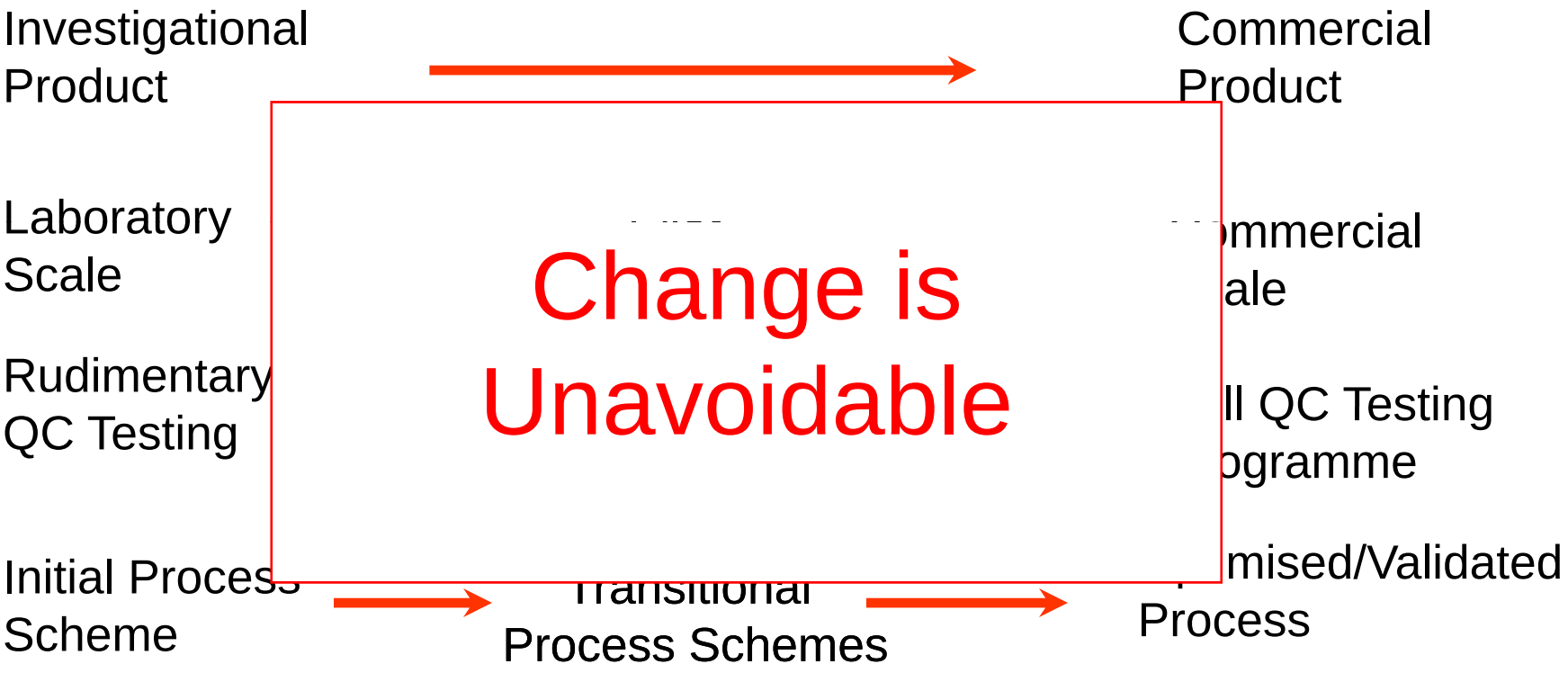
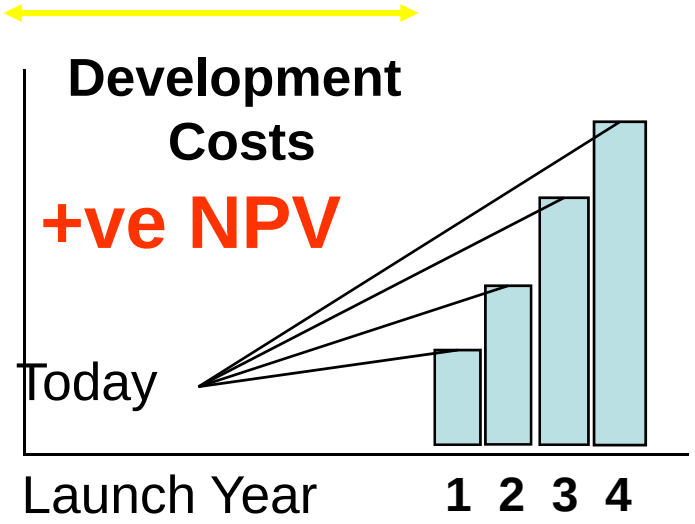


Part 2 The ‘Real World’ Scenario: *Product Development Plan*

Product Profile
Target Indication
Target Dosing Regimen (dose/route/freq)
Efficacy Claims
Pharmacoeconomic Rationale



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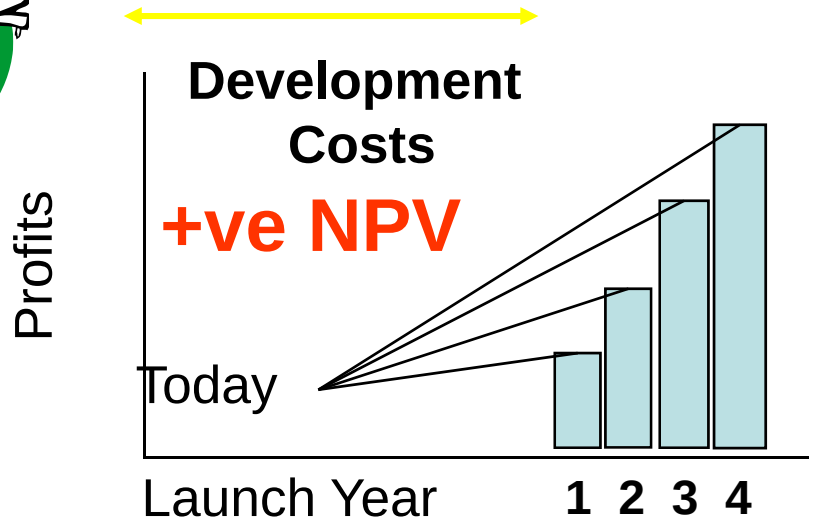
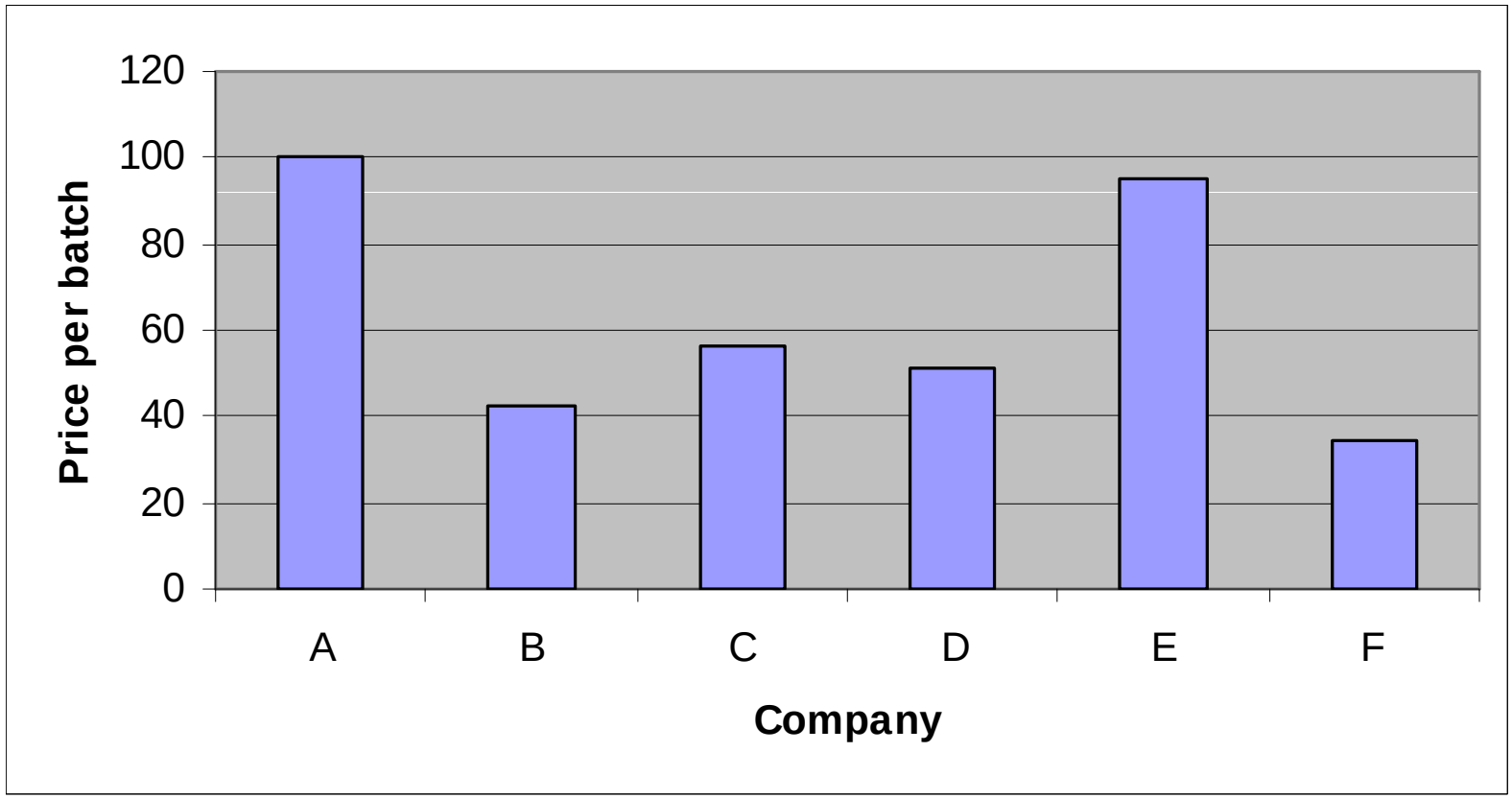


Part 2 The ‘Real World’ Scenario: *Selection of Contract Partners*

- Inadequate thought and clarity on clinical operating plan and hence CT supply plan.
- Inadequate detail of manufacturing requirements to permit meaningful dialogue.
- Wide range of knowledgeable contract companies but with a variety of strengths in depth.
- Potential contract partners of choice are both very busy and often too expensive since inadequate contracting out costs were incorporated into the initial business plan.
- GMP production capacity available but shortage of development skills to define process and analytics.

Part 2 The ‘Real World’ Scenario: Selection of Contract Partners

Wide Price Variation



Normalised as a % to the highest price quotation

Part 2 The 'Real World' Scenario: *Technology Transfer*

- Technology Transfer protocol.
  - Absent or incomplete.
  - Not followed due to time or resource pressures.
- Technology transfer completed several times.
  - Research lab to site for production of Pre-Clin & Phase I CT supplies.
  - From a Phase I site to new site for Phase II supplies (quite often).
  - From a Phase I site to a new site for Phase III supplies (very often).
- Several interfaces to be managed.
  - Production site and analytical testing site.
  - Production of bulk purified product.
  - Production of medicinal product.
  - Packaging and shipment of clinical supplies.

Part 2 The ‘Real World’ Scenario: *Technology Transfer*

Technology Transfer

Often associated with

Start Up/ Scale Up

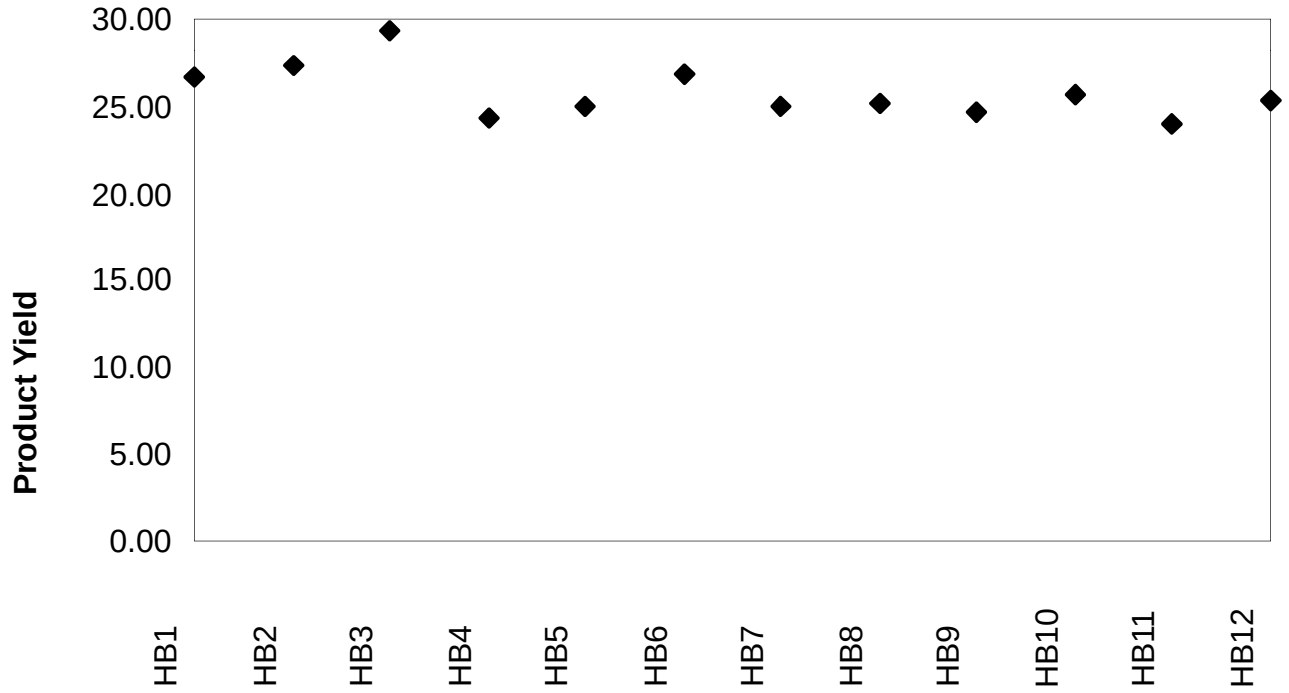
Always results in

Multiple Challenges

PEOPLE PLANT PROCESS

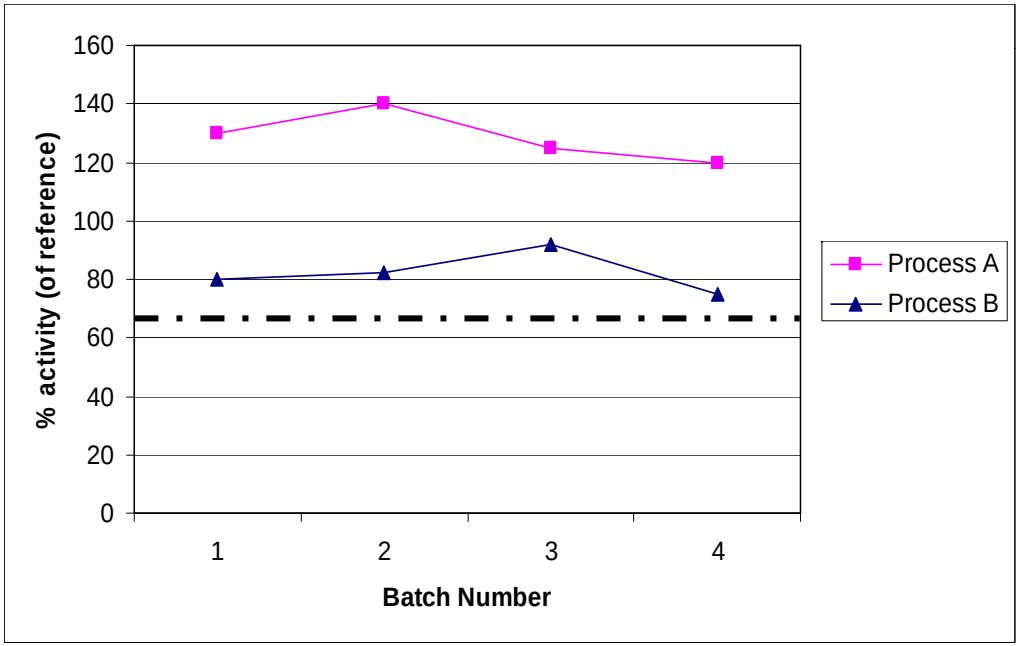
Part 2 The ‘Real World’ Scenario: *Technology Transfer*

Variability often greatest at start-up



Part 2 The ‘Real World’ Scenario: Technology Transfer

Processes and product are not comparable even with successful technology transfer



Part 2 The ‘Real World’ Scenario: *Regulatory Approval*

- Company considers IND/CTX’s Agency approval of process and analytics and under resources the Development function.
- Agency questions about the appropriateness of integrating the clinical data base from clinical materials produced from transitional processes.
- Lack of documented evidence of technology transfer.
- Data integrity and availability to respond to questions impaired since not actively managed.
- Support from previous contract partners where relations have been severed.

FDA's List of Tech Transfer 483s

- No method transfer study performed when methods transferred between sites
- No change control
- No procedure for verifying methods from outside sources
- Transfer not formerly approved by QC/QA
- Method modification without demonstrating verification between sites
- Method changes which have not been properly justified

Part 2 The ‘Real World’ Scenario: *Clinical Trial Supply*

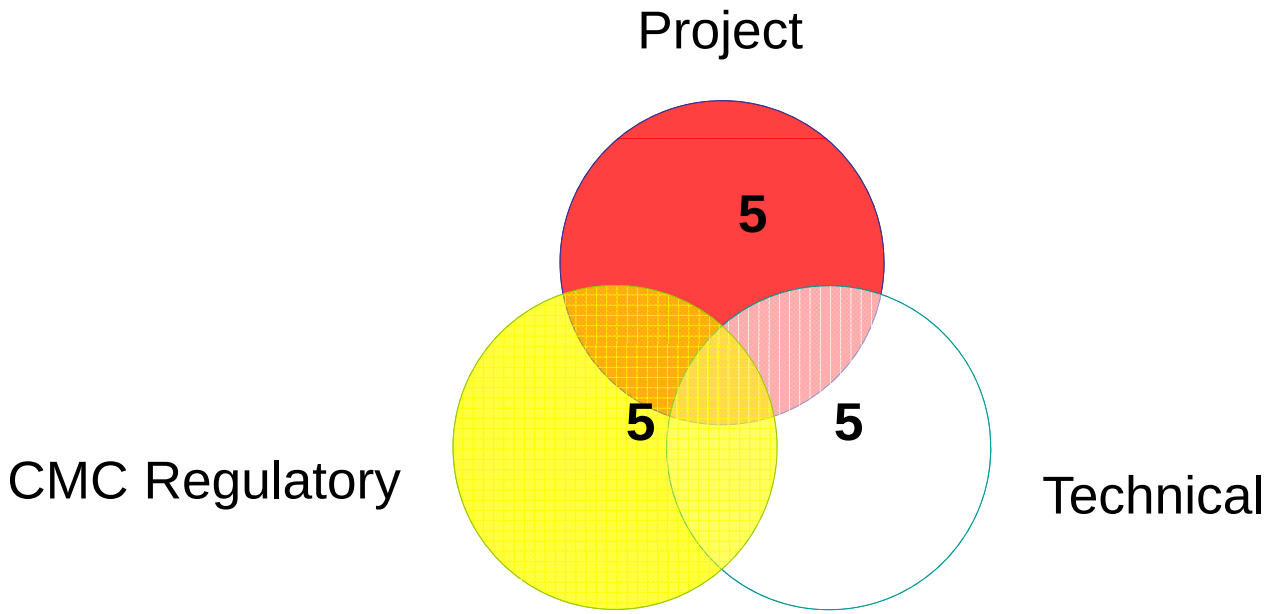
- Clinical operating plan changes at the last minute.
- Recruitment rates dictate CT supplies need to be over labelled with new expiry date.
- Importation licences create transportation difficulties.
- Thermal tracking of clinical supplies indicates they exceed stated tolerance.

Part 3 Biopharmaceutical Development: Most Common Problems

Analysis of >50 projects

1. Design of Product Development Programmes, including Outsourcing Management
2. Process and Analytical Science, Rapid Troubleshooting and Problem Solving
3. CMC Regulatory Services
4. Clinical Trial Supply Logistics

Part 3 Biopharmaceutical Development: Most Common Problems



Part 3 Biopharmaceutical Development: Most Common Problems

Top 5 Most Common Technical Problems

5) Equipment Calibration & Maintenance

Part 3 Biopharmaceutical Development: Most Common Problems

Top 5 Most Common Technical Problems

4) Process Robustness
5) Equipment Calibration & Maintenance

Part 3 Biopharmaceutical Development: Most Common Problems

Top 5 Most Common Technical Problems

3) Process Scale-Up
4) Process Robustness
5) Equipment Calibration & Maintenance

Part 3 Biopharmaceutical Development: Most Common Problems

Top 5 Most Common Technical Problems

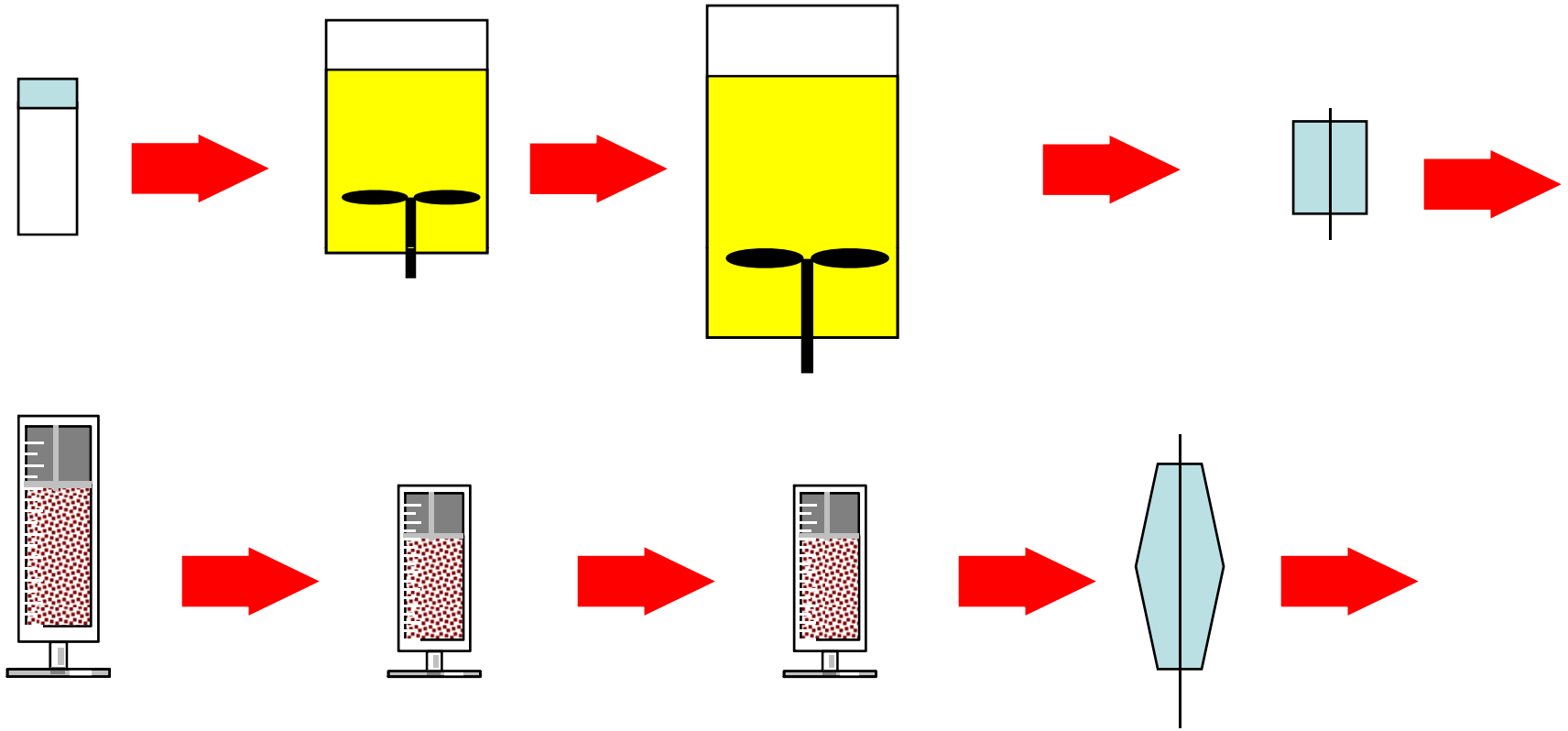
2) Analytical Tech Transfer
3) Process Scale-Up
4) Process Robustness
5) Equipment Calibration & Maintenance

Part 3 Biopharmaceutical Development: Most Common Problems

Top 5 Most Common Technical Problems

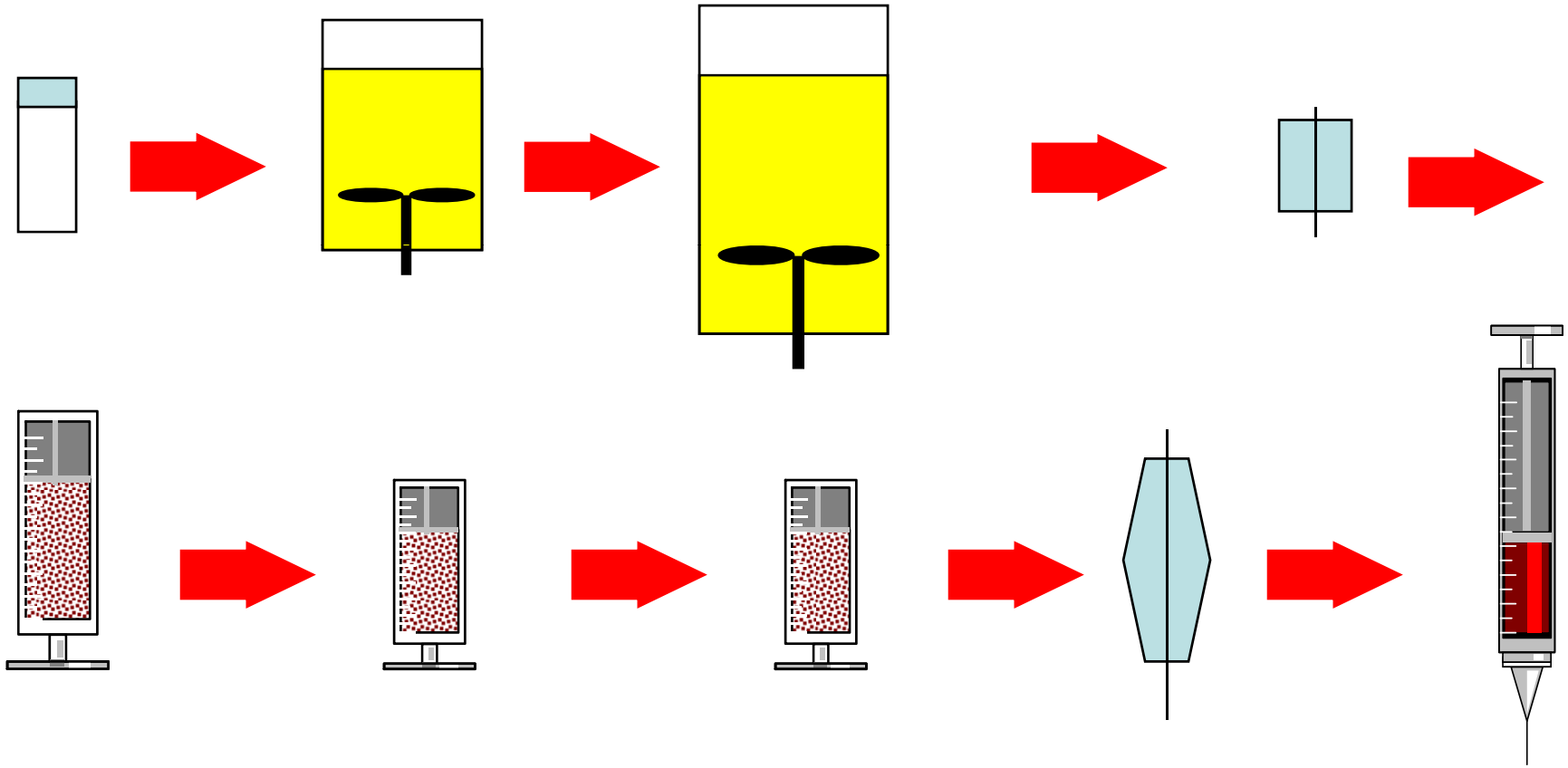
1) Formulation Issues
2) Analytical Tech Transfer
3) Process Scale-Up
4) Process Robustness
5) Equipment Calibration & Maintenance

Part 3 Biopharmaceutical Development: Most Common Problems



Focus on Drug Active not Drug Product

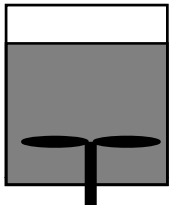
Part 3 Biopharmaceutical Development: Most Common Problems



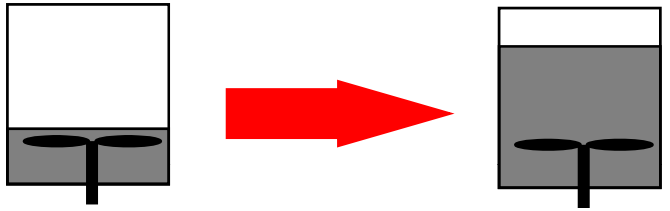
Focus on Drug Active not Drug Product

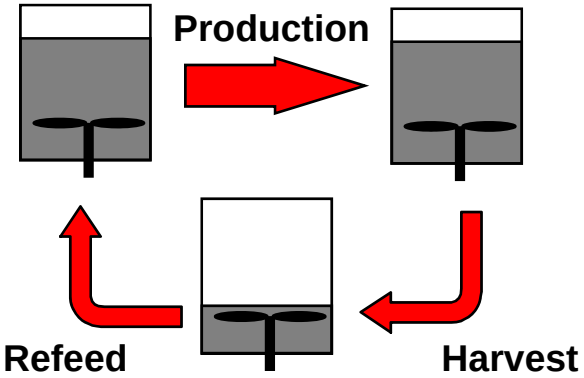
Part 3 Biopharmaceutical Development: Most Common Problems

BATCH



FED-BATCH





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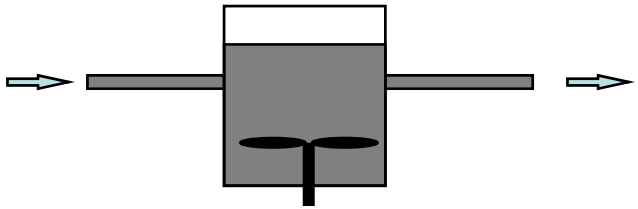
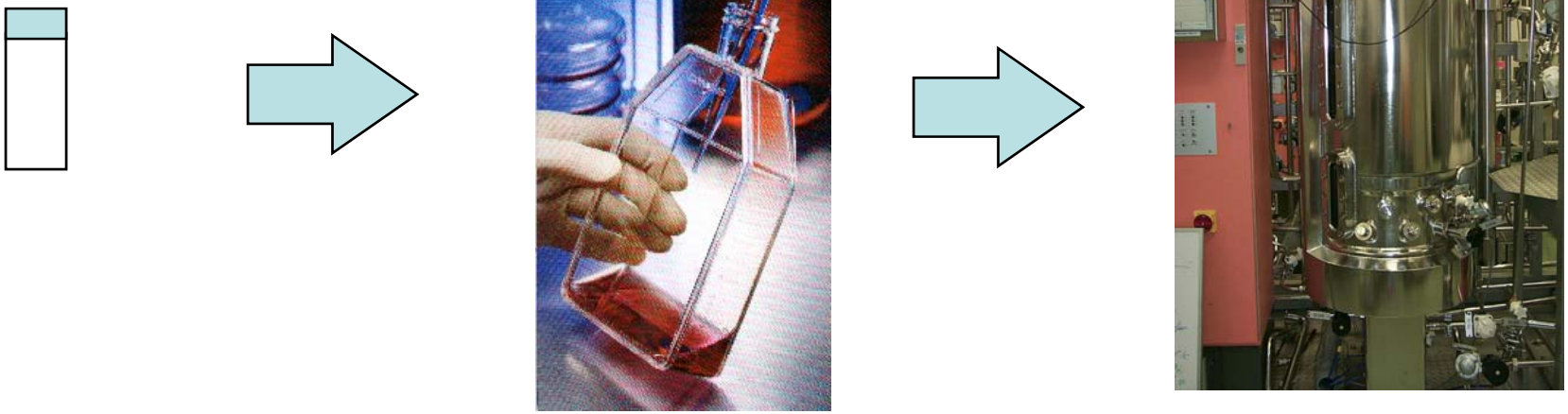


CONTINUOUS

Process Design: unnecessary complexity

Part 3 Biopharmaceutical Development: Most Common Problems

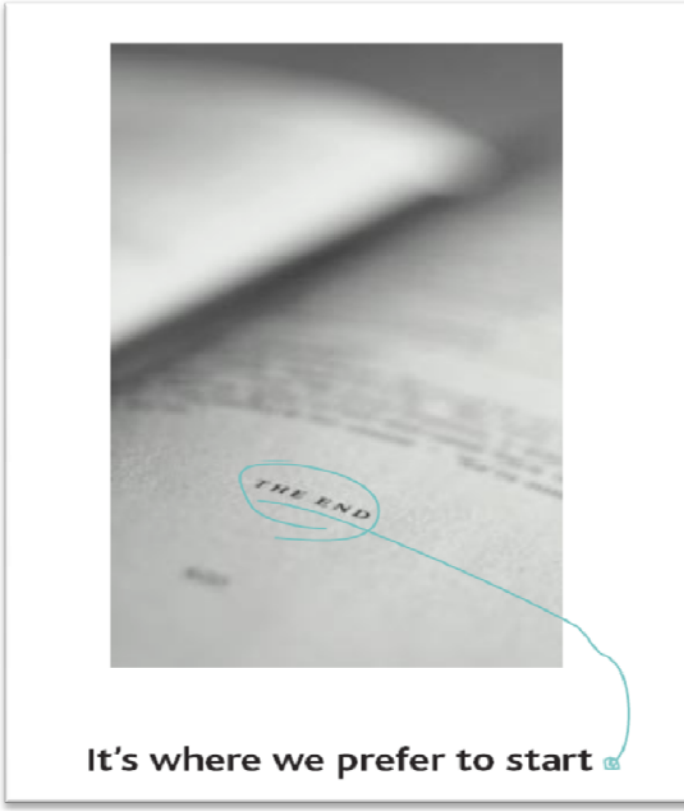


Importance of Inoculum Quality “Can’t make a bad fermentation better”

Part 3 Biopharmaceutical Development: Most Common Problems

Top 5 Most Common Project Problems

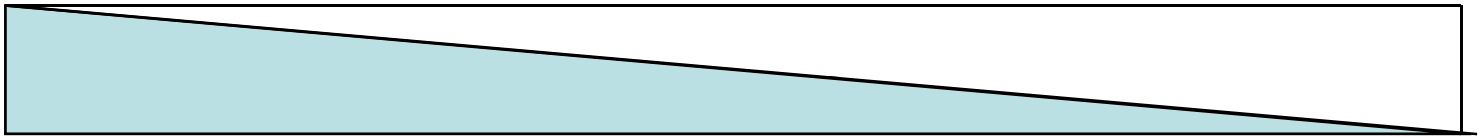
1) Lack of holistic thinking.
2) Underestimate of Resource
3) Resource focus on R& D not Quality
4) No formal risk management
5) Prejudice of one group against the other
   - Development
   - Quality
   - Regulatory



Part 3 Biopharmaceutical Development: Most Common Problems

clear responsibilities essential

Research → Clinic



Discovery

Analytical Research

Process/Product Research

Product Development

Manufacture

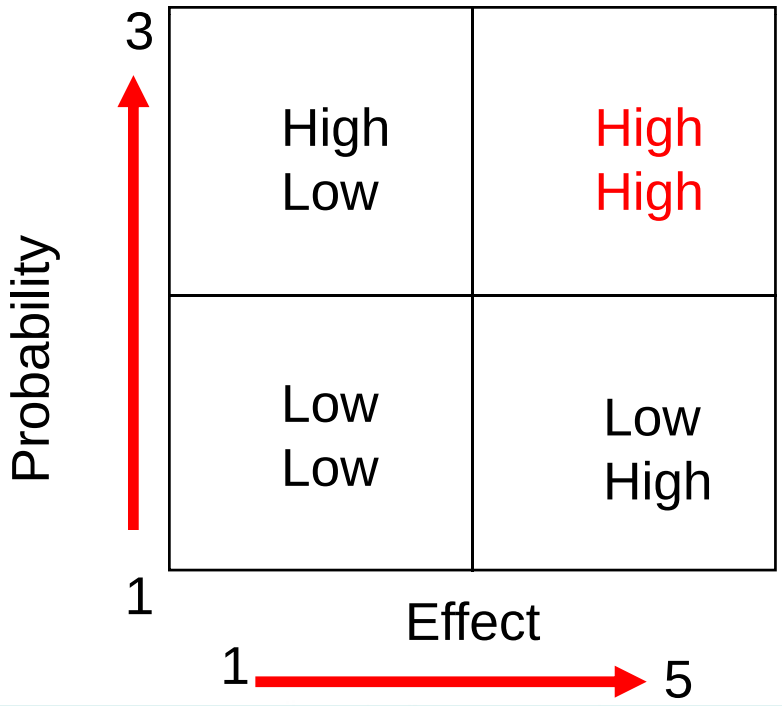
Regulatory

Clinical Development

Quality

Part 3 Biopharmaceutical Development: Most Common Problems

Actively manage the high risks



- Product Quality
- GMP Compliance
- Process Validation
- Assay Validation

Part 3 Biopharmaceutical Development: Most Common Problems

Pre clinical	Phase I / II Clinical	Phase III Clinical	Application Submission	Post Approval
• Cell banking • Analytical support • QA • Fermentation • Yield optimisation • Recovery • DSP • Viral inactivation • Assay development • Characterisation • GMP documentation • Formulation development • QA • Equipment qualification	• Clinical trial supply • Scale up • Validation: -Process -Analytical -EQ (IQ/OQ/PQ) • Implement GMP -MI generation -Documentation • Formulation development • Equipment validation • Stability • QA • Product release testing	• Clinical trial supply • Scale up • Conformance batches • Validation: -Process -Analytical -EQ (IQ/OQ/PQ) • Formulation development • Stability • QA • Product testing	• Dossier compilation • QA • Responses to questions arising from review • Analytical and process support	• Commercial Manufacture • Co-ownership • Phase IV clinical trial supplies • Contract formulation / filling • QA • Product testing • Process refinement • PLV compilation • Analytical support for post license commitments

Understand resource requirements

Part 3 Biopharmaceutical Development: Most Common Problems

Top 5 Most Common CMC Regulatory Problems

5) Analytical Strategy: Link to Key Product Attributes

Part 3 Biopharmaceutical Development: Most Common Problems

Top 5 Most Common CMC Regulatory Problems

4) Transitional Processes
5) Analytical Strategy: Link to Key Product Attributes

Part 3 Biopharmaceutical Development: Most Common Problems

Top 5 Most Common CMC Regulatory Problems

3) In-Process Specifications
4) Transitional Processes
5) Analytical Strategy: Link to Key Product Attributes

Part 3 Biopharmaceutical Development: Most Common Problems

Top 5 Most Common CMC Regulatory Problems

2) Development Genetics
3) In-Process Specifications
4) Transitional Processes
5) Analytical Strategy: Link to Key Product Attributes

Part 3 Biopharmaceutical Development: Most Common Problems

Top 5 Most Common CMC Regulatory Problems

1) End-Product Specifications, esp. bioassay
2) Development Genetics
3) In-Process Specifications
4) Transitional Processes
5) Analytical Strategy: Link to Key Product Attributes

Conclusion and Recommendations:
Creating and maintaining commercial value during biopharmaceutical development

1. Include outsourcing costs and time: both external and internal as a key component of business planning.
2. Licensing Packages: coherent linkage of process and analytics from research and across each clinical study.
3. Documentation: Basis of building and locking in value.
4. Develop a positive two-way relationship with all contract development and manufacturing partners.
5. Anticipate and proactively manage risk: expect challenges!

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Thank you