A Molecule's Journey

Breaking Down Roadblocks to Commercial Success

Navigating through the important considerations necessary to successfully bring a biologic molecule to market

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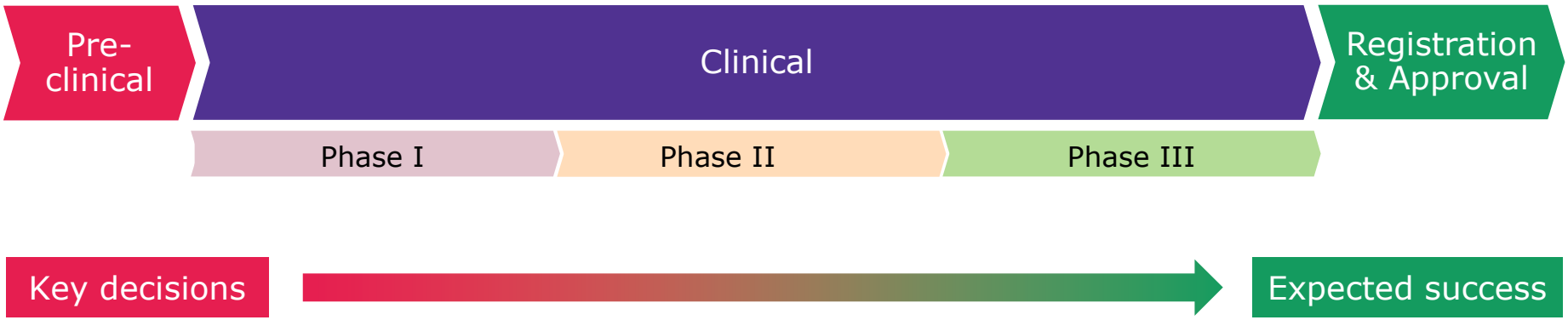
A long Journey from decisions to success



Make the right decisions at the right time

- Business considerations
- Cell line development considerations
- Process development considerations
- Technology considerations
- Regulatory & Risk Assessment considerations

Business considerations
Speed to Clinic

No revenues before approval

Time is money…

3 possible strategies during clinical development:

- ✓ Out-license molecule to generate revenues before approval
- ✓ Outsource manufacturing to reduce CapEx and maintain rights to the molecule
- ✓ Internalize and invest in biomanufacturing facility

Originator or Biosimilar?

Target market? Patient population?

Business considerations
Filing Strategy

Filing can be either global or local

- ✓ Ease of conducting clinical trials
- ✓ Patient population
- ✓ Doctors population & infrastructure
- ✓ Time to obtain approval

Assess carefully local environment

Which country to file drug first for quick market access?

Business considerations
Process Efficiency over Speed

No revenues before approval

Time is money…

Speed through clinic at the expense of Process efficiency… Not good!

- ✓ A poorly developed process can backfire in the later stage
- ✓ Inefficiency can make the drug too expensive to produce

Process efficiency should be addressed at early clinical stages

Choose carefully your service provider

- **Expertise, capabilities, proven track record, speed**

Case study
From clinical stage to commercial production

- ✓ Drug in early clinical for treatment of brain cancer for infants/
- ✓ Breakthrough therapy designation from FDA

Multiple constraints

1. Speed through clinic and to market – Life savings drug
2. « Old style » process - hybridoma cell line, poor performance
3. Small commercial production forecast – unattractive to CMO's

What was achieved… **within 9 months**

- ✓ Develop a robust and industrialized process
- ✓ Produce and release 1st GMP clinical batch/ commitment for future routine commercial production

Cell line development considerations
Choose the right host

Choosing a cell line

- ✓ Cells ability to produce the biologic of interest
- ✓ Clone that can produce at high productivity (titer)
- ✓ High protein quality

Biosimilar vs. originator molecule

Large choice of host cell lines can hide key questions

- ✓ Cost of a license
- ✓ Expected productivity (titer)
- ✓ Track record for market approval

Risk vs Cost

Cell line development considerations
Bank your Clone

- ✓ A **Cell Bank** ensures robustness over development
- ✓ Cell bank establishment takes 28-30 days
- ✓ Safety testing is a regulatory requirement
- ✓ Cell banking is the first GMP activity

If outsourcing CLD, choose a provider who can produce clinical material

- **Identify right clone, demonstrate proof of concept, conduct testings which will satisfy regulatory bodies**

Cell line development considerations

Ensure genetic stability

Highest productivity but also genetically stable..

- ✓ 60 generations with stable productivity and protein quality - Takes 60 to 120 days
- ✓ Cell line characterization: genetic stability testings (DNA sequencing, copy number determination..)

Cell line development considerations
Perform robustness studies

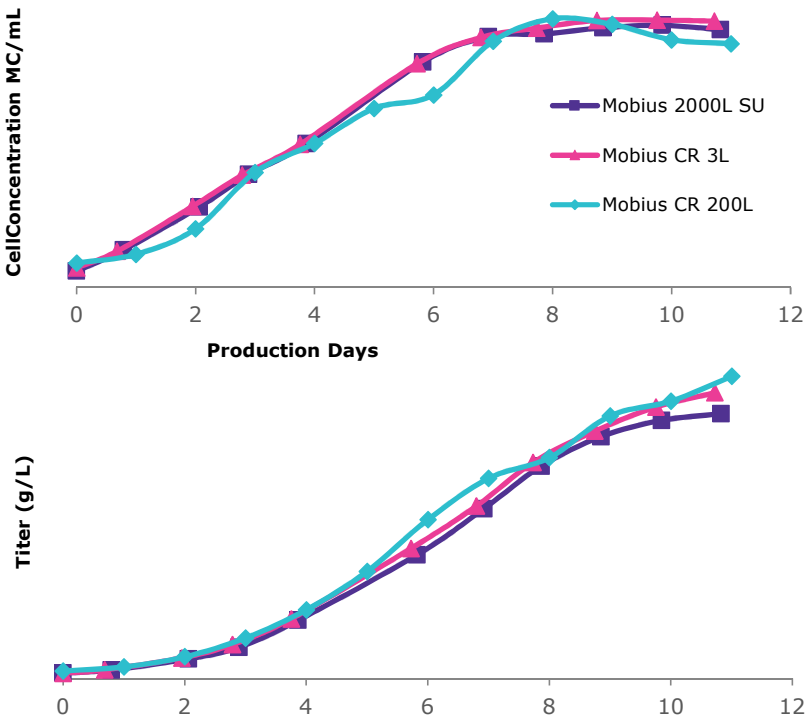
Determine the ability of cells to perform in scaled up conditions

- ✓ Replicate cells physical environment in scaled-up conditions
- ✓ Aeration rate, agitation, shear forces..
- ✓ Confirm productivity and product quality characteristics

Avoid to restart from scratch if cells cannot withstand bioreactor conditions

Process development considerations

Ensure process efficiency and viability



The process should be viable and efficient

- ✓ through scale-up/ scale-down
- ✓ through tech transfer

Engineer in-process efficiency from the beginning

- ✓ Eliminate wasteful steps

Process viability = robustness as well as its ability to meet economic goals of the project over time

Process development considerations
Ensure process efficiency and viability

Upstream optimization is key…

1. Media & Feed screening

- ✓ Define the 3 best combinations medium and feed
- ✓ Assessment of up to 20 combination in duplicate

2. Confirmation at 3L scale in 3L SUB

- ✓ Confirm productivity and cell growth
- ✓ Confirm product quality characteristics

3. Quality controls

- ✓ Cell density and viability
- ✓ Metabolite profile (Gluc, Lac, pH, pO2…)
- ✓ Titer (Biacore, PA-HPLC, Octet, ELISA)
- ✓ …

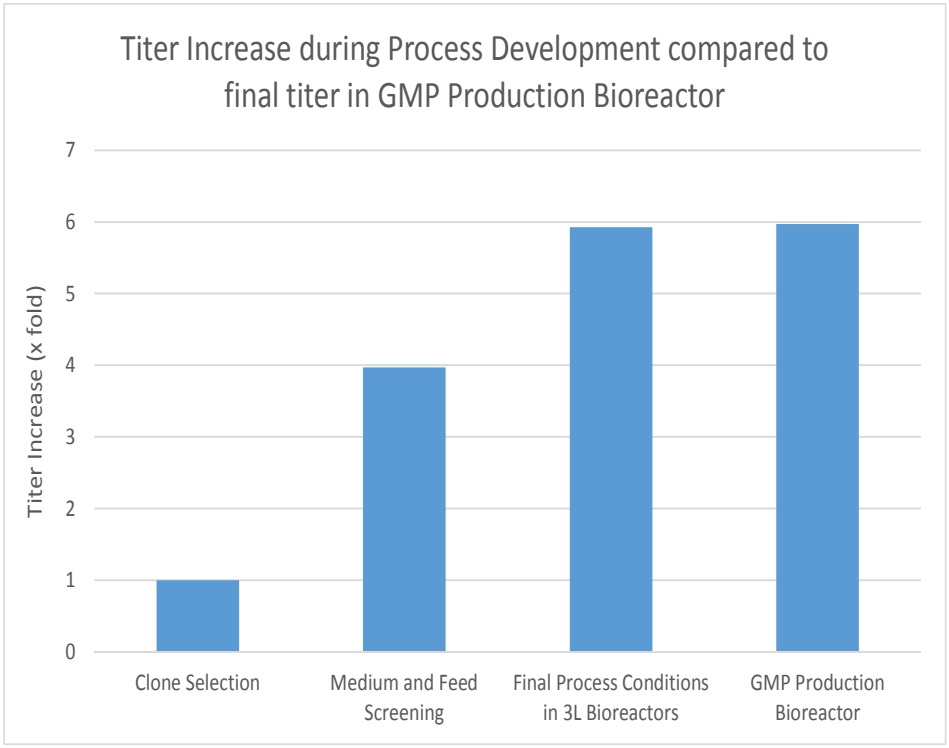
Experience:

Cell types: CHO-K1, CHO-S, CHO-M, DG44, DXB11, DUKX, hybridoma

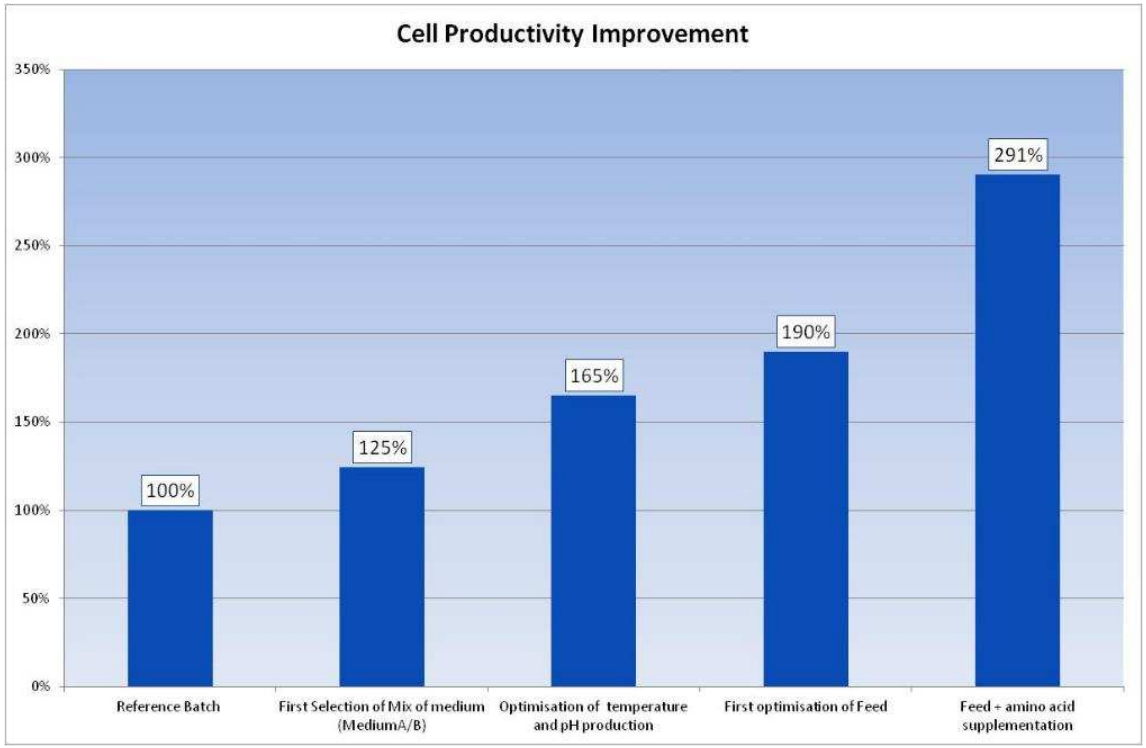
Molecules: Monoclonal antibodies, Recombinant proteins, originators or biosimilars

Process development considerations

Ensure process efficiency and viability



CHO DUKXB11 cells producing monoclonal antibody



CHO S cells producing monoclonal antibody

Process development considerations
Financial viability over Productivity

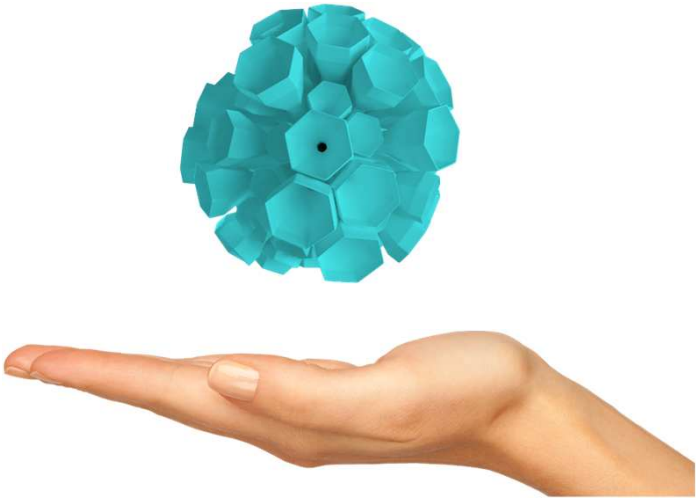
Consider the end-product and its expected cost

- ✓ Cost of raw-materials
- ✓ Upstream titer
- ✓ Downstream efficiency
- ✓ Dose per patient
- ✓ Medical needs

Determine the optimal yield of your process

Process development considerations

Need to outsource? Ask the right questions…



Reduce time and complexity

- ✓ Process templates based on experience with previous molecules

Ask the right questions

- ✓ What is your experience?

But also…

- ✓ What were last 10 different PD problems you had to solve?
- ✓ What were the solutions you implemented?

Case study
Speed up Process Development & mitigate risks

- ✓ Medium size biotech company
- ✓ Advancing Mab clinical pipeline to generate value, then out-license
- ✓ Process Development strategy: **speed up while mitigating risks**
    1. Assessing existing old process
    2. Opportunities to optimize this process
    3. Development of a new process

Flexibility, Flexibility, Flexibility…

- ✓ Parallelize & cut activities to focus on most promising
- ✓ Once best option defined: take it through Phase II, Phase III and commercial

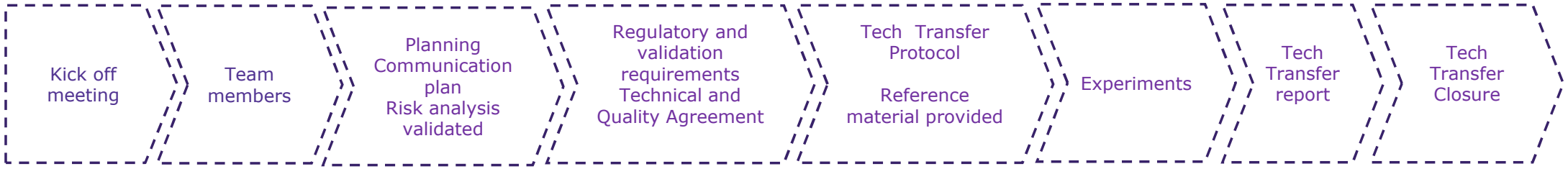
Case study
In tech transfer of a cell line

- ✓ Program management executed by customer R&D (IT)
- ✓ CLD sub-contracted to company in US *(SE)*
- ✓ USP/ DSP PD & clinical supply sub-contracted to MS in FR *(RE)*

- ✓ TT of the cell line from *SE* in US to *RE* in France
  - ➢ Considered "simple" project/ activity by *SE*
  - ➢ Underestimation of TT complexity
  - ➢ Program Manager under time pressure/ *SE* look for time savings **=> TT document unfilled**

- ✓ Cell line and CCM transferred to *RE* **=> cell growth issue**
  - ➢ No defined process of cloning/ sub-cloning from *SE*
  - ➢ Composition of Cloning medium modified. (Gln ⇔ Gltmx)
  - ➢ No proof of clonality
  - ➢ Shift from 2 weeks initial schedule to **6 months investigation & CA**

Case study
In tech transfer of a cell line



Kick off meeting : Scope, transfer timelines and team members are defined

Team members : At least composed of a project manager, a technical leader and a tech transfer team

Communication plan :
Deliverables
Team members with their respective responsibilities
Communication flow path
Meeting frequency

Tech transfer protocol:
Equipment
Raw materials and consumables
Detailed process description including critical parameters
Analytical methods

Technology considerations

Flexibility can reduce the cost of goods

Process Flexibility

Ease of Use

Reduction of Contamination Risks

Flexible Factory Concept

Rapid suits configuration for a variety of processes

Rapid changeovers between batches

Less CapEx
Facility / Equipments

Less OpEx

Closed processes

Sterile pre-assembled disposable assemblies
Sterile connectors / Tube welders

Technology considerations
Flexibility can reduce the cost of goods

New single-use tools – Real advantages

- ✓ Disposable mixers for viral inactivation
  - ➢ No cleaning (No cleaning check)
  - ➢ No sterilization
  - ➢ No spare parts

- ✓ Prepacked columns
  - ➢ No packing time
  - ➢ No HEPT

- ✓ Platforms
  - ➢ Reduce tubing preparation
  - ➢ Towards a fully closed process
  - ➢ Reduce mistakes
  - ➢ Common software from PD to manufacturing
  - ➢ Easy to connect all the steps

Technology considerations

Flexibility can reduce the cost of goods

Technology considerations
Flexibility can reduce the cost of goods

Process equipment shared by DSP suites

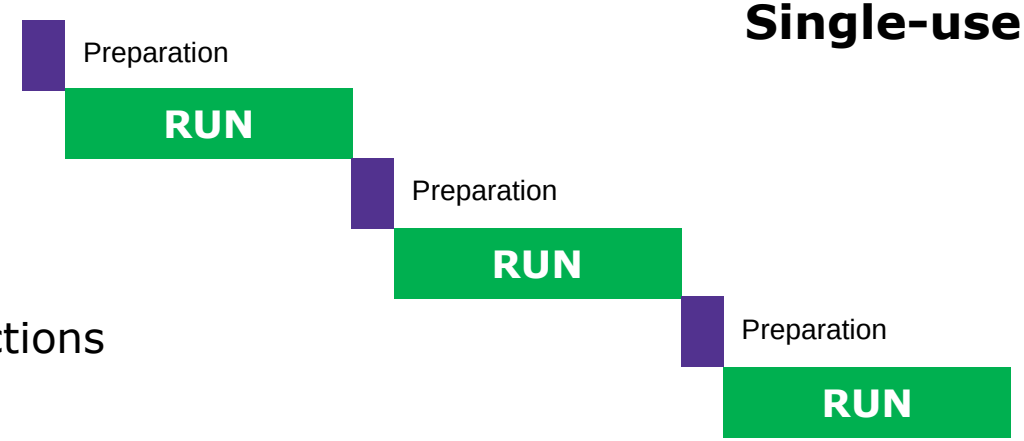
Technology considerations

Flexibility can reduce the cost of goods

- ✓ Elimination of clean-in-place
- ✓ Reduced energy requirement
- ✓ Reduced time requirement

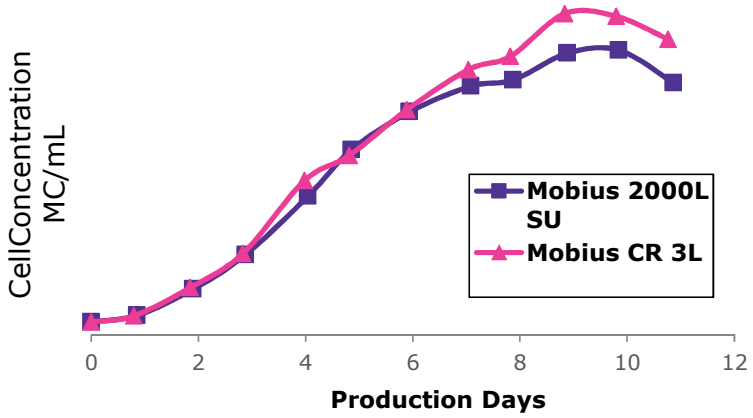
Stainless Steel Bioreactors

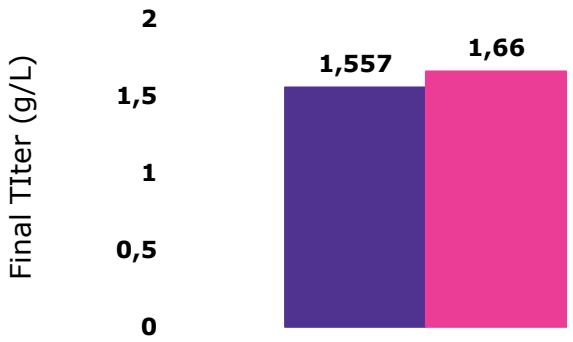
Single-use Bioreactors



- ✓ Equipment mobility
- ✓ Pre-sterilized assemblies
- ✓ In-process aseptic connections

Technology considerations
Scalability is key





CHO-K1 SV cell line producing monoclonal antibody

The use of a bioreactor with proven scalability is a way to ensure success through clinical development

Technology considerations
Evaluate for ease of use

Wrong technology choices in the bioproduction facility can have long term negative consequences upon multiple projects…

- ✓ Cost of quality (failed batches/ scrap)
- ✓ Process inefficiency due to unnecessary complexities

Choose technologies that exhibit a logical simplicity in use and flexibility in utility

Technology considerations
Evaluate for ease of use

Areas of improvement with Single-use Systems

✓ Training

Operators require less training than they do with stainless steel equipment because the equipment is much simpler (i.e. less piping and/or no spare parts)

✓ Pre-configured Assemblies

Single-use assemblies, or "Flexware," are usually preconfigured for quick and easy installation

✓ Automation

Operations are mostly automatic and the recipes used are virtually foolproof

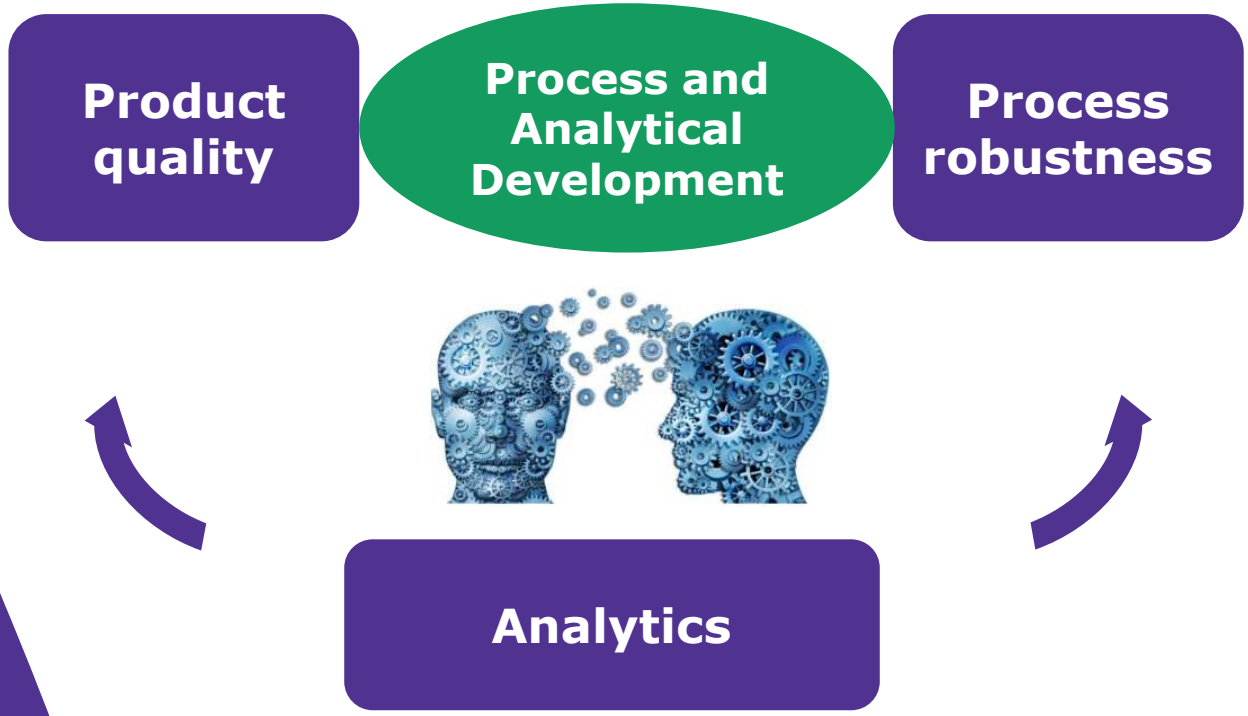
Regulatory considerations
Patient safety is always priority

Main driver for regulations : Patient Safety

- ✓ Start early in clinical development
- ✓ Obtain deep knowledge of the product early in Dev to understand potential safety issues
  - Toxic product isoforms
- ✓ Cross contamination risks
  - Product flow/ personal flow/ waste flow
  - Risk mitigation strategies

Regulatory considerations

Ensure product quality and process robustness



Collect data supporting product quality and process robustness

- ✓ Start early in clinical development
- ✓ Analytical methods should be developed in parallel with the process
- ✓ Focus on establishing critical quality attributes
- ✓ Monitor closely after injection to patient

Regulatory considerations

Engage regulatory authorities throughout development

Drug filing strategy will dictate regulatory strategy

- ✓ which regulations to adhere to
- ✓ Which regulatory agency will inspect the facility
- ✓ ICH becoming world basis for all countries

Best practice: engage in discussions with regulatory authorities both upfront and regularly to validate development approach

Conclusion & Case Study
Full support

- ✓ Company moving into biosimilars on its local market

Multiple needs:

- ✓ Support their business case and regulatory strategy
- ✓ Full PD & clinical supply Ph II through Ph III for their biosimilar portfolio
- ✓ Support for designing their future pilot & commercial facility
- ✓ Support hiring process for their staff (PD, Manufacturing, Quality..)
- ✓ GMP operators training
- ✓ Backbone of their future quality system

A Molecule's Journey

Breaking Down Roadblocks to Clinical Success

BUSINESS

Speed to Clinic
Choose the appropriate strategy

Strategy
Identify the right country

Efficiency
Ensure a consistent and reliable process

CELL LINE DEVELOPMENT

Choose
Protein quality is of particular concern

Perform
Replicate the physical environment

Ensure
Conduct genetic stability tests

PROCESS DEVELOPMENT

Ensure Viability
Meet economic goals

Financial Viability Over Productivity
Avoid negative impacts on commercial success

Ask the Right Questions
First-hand experience matters

TECHNOLOGY

Reduce COGS
Ensure process flexibility and equipment mobility

Scalability is Key
Put in place an efficient scale-up process

Evaluate
Select technologies that exhibit a logical simplicity

REGULATORY & RISK ASSESSMENT

Patient Safety is Priority
Put in place milestones for assessment

Ensure Product Quality
Collect data as early as possible

Engage Regulatory Authorities
Ensure that you go in the right direction

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A Molecule’s Journey

Guidebook: Break Down Roadblocks to Clinical Success

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