

# A Risk-Based Approach to the Implementation of a Control Strategy for Advanced Therapy Medicinal Products

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# The Knowledge Doubling Curve:

“Before the 20<sup>th</sup> century, human knowledge doubled every century. By the 1950s, it doubled every 25 years. Today, it is doubling about every 13 months.”



- *Source: Thoughts on the future of human knowledge and machine intelligence*  
- London School of Economics and Political Science

# AGENDA

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Level Set: Quick Intro to ATMPs and the Process Validation Lifecycle

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Risk-Based Approach to Process Qualification (Stage 2)

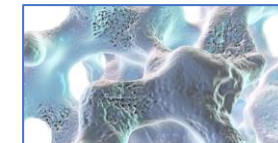
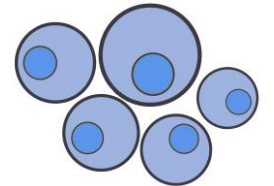
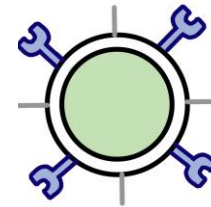
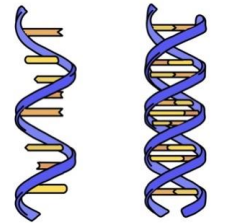
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Unique Challenges and Considerations for ATMPs

# Advanced Therapy Medicinal Products

## ATMPs

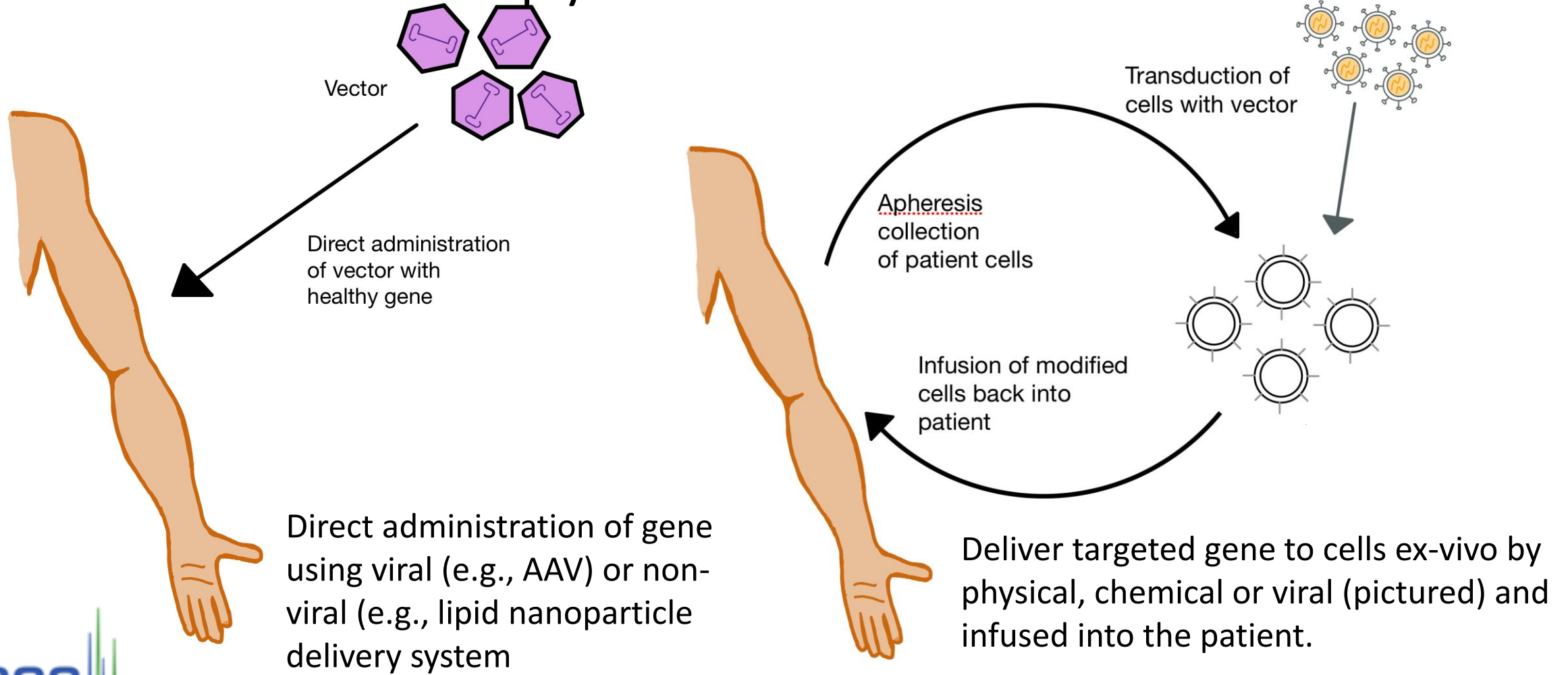
- **Gene Therapy Medicinal Products:** healthy gene is packaged within a delivery system (a “vector”) that is administered to patient leading to a therapeutic, prophylactic, or diagnostic effect.
- ||
- **Cell Based Advanced Therapy Medicinal Products:** contain cells that have been manipulated to change their biological characteristics or cells not intended to be used for the same essential functions in the body.
- ||
- **Tissue-engineered products:** contain cells or tissues that have been modified so they can be used to repair, regenerate, or replace human tissue



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# Advanced Therapy Medicinal Products



# Advanced Therapy Medicinal Products

987+ companies developing ATMPs worldwide

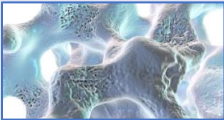
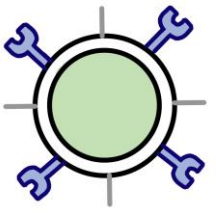
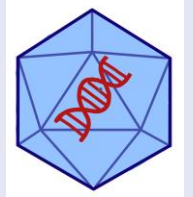
1,066 clinical trials underway (thru 2019)

Source: Alliance of Regenerative Medicine



“The activity reflects a turning point in the development of these technologies and their application to human health. It’s similar to the period marking an acceleration in the development of antibody drugs in the late 1990s, and the mainstreaming of monoclonal antibodies as the backbone of modern treatment regimens.”

– Scott Gottlieb, ex-FDA Commissioner in 2019



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# Advanced Therapy Medicinal Products

Some examples of Gene Therapy Products that have been approved:

**Glybera** – uniQure (first gene therapy for an inherited disease approved in Europe in 2012, subsequently pulled from market in 2017)

- Treats lipoprotein lipase deficiency (ultra rare disease)



**Zolgensma** (onasemnogene abeparvovec-xioi) - Novartis / Avexis

- Treats infant spinal muscular atrophy (SMA); approved in 2019
- EMA Conditional approval (May 2020)



**Luxturna** (voretigene neparvovec-rzyl) – Spark Therapeutics

- First medicine approved for an inherited genetic disorder in 2017 by FDA
- Treats biallelic RPE65 mutation-associated retinal dystrophy



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# Advanced Therapy Medicinal Products

Recent Ex-vivo Autologous Cell Therapy products approved by the FDA:

**Kymriah** (tisagenlecleucel) – Novartis

Approved in 2017 by FDA

Treatment of patients up to 25 years age for r/r B-cell acute lymphoblastic leukemia



**Yescarta** (axicabtagene ciloleucel) – Kite Pharma (Gilead)

Approved in 2017 by FDA

Treatment for adult patients with relapsed, refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma



**Zynteglo** (Autologous CD34+ cells encoding  $\beta^{A-T87Q}$ -globin gene) –

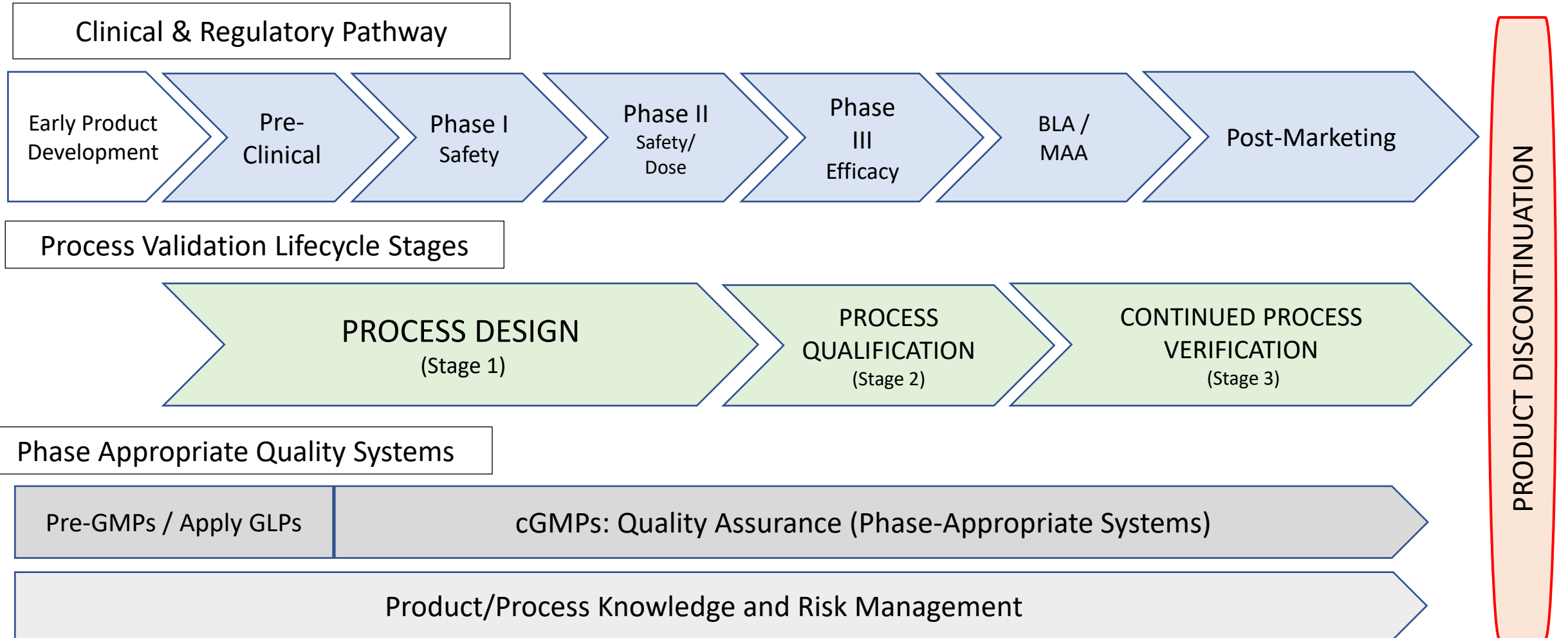
Bluebird bio -- Approved in 2019 by FDA

Treatment for B-thalassaemia (TDT) = patients cannot make enough haemoglobin thus are anemic (patient age: 12 years and older)





# Process Validation Lifecycle Approach



# Process Validation Lifecycle Approach



Process and product knowledge are explored to establish a control strategy for manufacture. The product control strategy is defined.

Stage 2A is the qualification of GMP manufacturing systems (facility/utilities/equipment); Stage 2B is the Process Performance Qualification (PPQ) based on the process control strategy.

On-going monitoring of the process control strategy through the manufacture of commercial product lots. Continual process improvement based on monitoring.



Stage 1: Key Output is the **“Process Control Strategy”**

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# Process Validation Lifecycle Approach



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**Stage 2: Goal is a “Successful PPQ campaign”**

# Process Validation Lifecycle Approach



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Stage 3: Goal is to **“Continuous Improvement”**

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# Process Validation Lifecycle Approach



## [Question]

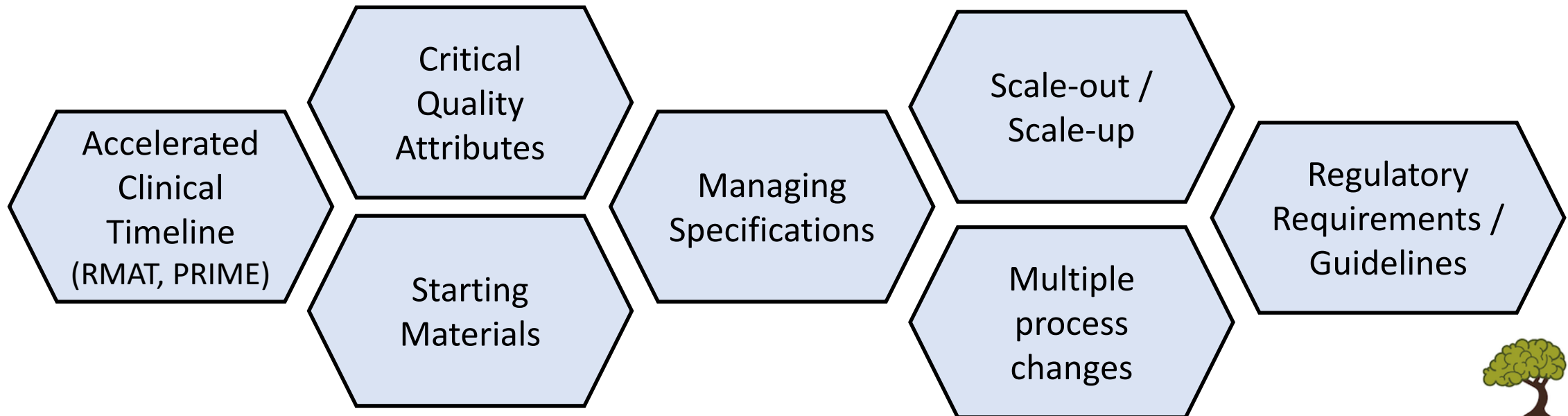
When can the Process be considered as Validated?

- Stage 1
- Stage 2
- Stage 3

# Process Validation Lifecycle

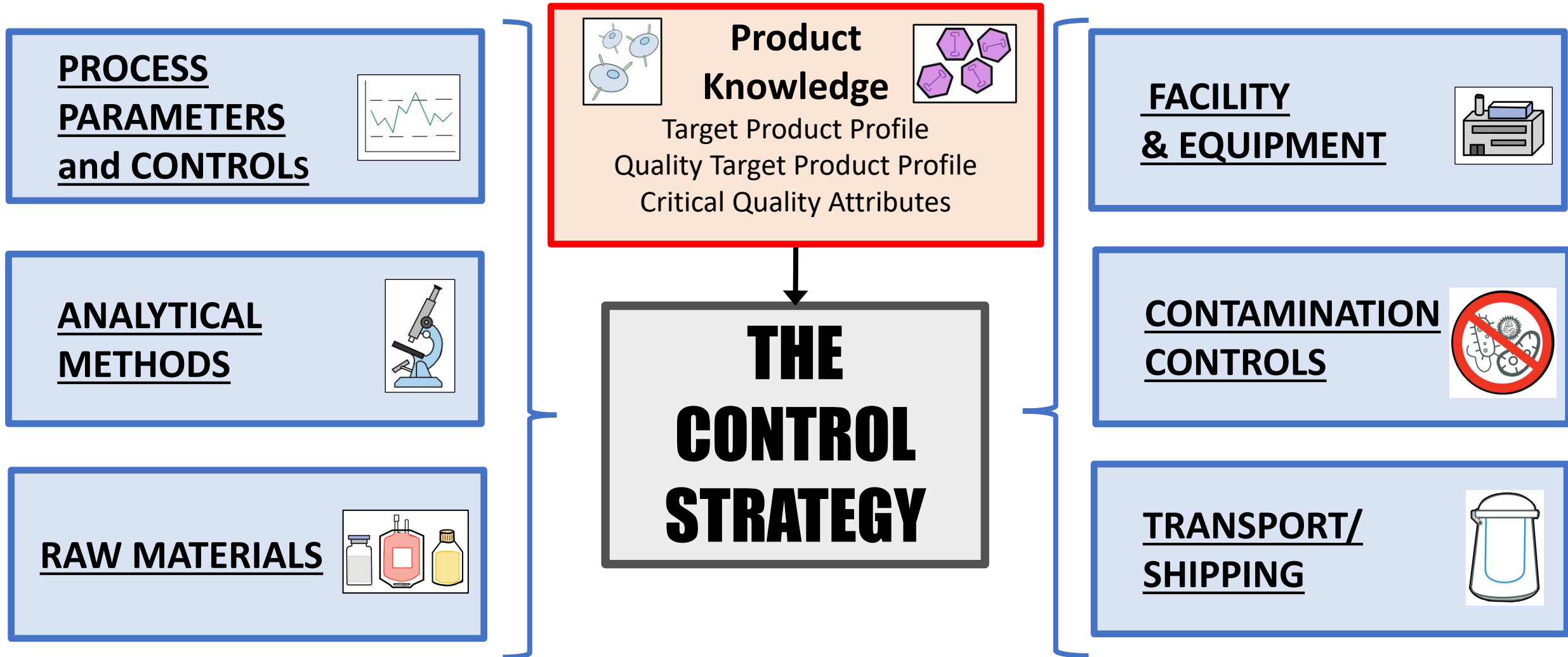
## Unique Challenges for Development of ATMPs

“In manufacturing, they need to focus on producing quality products by design in scalable processes, so that if early clinical trials are promising, they can advance development rapidly.” -- Peter Marks, Director CBER



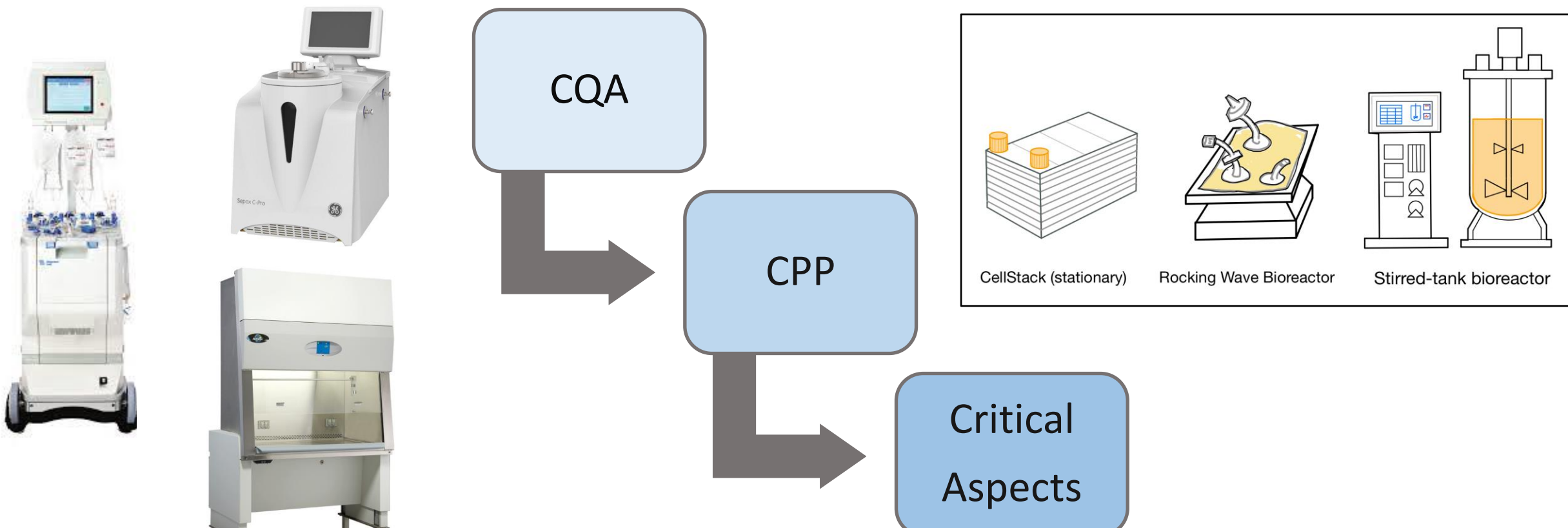
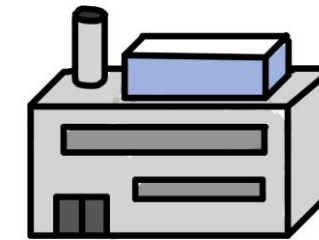


# Elements of the Overall Control Strategy



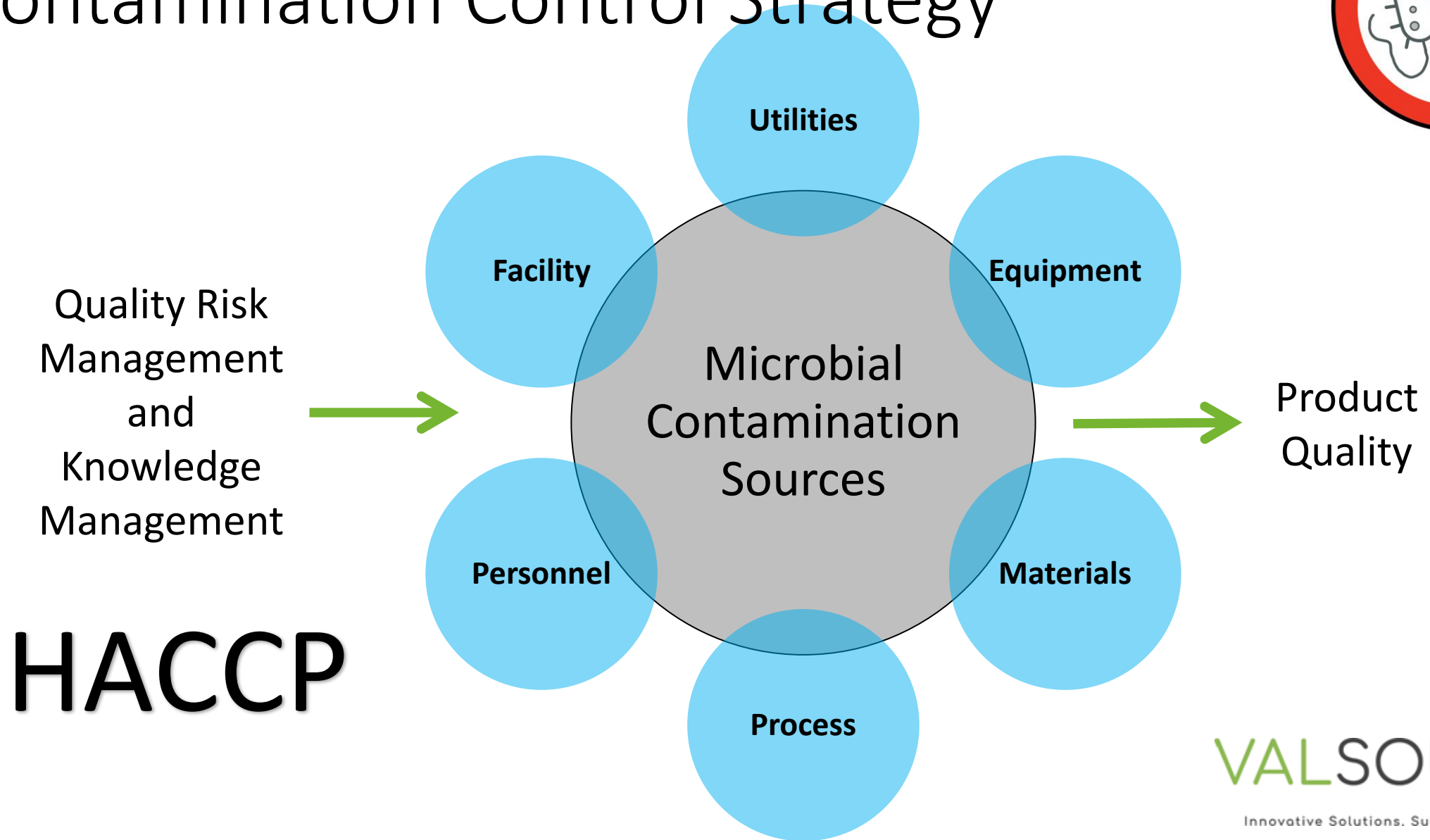
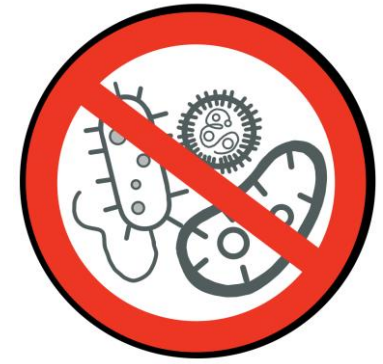
# Facilities/Utilities/Equipment

Process Control Strategy translates to Facilities/Utilities/Equipment design, qualification, and maintenance using risk-based approach



Apply risk assessment based on the product attributes early – if possible, before Facility and Equipment Design.

# Contamination Control Strategy

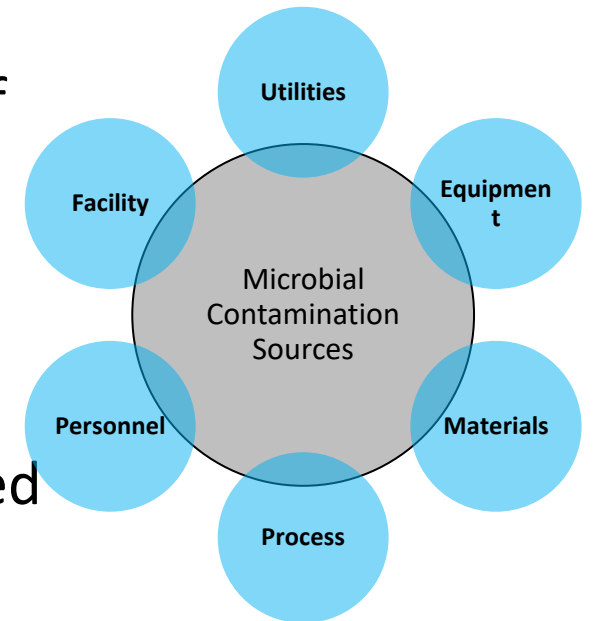


# Contamination Control Strategy



## Unique Challenges for ATMPs

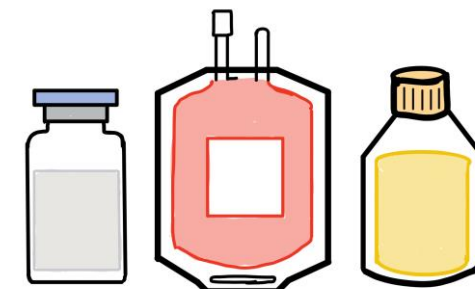
- No terminal sterilization for cell-based products
- Aseptic manipulation of the product throughout the entirety of the manufacturing process
- Lack of dedicated viral clearance steps
- Product segregation - multiple products / patient lots / viral vectors concurrently manufactured
- One lot per one patient (autologous) thus risk of a contaminated batch is higher severity for risk assessment



**EMA Annex 1 in revision – Contamination Control Strategy!**

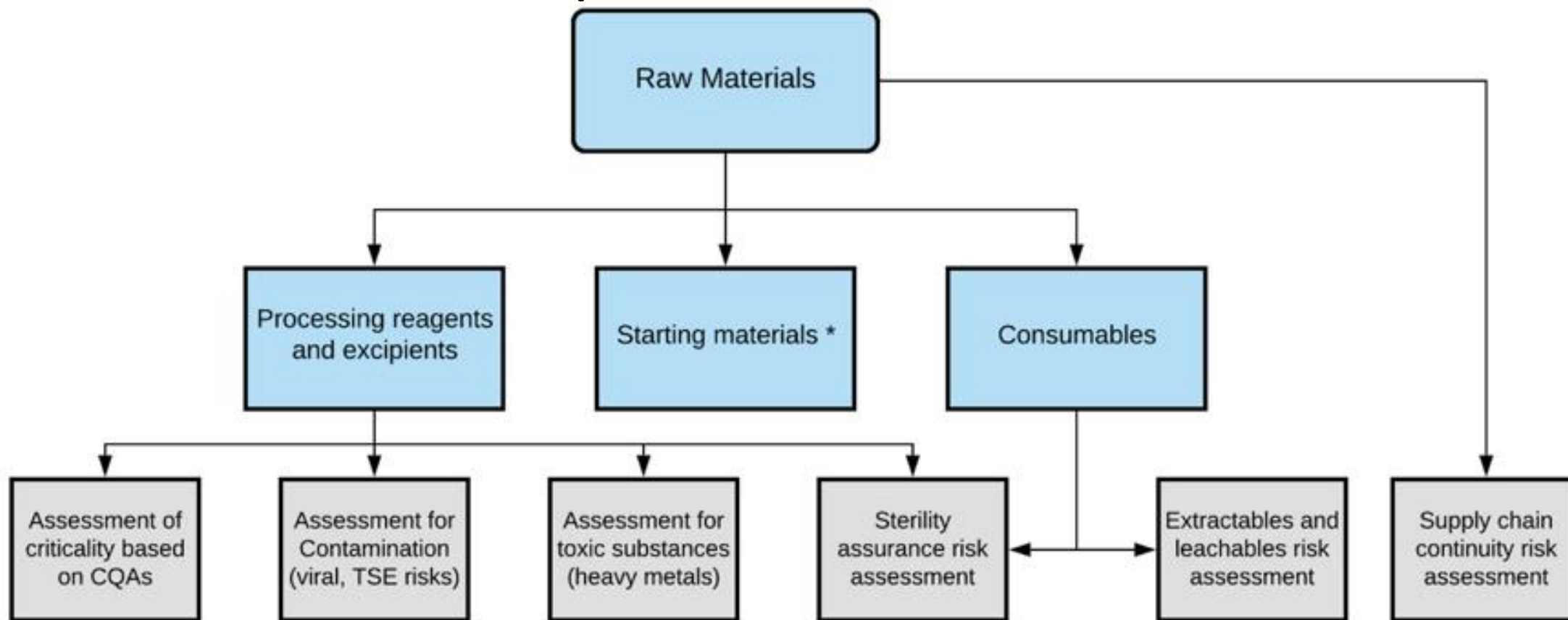
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# Raw Materials Control Strategy

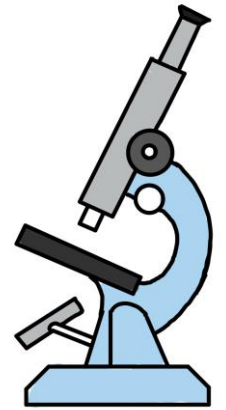
Risk assessment is key to develop robust control and monitoring plan for raw materials used in the process!



A unique assessment employed for each of these types of materials

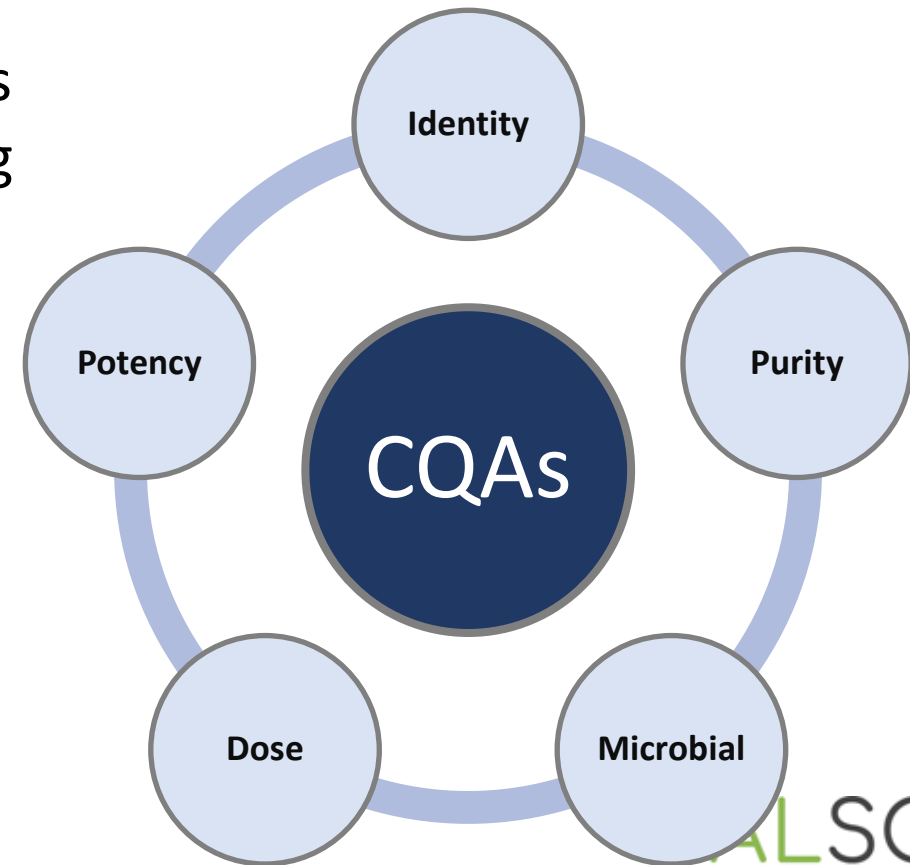
# Analytical Methods Control Strategy

Lifecycle approach also applies to analytical procedures through method development, qualification/validation, and continued monitoring.



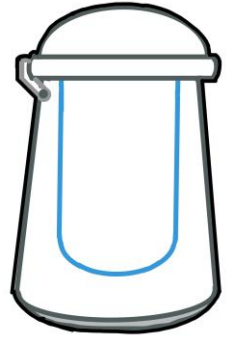
## Analytical Development Challenges for ATMPs

- Complexity, variability, and stability of living cell products
- Fast turnaround for release testing in order to meet individual patient needs
- Limited material (product in 1° containers) for analysis/retain/retest
- Product Comparability
- Stability indicating





# Product Shipping Control Strategy



## Unique Challenges for ATMPs – Shipping Controls & Monitoring

Risk Assessment is crucial for developing a robust Shipping Control Strategy

- Vein to vein (for individualized autologous therapies) – “manufacturing” and Quality oversight start and end at the clinic
- Essential to maintain product quality throughout the process including shipping and transport but it is commonly overlooked in early clinical stage
- Developing technologies
  - Physical shipping conditions
  - Product tracking: CoI / CoC

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# Process Validation Lifecycle

## Recent Regulatory Guidance specific to the Validation of ATMP Processes

- FDA – 2020 Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
- FDA – 2011 Guidance on PV – continues to withstand the test of time...applies to ATMPs
- EMA – 2017 EudraLex Volume 4 Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products



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# Process Performance Qualification

Are we ready for Stage 2B – Process Performance Qualification?

- Process Capability Assessment

$$S \times O \times D = RPN$$

**Severity x Occurrence x Detection = Risk Priority Number**

- By PV Stage 2B this “process capability assessment” needs to be primarily based on EMPIRICAL data and less human BIAS.
- Mitigations...aAre you sure you can move forward with those HIGH/MEDIUM risks?

# Process Performance Qualification

## Design of the PPQ – What to Evaluate and Corresponding Acceptance Criteria?

- Critical Process Parameters and Proven Acceptable Ranges – inputs linked to CQAs w/ PARs based on Characterization studies
- Process Performance Indicators and Operating ranges, e.g. product yield w/ ranges based on capability analysis
- Critical Material Attributes – use multiple lots of critical materials
- In-Process Controls – verify CQAs met at critical control points
- Product (release) specifications
- Non-processing holds of intermediates – stability / microbial evaluation
- Stability – put the PPQ lots on stability
- Analytical Retains – take as many as possible and store for future use and testing

# Process Performance Qualification

## Regulatory Oversight FDA – 2020 Guidance is IND focused



- Process Validation [3.2.S.2.5] “We recommend that you use early stage manufacturing experience to evaluate the need for process improvements and to support process validation studies in the *future*.”
- Batch Analysis [3.2.S.4.4] – “We recommend that you retain samples of production lots for use in *future* assay development, validation, or comparability studies.”
- Control of Critical Steps [3.2.S.2.4] “The duration of production steps and hold times should be controlled and recorded to facilitate the establishment of process limits and to allow for future validation of each step and hold time within the proposed limits in support of a license application.”

# Process Performance Qualification

## Regulatory Oversight EMA – GMPs for ATMPs

### [10.3] Process Validation.

“While it is acknowledged that some degree of variability of the finished product due to the characteristics of the starting materials is intrinsic to ATMPs, the aim of the process validation for ATMPs is to demonstrate that the finished product characteristics are within a given range (in compliance with the terms of the marketing authorisation).”

Product / process knowledge – e.g., understand the Critical Material Attributes of starting materials (i.e., the transducing vector, plasmids, and the apheresis (for individual, autologous therapies)



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# Process Performance Qualification

## Regulatory Oversight EMA – GMPs for ATMPs



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[10.41] Validation with surrogate materials.

“The use of surrogate material may be acceptable when there is shortage of the starting materials (e.g. autologous ATMPs, allogeneic in a matched-donor scenario, allogeneic where there is no expansion of cells to MCB).”

“The representativeness of surrogate starting material should be evaluated.”

Yes, you can justify the use of surrogates, however need to compare and show that this material is representative and understand impact of any differences observed.

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# Process Performance Qualification

## Design of the PPQ – # of PPQ runs?

A risk-based approach should be taken to determine the number of manufacturing runs to perform in the PPQ campaign.

### What to consider?

- Capability - Understand the sources of process variability and impact on product quality
- Process History – Failure rate? Recent process change(s)?
- Extent and relevance of process development data (e.g., process characterization studies)
- Clinical Manufacturing experience, e.g. success rate % of mfg runs
- Complexity of the process (multiple processing equipment, equipment trains, workstations)

# Process Performance Qualification

## Regulatory Oversight EMA – GMPs for ATMPs - # of PPQ runs

[10.3] Process Validation. "It is generally accepted that, as a minimum, three consecutive batches manufactured under routine conditions constitute a validation of the process. *An alternative number of batches may be justified* taking into account whether standard methods of manufacture are used, whether similar products or processes are already used at the site, the variability of starting material (autologous v. allogenic), clinical indication (rare disease: only few batches will be produced) ."



# Process Performance Qualification

Goal of the PPQ is to show that the Process Control Strategy can provide product with consistent quality and process performance.

- The ultimate success of the PPQ is based on the strength of the Process Control Strategy from Process Design Stage 1.
- The PPQ is a snapshot in time. However, you will have many “headaches” in commercialization PV Stage 3
  - Batches that do not meet product specifications
  - Significant process changes with many Regulatory and Product Comparability challenges
- Thus heightened monitoring of the process (as performed during the PPQ) should be subsequently continued through on-going monitoring post-PPQ and into Stage 3 CPV for most ATMPs.

# IN SUMMARY

- ✓ For ATMPs, a risk-based approach needs to be taken for the ultimate success of the validation efforts through the lifecycle and to support successful commercialization.
- ✓ This approach has many benefits including (and not limited to)...
  - ORGANIZE the rapidly increasing product and process knowledge
  - FOCUS on critical elements and identify risks that need to be mitigated
  - IDENTIFY also what you do not know (uncertainty) and how to address
  - COMMUNICATE information and data across business units and external
  - READY organization ultimately for long-term successful commercialization

# Interesting Reads on Risk and Covid-19

## Recent articles on managing risk and uncertainty

- **How Military Thinking Can Improve Pharma Decision Making Under Stressful Conditions**  
<https://www.lifescienceleader.com/doc/how-military-thinking-can-improve-pharma-decision-making-under-stressful-conditions-0001>
- **Making Decisions In A COVID-19 World: How To Combat Stress With Quality Risk Management**  
<https://www.pharmaceuticalonline.com/doc/making-decisions-in-a-covid-world-how-to-combat-stress-with-quality-risk-management-0001>
- **High Absenteeism & The Production Of Medically Necessary Drugs During COVID-19**  
<https://www.pharmaceuticalonline.com/doc/high-absenteeism-the-production-of-medically-necessary-drugs-during-covid-0001>

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