Establishment & Implementation of the Process Control Strategy: The Unique Challenges for Cell Therapy Products

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Innovative Solutions. Sustainable Results.

The Knowledge Doubling Curve

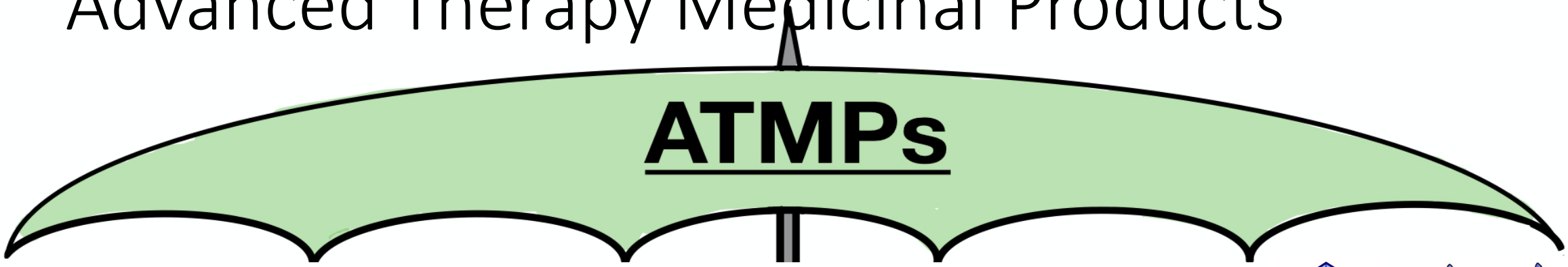
"Before the 20th century, human knowledge doubled every century. By the 1950s, it doubled every 25 years. Today, it is doubling about every 13 months."

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

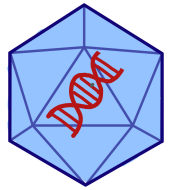
AGENDA

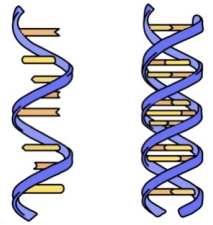
- Brief Intro to Cell Therapies (ATMPs)
- Define Process Validation Lifecycle
- Risk-Based Approach to Development
- Unique Challenges for Cell Therapies

Advanced Therapy Medicinal Products

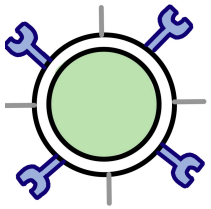


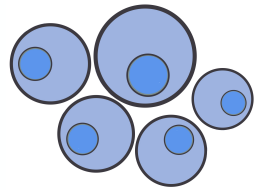
- ***Vector Based Gene Therapy Medicinal Products***: healthy gene is packaged within a delivery system (a "vector") that is administered to patient leading to a therapeutic, prophylactic, or diagnostic effect.



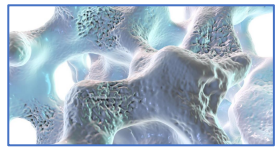


- ***Cell Based Advanced Therapy Medicinal Products:*** contain cells that have been manipulated to change their biological characteristics or cells not intended to be used for the same essential functions in the body.





- ***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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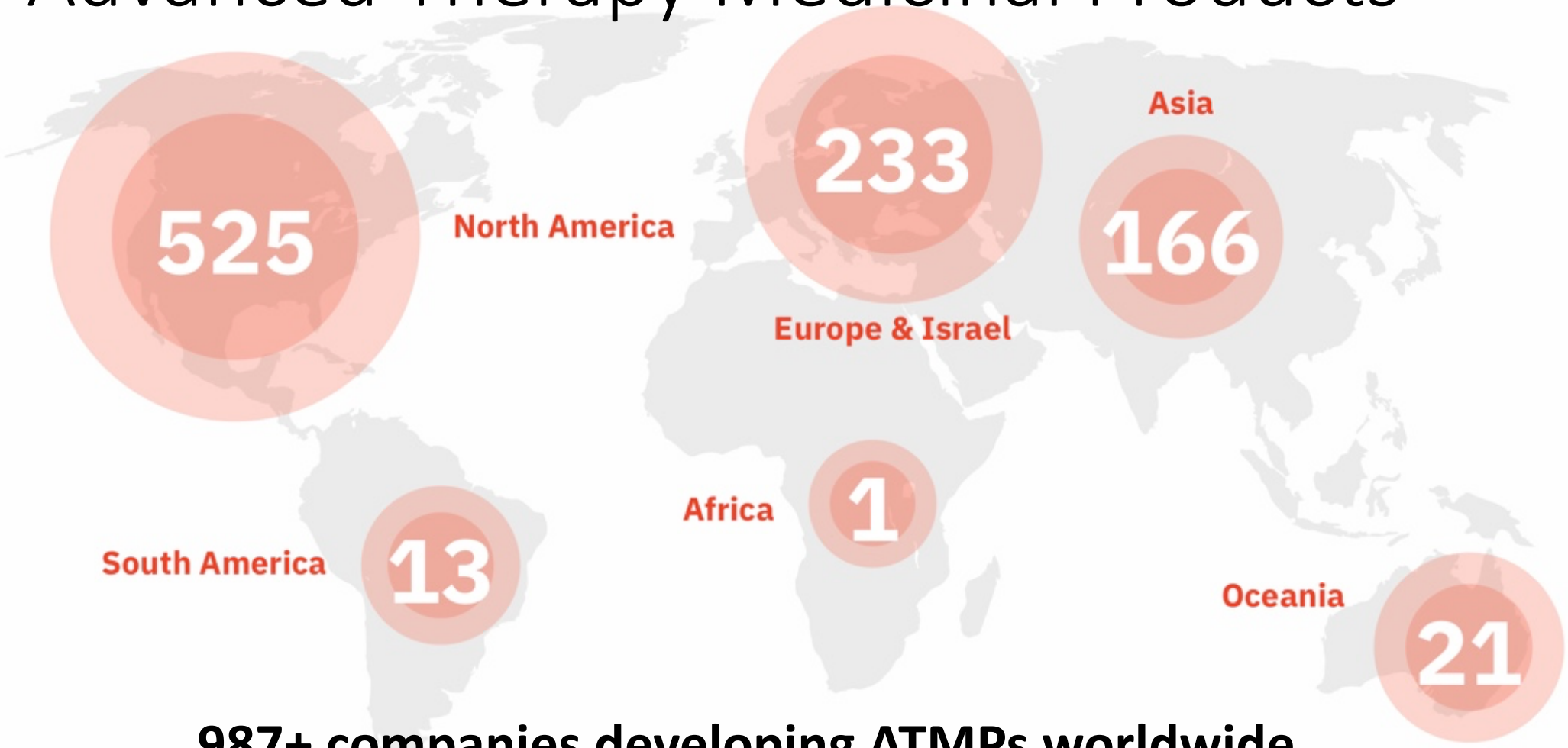
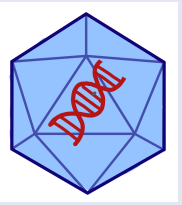
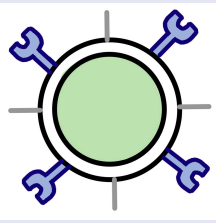
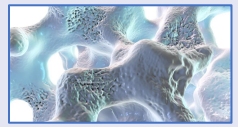
Advanced Therapy Medicinal Products









987+ companies developing ATMPs worldwide

1,066 clinical trials underway (thru 2019)

Source: Alliance of Regenerative Medicine

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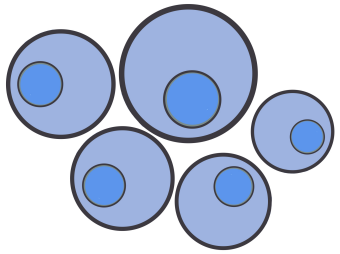
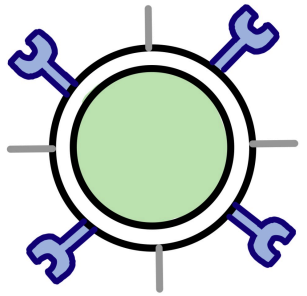
Advanced Therapy Medicinal Products



Cell-based therapies are **autologous, allogeneic, or xenogeneic** cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics *ex vivo* to be administered to humans and applicable to the prevention, cure, diagnosis, or mitigation of disease or injuries.



Autologous: cells derived from the same individual (same donor and recipient)

Allogeneic: cells derived from a donor intended for use in another person (different donor and recipient)

Xenogeneic: cells derived from an animal source

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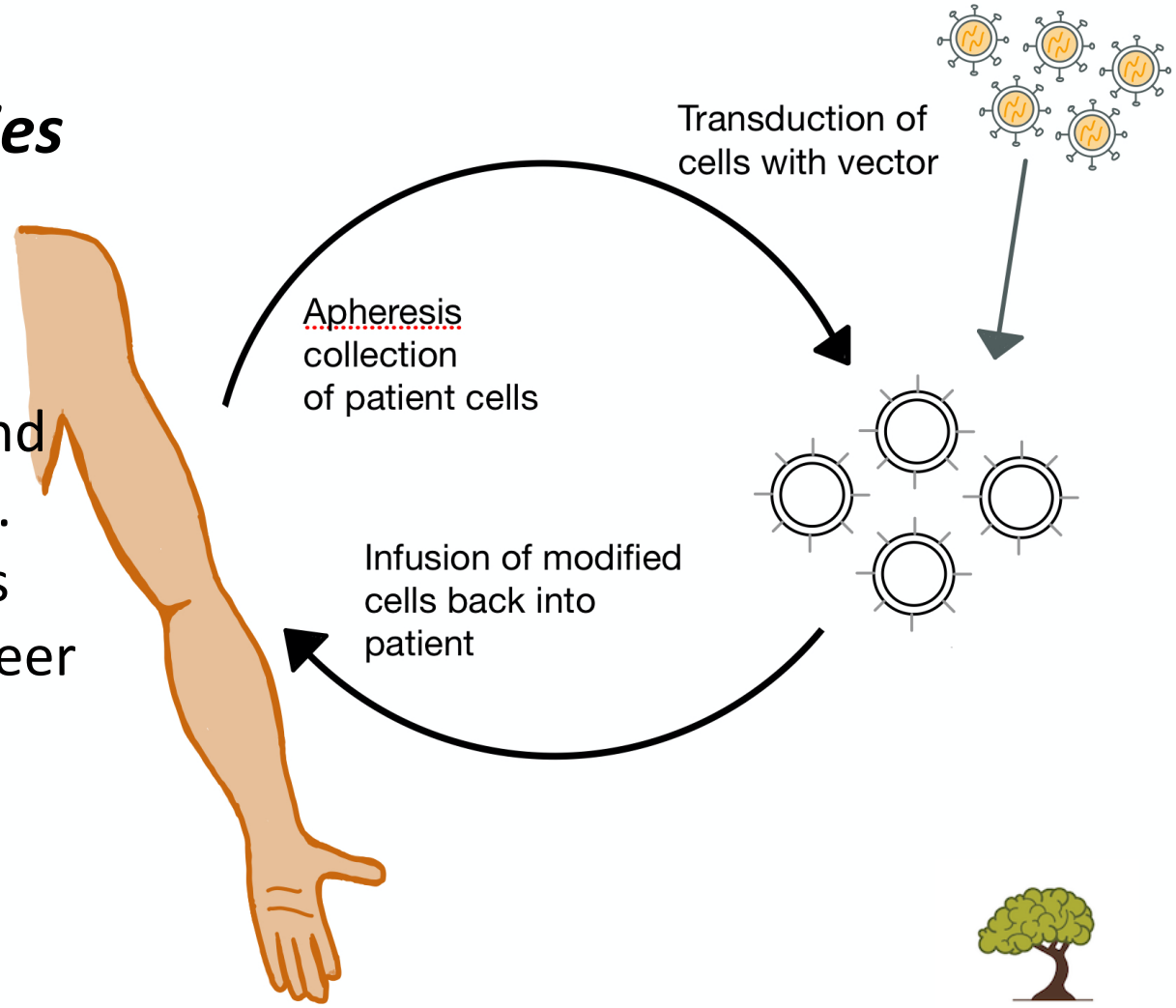
Engineered Cell-Based Therapies

Ex-vivo Autologous Cell-Based Therapies

- T cells obtained from patient by apheresis
- Ex vivo transduction with a vector carrying gene to equip the new T cell receptor
- Cells are then expanded to target a dose and then re-infused back into the same patient.
- Choose an optimal target for each patient's tumor and distinct types of T cells to engineer to further personalize to the individual.



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Engineered Cell-Based Therapies

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

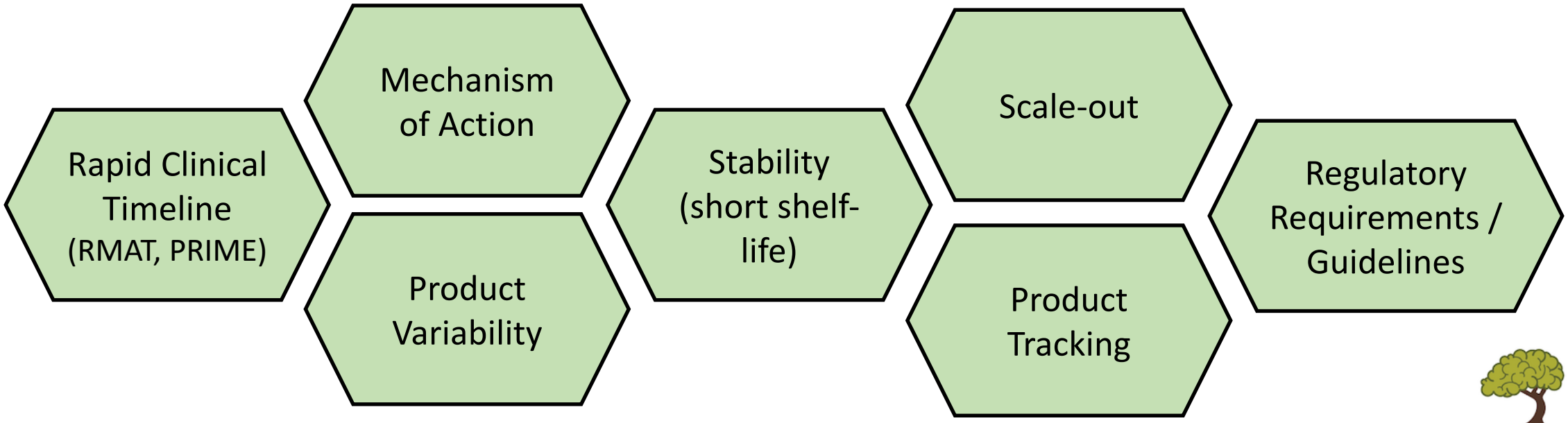
Yescarta (axicabtagene ciloleucel) – Kite Pharma (Gilead)
Approved in 2017 by FDA
Treatment for adult patients with relapsed, refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma

Zynteglo (Autologous CD34+ cells encoding $B^{A\text{-}T87Q}$-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)

Engineered Cell-Based Therapies

Unique Challenges for Development of Cell Therapies

"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 at US FDA



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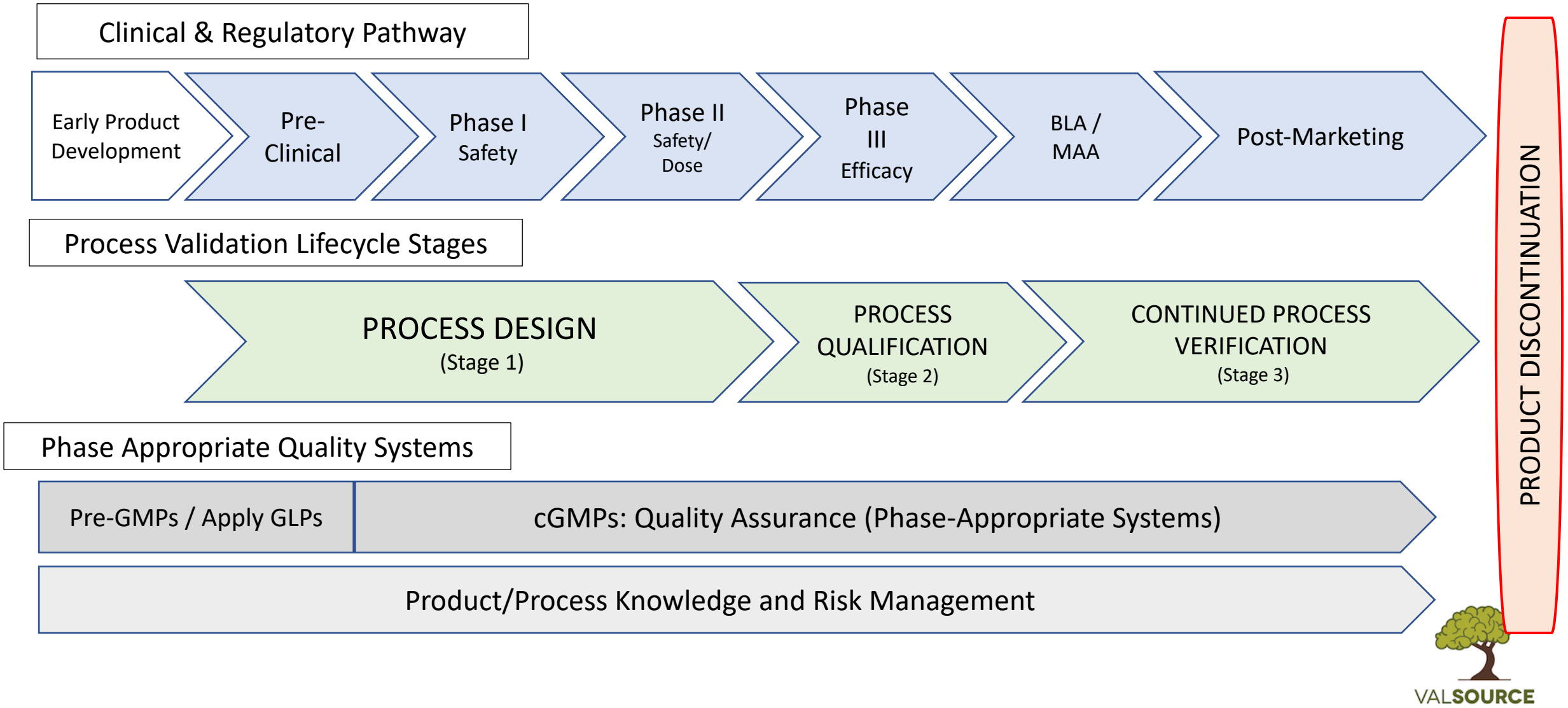
The Product & Process Lifecycle



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Product & Process Lifecycle Approach

Stage #1: Process Design
Process and product knowledge are explored to establish a control strategy for manufacture. The product control strategy is defined.

Stage #2: Process Qualification
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.

Stage #3: Continued Process Verification
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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Product & Process Lifecycle Approach

Benefits include…

- Organize important information for purposes of internal and regulatory communications
- Focus development, characterization and robustness studies.
- Understanding which process steps and systems are critical and the scope of subsequent qualification activities for commercialization.
- Understand Regulatory requirements (FDA, EMA, RoW).
- Manufacturing tech transfer to CMOs and support process changes.
- Clear understanding of raw materials impact on product quality.

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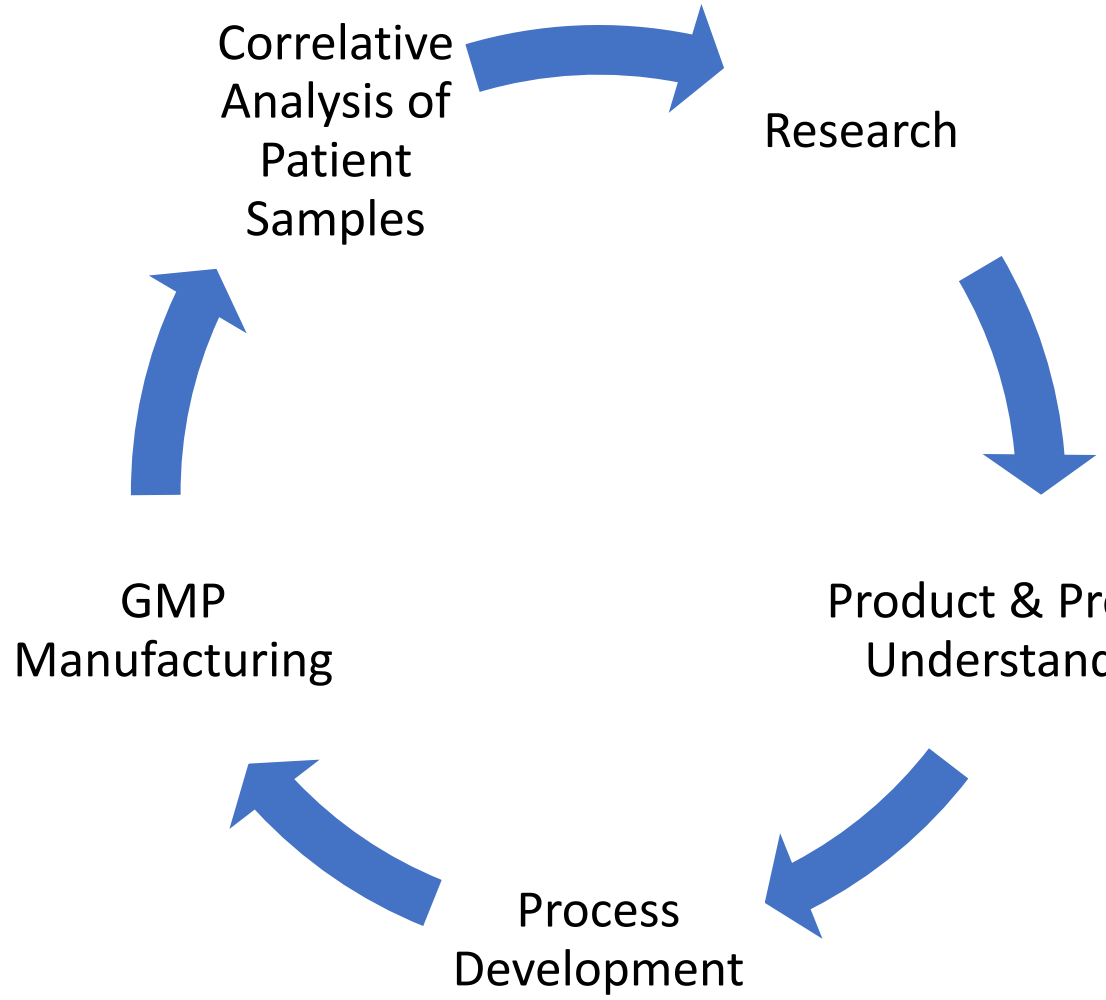
Product & Process Lifecycle Approach

LIFECYCLE APPROACH TO PRODUCT AND PROCESS UNDERSTANDING

- Utilize key information from each stage of product development to better inform CMC decisions
- Understand the desired characteristics of the product (e.g., phenotypic, functional)
- Link those characteristics to process parameters and enable a robust control strategy to deliver them consistently



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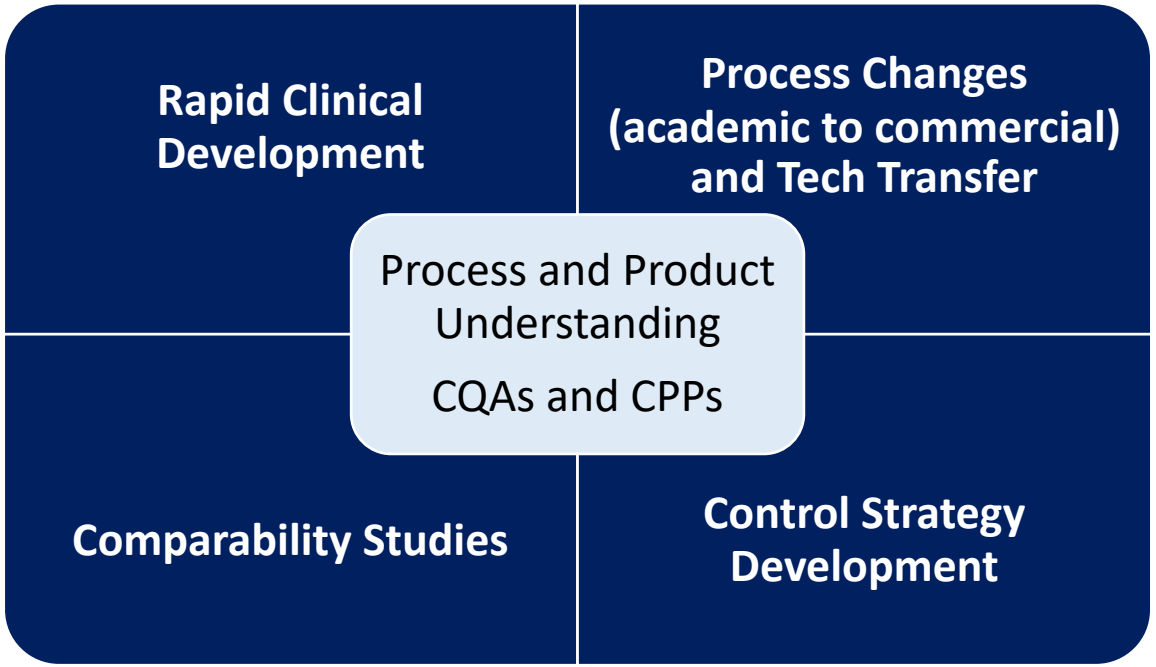
Product & Process Lifeycle Approach

KEY CHALLENGES & CONSIDERATIONS FOR CELL THERAPIES:

- Rapid clinical development and multiple process changes drive the requirement for enhanced process and product understanding
- Multi-functional teams required (Process and Analytical Development, Manufacturing, QA, Regulatory, Research, Clinical, Pre-clinical, etc…)



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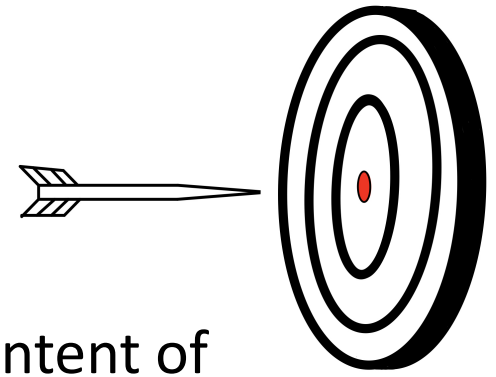
Target Product Profile (TPP)



- A strategic development tool that provides a statement of the overall intent of the drug development program, and gives information about the drug at a particular time in development [FDA Draft Guidance 2007]
- Used to facilitate a common vision across all disciplines in order to guide the development, conduct, and analysis of clinical trials by focusing on strategic product label claims and to maximize the efficiency of the development program.
- The TPP should be developed at the initiation of product development by a cross-functional team and changes as knowledge of the drug increases.
  - The TPP embodies the notion of **“beginning with the goal in mind”**

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Target Product Profile (TPP)

Examples of the various aspects of a TPP and considerations for Cell Therapies

Product Aspect	General considerations
Therapeutic Indication	Identify the therapeutic indication (e.g., genetic blood disorder, neurodegenerative, cancer)
Target Patient Population	Determine the patient population, population size, and clinical trial design
Product Classification	Establish type of regenerative therapy (in-vivo viral vector, ex vivo transduced cells) and consider potential GMO regulatory implications
Cell Source	Identify the source of the cells that constitute the final product (e.g., leukapheresis, tissue biopsy)
Dosage Form	Form of the dose that the patient receives (e.g., liquid suspension, frozen, cryo-frozen)
Mode of Action	Identify the biochemical interaction through which the drug produces a pharmacological effect
Route of Administration	How the patient receives the product (e.g., IV infusion, injectable, implantation)
Dosage and Regimen	Measure of the product received by the patient, (e,g, mass, volume) and frequency of dosage (e.g., single administration, weekly, monthly) – dose escalation studies
Market Scale & Demographics	Understand the scale of the market and what geographical market or patient population will be targeted

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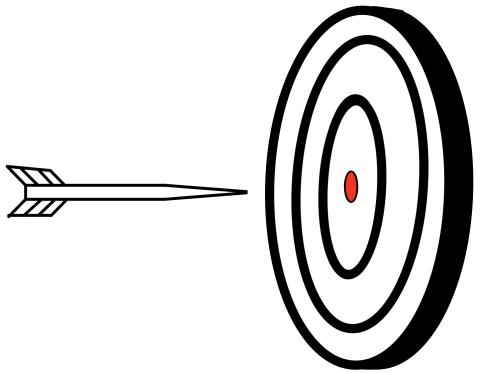
Quality Target Product Profile (QTPP)



- A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy. [ICH Q8(R2)]
- Tactical implementation of the strategic vision outlined in the TPP. Modified throughout the product lifecycle as knowledge of the drug increases.

- The **QTPP** describes the design criteria for the product.
  "…the protection of the patient by managing the risk to quality should be considered of prime importance." [ICH Q9]

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Quality Target Product Profile (QTPP)

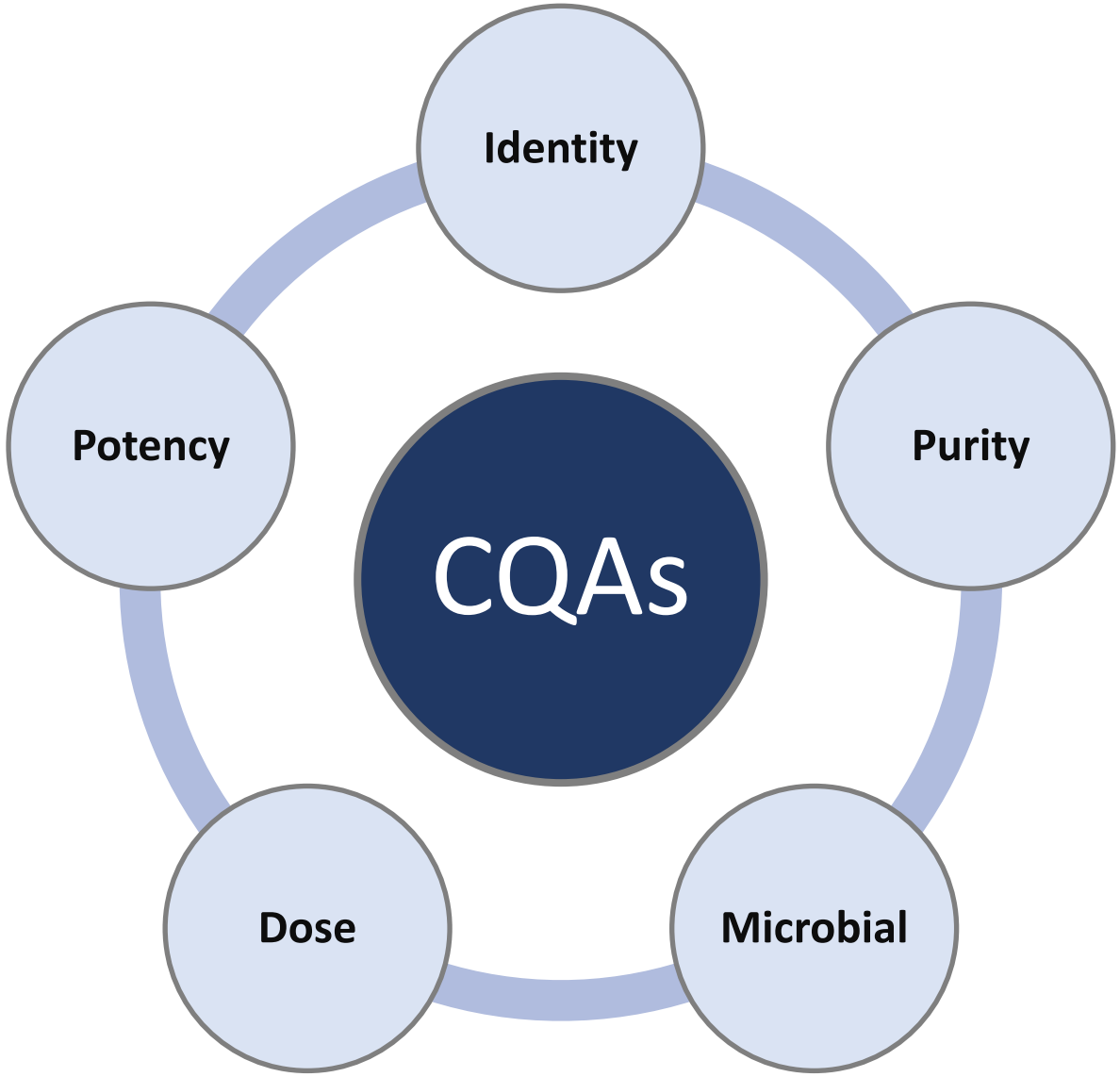
Elements of the **QTPP** and corresponding general considerations for ATMPs

Aspect	General considerations
Dosage Form / Volume per Dose	Liquid suspension or tissue equivalent (i.e., delivered as mL product/kg patient weight).
Stability and storage conditions	Description of the product storage conditions (e.g., temperature, equipment type) and maximum duration (on-going stability studies). Many cell therapy products are cryopreserved.
Container Closure	Common primary containers for gene therapies may include vial, bag, sterile sealed container
Product attributes	Attributes related to the safety, efficacy, and quality of the product. These attributes are further assessed for level of criticality (determination of CQAs)
Safety	Microbial controls and testing based on the nature of the product (i.e., cell therapy products must be sterile for purposes of infusion)
Identity	Use of an analytical test to determine the chemical and biochemical identity of a material. (i.e., phenotype, genotype, gene expression)
Dose / Content	Measure of the active product received by the patient, (i.e., viable cells or viable transduced cells)
Purity / Impurities	Tests to assess the purity of the product, considering the product (e.g., live cells, dead cells)

Critical Quality Attributes (CQA)

A **CQA** is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product **quality**.

What are the **CQAs** for a Cell Therapy Product???



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Critical Quality Attributes (CQA)

Determination of the Criticality of a Product Attribute – Severity x Uncertainty

Assess the severity of harm and impact to patient of each attribute

Impact Assessment	Patient Safety / Immunogenecity	Efficacy / Potency
HIGH	Life threatening or irreversible adverse event	Significant potential to change the risk/benefit profile of the product
MEDIUM	Adverse event that can be managed by clinical treatment	Small potential for patient impact that does not change the overall risk/benefit profile for the product.
LOW	No patient harm	Marginal to no patient impact

Determine the current level of product knowledge for assigning criticality of each attribute

Uncertainty Assessment	Current level of product knowledge and clinical experience (uncertainty?)
HIGH	Limited scientific understanding of the attribute; limited in-house data and little to no clinical experience
MEDIUM	An understanding of the attribute based on scientific rationale with some in-house data available.
LOW	Extensive scientific literature and/or in-house data is available to clearly define the relation of the attribute to patient safety and efficiacy.

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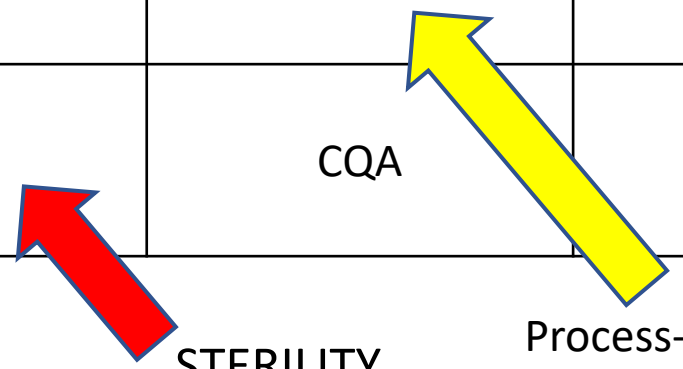
Critical Quality Attributes for ATMPs

Classification of product attributes using Impact x Uncertainty Matrix.

Impact (severity) and Uncertainty (level of product knowledge) are used to classify the criticality of the product attribute.

- CQA
- Potential CQA
- Non-CQA

Impact / Severity	Uncertainty		
	Low	**Medium**	**High**
Low	Non-CQA	Non-CQA	CQA
Medium	Potential CQA	Potential CQA	Potential CQA
High	CQA	CQA	CQA



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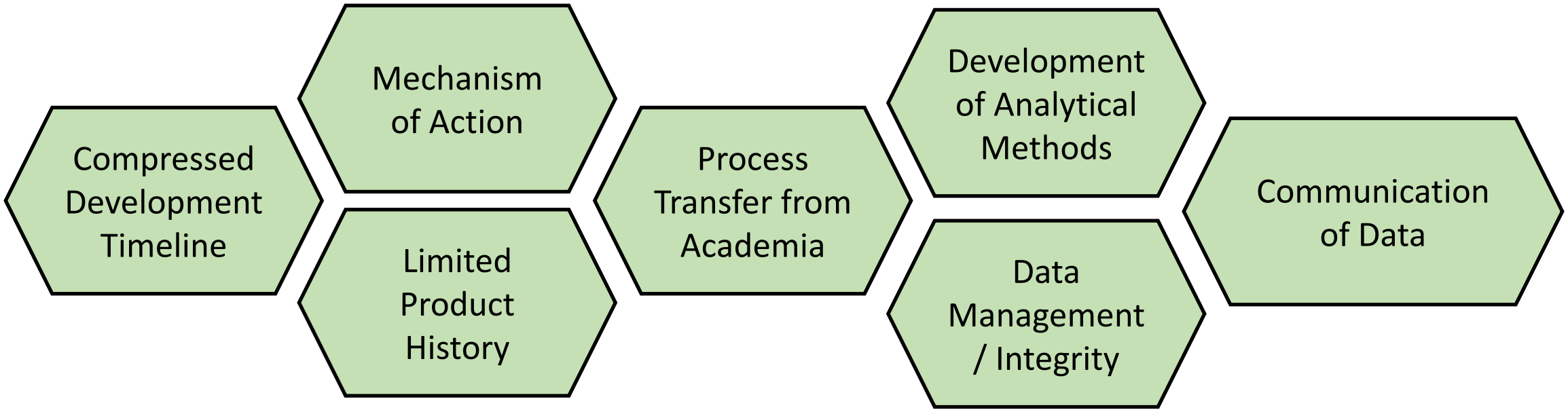
Critical Quality Attributes for Cell Therapies

Unique Challenges in Developing Product Profiles & CQAs



Rapidly increasing Product Knowledge → communication of process + analytical + clinical + translational data is so important!

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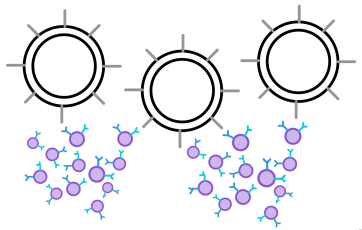
Critical Quality Attributes (CQA) for ATMPs

Examples of Product Attributes that may be Critical for a Cell Therapy Product

ATTRIBUTE	DESCRIPTION
Dose/Strength	Based on number of transduced target cells (minimum percent transduction of cells)
Identity	Ensure the patient receives the correct drug product. Should include an assay to detect the presence of the intended genetic modification and an assay specific for the cell population
Appearance	Color, opalescence, visible foreign particulates (general safety concern for parenterals)
Potency (functional activity)	Activity of cell product based on cytotoxicity (target cell killing), secretion of cytokines / IFN-gamma (matrix of assays may be applied)
Cell viability (dead cells)	Low viability may be less efficacious, high number of dead cells may impact patient safety
Vector copy number (VCN)	High VCN has potential for oncogenesis (patient safety concern)
Replication competent retrovirus	Theoretical risk to patient safety due to replication of retroviruses
Product-related impurities	Other cell types, non-transduced cells, phenotypes, residual virus
Process-related impurities	Additives, selection agents, media components
Microbiological attributes (Safety)	Sterility, endotoxins, mycoplasma, adventitious viruses

Establishment of the Process Control Strategy

Process Map Example for an Autologous Ex-vivo Genetically Modified Cell Therapy

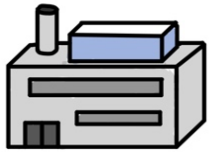


Patient apheresis collection (@clinic)

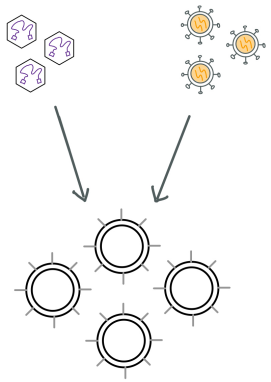
Ship to Site of Manufacture

Apheresis Wash and Cryopreservation

T-cell Selection and Stimulation

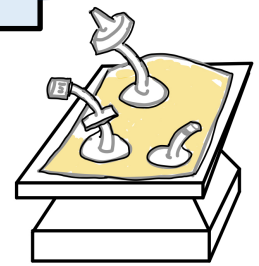


Gene Delivery by Viral Vector Transduction

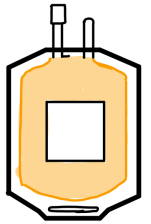


Viral Vector (Transducing) Production

T-cell Expansion in Bioreactor



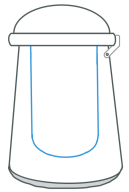
Cell Isolation and Formulation

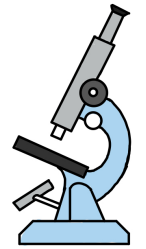


Drug Product Cryopreservation

Ship to Clinic/Hospital

Product administration to patient (@clinic)





QC Release Testing

1 Patient = 1 MFG Batch

"Vein-to-Vein" Process

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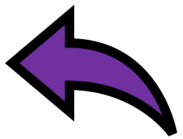
Establishment of the Process Control Strategy

List all **Process Variables** for each of the unit operations identified in the **Process Map.**

Categorize process variables as either:

Input variables: operational parameters that can be controlled or modified directly.

- Identified as "**Process parameters"**



Output variables: dependent variables that are a result of the process.

- Identified as **"Product quality attributes"** or **"Process performance attributes"**

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Establishment of the Process Control Strategy

Assess the criticality of each of the Process Parameters

Critical or Not Critical???

- Define the link between the Process Parameter and the CQAs
- Ask how does the variability of the Process Parameter when operated within a range has the potential to impact a CQA?

IMPACT		CRITERIA
High potential		A small to moderate change in this process parameter has a significant impact on one or more CQAs
Moderate or unknown potential		A large change, or a small change in combination with other factors, could have a significant impact on a one or more CQAs
Low or negligible potential		The parameter has no impact any of the CQAs

Table from PDA Technical Report 81.

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Establishment of the Process Control Strategy

Parameter Criticality Assessment for an Autologous Cell Therapy (Example)

Unit Operation – Cryopreservation of Cell Product [Initial Assessment]								
Parameter [Units]	CQA1 Gene Expression	CQA2 Potency	CQA3 Cell viability	CQA4 T cell composition	CQA5 Impurities (product-related)	CQA6 Impurities (process-related)	Criticality Classification	Rationale
Cell Concentration [x10^9 viable cells/mL]							pCPP	Perform Process Character-ization Studies and Determine Proven Acceptable range
Cryoprotectant Concentration [%]							CPP	
Exposure to Cryoprotectant [minutes]							CPP	
Rate of Freeze [°C]							pCPP	

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Establishment of the Process Control Strategy

Parameter Criticality Assessment for an Autologous Cell Therapy (Example)

Unit Operation – Cryopreservation of Cell Product [Final Assessment]								
Parameter [Units]	CQA1 Gene Expression	CQA2 Potency	CQA3 Cell viability	CQA4 T cell composition	CQA5 Impurities (product-related)	CQA6 Impurities (process-related)	Criticality Classification	Rationale
Cell Concentration [x10^9 viable cells/mL]							Non-CPP	Process Studies Support Parameter Classification and PARs for Control Strategy
Cryoprotectant Concentration [%]							CPP	
Exposure to Cryoprotectant [minutes]							CPP	
Rate of Freeze [°C]							Non-CPP	

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Establishment of the Process Control Strategy

Process Capability Assessment

- Evaluate the ability to control and detect out-of-range process parameters.
- Determine how well the parameter is controlled – Focus development/optimization

Occurrence (Likelihood) Scoring

Rating (Score)		CRITERIA
Frequently	10	Parameter exceeding the acceptable range is likely to happen frequently. Manual activities with high error rates.
Fairly frequently	7	Parameter exceeding the range fairly frequently; manual activities with moderate error rates,
Fairly infrequently	4	Parameter exceeds range fairly infrequently; manual operations with low error rates
Infrequently	1	Parameter not likely to exceed range; Negligible error rates

Detection Scoring

Rating (Score)		CRITERIA
Impossible	10	Parameter out of range not detected prior to drug administration to patient
Moderate	7	Parameter out of range can be detected during batch release
Likely	4	Parameter out of range detected downstream / prior to final unit operation
Highly Certain	1	Parameter out of range detected at step where remediation is possible

SEVERITY x OCCURRENCE x DETECTION = Risk Priority Number

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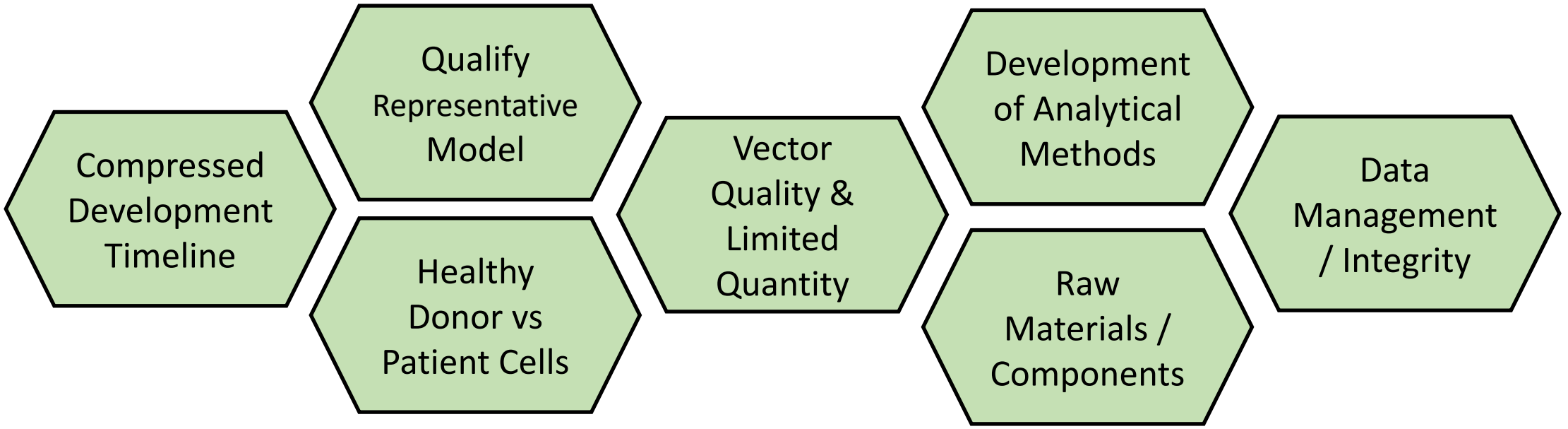
Establishment of the Process Control Strategy

Unique Challenges for Development of the Process Control Strategy



"Mature" Process Control Strategy for successful PPQ / Commercial

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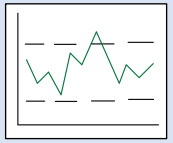
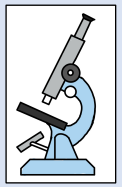
Elements of the Overall Control Strategy

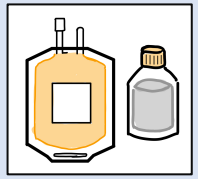
PROCESS PARAMETERS and CONTROLs

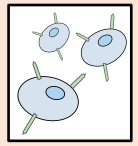


ANALYTICAL METHODS

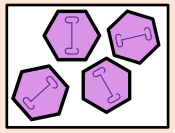


RAW MATERIALS





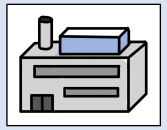
Product Knowledge



Target Product Profile
Quality Target Product Profile
Critical Quality Attributes

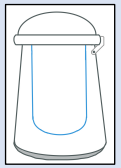
THE CONTROL STRATEGY

FACILITY & EQUIPMENT

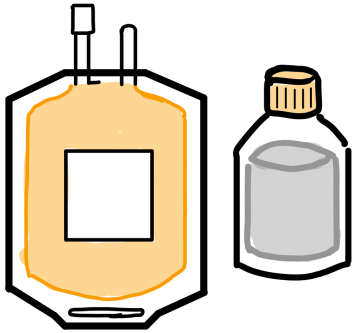


CONTAMINATION CONTROLS

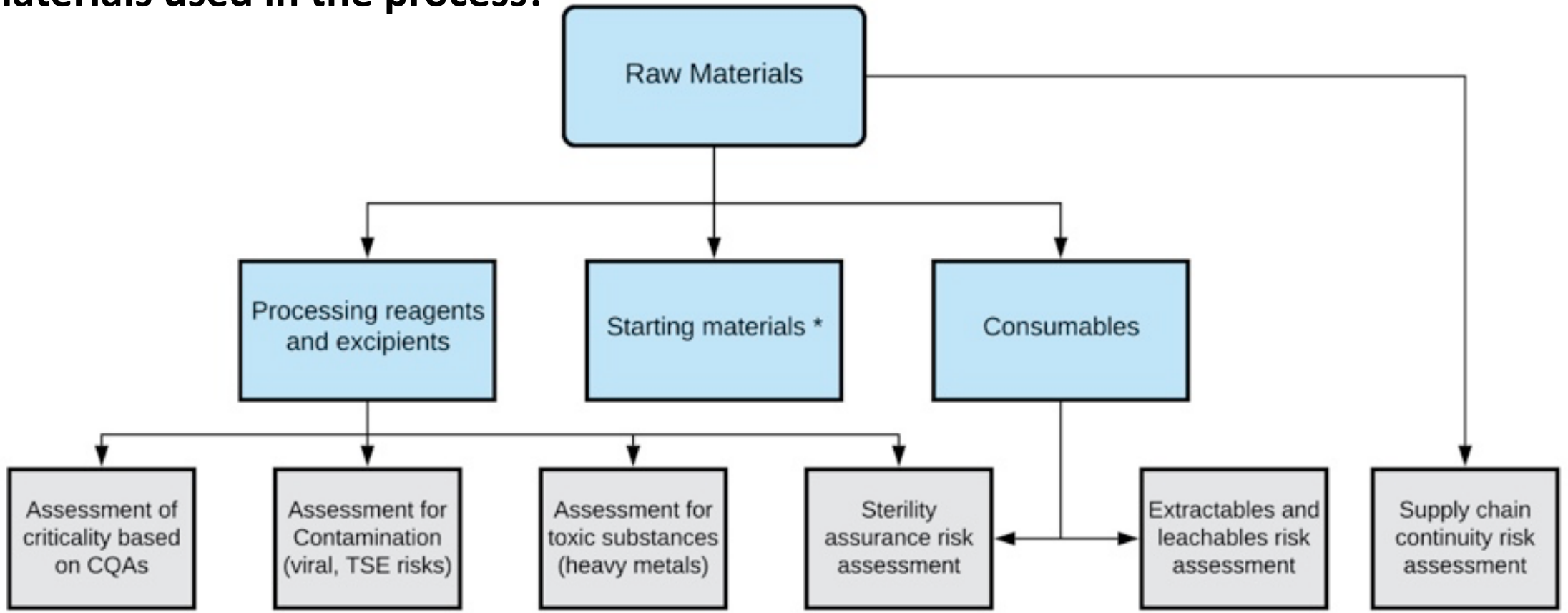
TRANSPORT/ SHIPPING



Raw Materials Control Strategy



Risk assessment is key to develop robust control and testing of raw materials used in the process!



Reference: PDA TR 81

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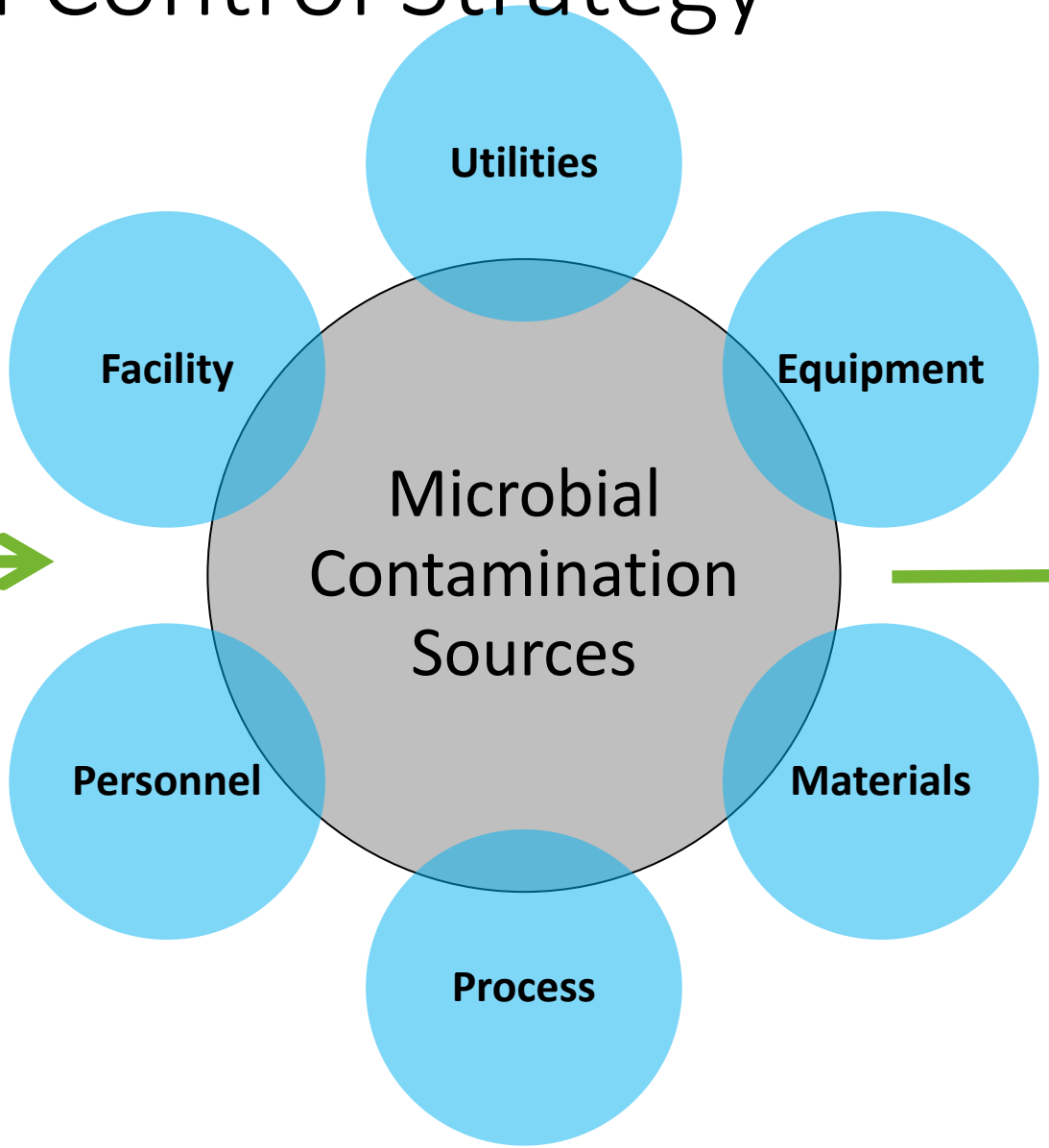
Contamination Control Strategy

Quality Risk Management and Knowledge Management



Product Quality

HACCP

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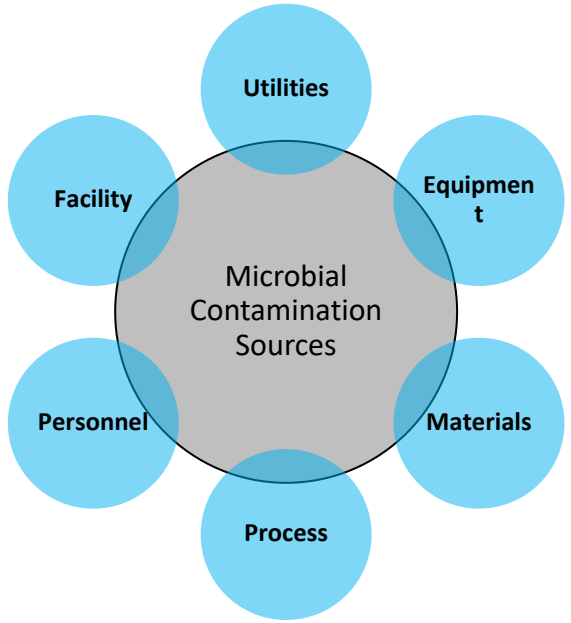
Contamination Control Strategy

Unique Challenges for Cell Therapy Products

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



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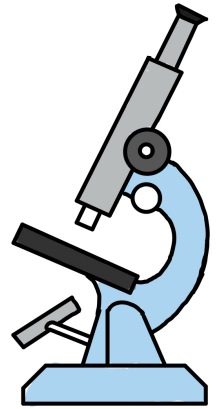
Analytical Methods Control Strategy



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

Analytical Development Challenges for an Autologous Cell Therapy

- 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

CQA	Analytical Test
Safety	Replication competent virus, vector copy number, adventitious agents
Identity	Cell type/phenotype (Flow cytometry)
Dose	Cell concentration, transduced cell numbers
Purity	Other cell sub-populations, residual host cell DNA, percentage of dead cells
Potency	Cytokine profile, bioactivity, cell killing

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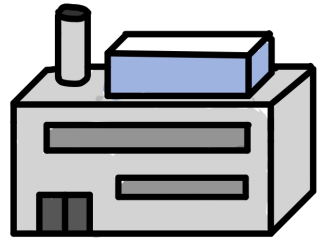
Facilities/Utilities/Equipment



Defining specifications and qualification strategy using risk-based approach

CQA

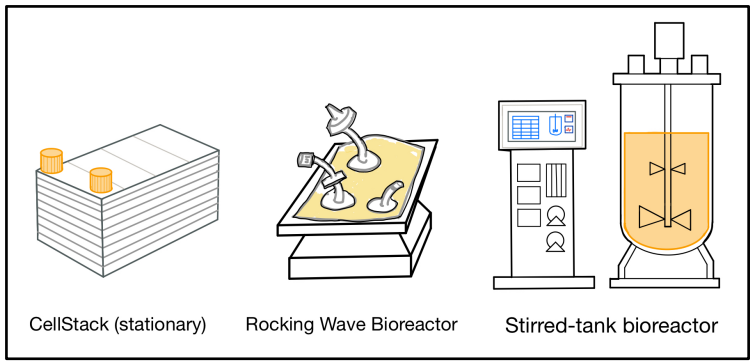
- Cell Viability

CPP

- Dissolved Oxygen

Critical Aspects

- Bioreactor Agitation Speed
- Air/O_2 Flow Rate



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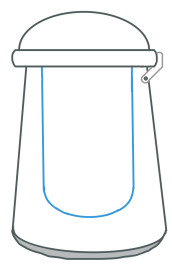
Product Shipping/Transport Control Strategy



Unique Challenges for Cell Therapy Products – Contamination Controls

Risk Assessment is crucial for developing a robust "Shipping Control Strategy"

- Vein to vein (for individualized autologous therapies)
- Maintain product quality throughout (ask what CQAs are potentially impacted?) – risk assess both apheresis and drug product transport
- Developing technologies:
  - Physical shipping conditions and monitoring devices
  - Product tracking: CoI / CoC

Get to know and better control your process and product!

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IN SUMMARY

A risk-based approach can be applied to the establishment of the Process Control Strategy as part of the overall Lifecycle Approach to Process Validation

This approach has many benefits including (though not limited to)…

- ORGANIZE the rapidly increasing product and process knowledge
- FOCUS on critical elements of product and process
- IDENTIFY what you do not know (uncertainty) and how to address
- COMMUNICATE new learnings across multiple disciplines
- DEFINE roles & responsibilities of business units
- READY organization ultimately for successful commercialization

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PDA
Parenteral Drug Association

pda.org/2020atmps

2020 PDA Advanced Therapy Medicinal Products Month Webinar Series

WHEN: 11:00 a.m. ET every Tuesday and Thursday in June

WHERE: From the convenience of your own computer or mobile device.

WHAT: A series of nine webinars featuring industry and regulatory experts. Each webinar includes ample opportunity for a live Q&A with the presenters.

COST: $200 for each individual webinar. Make the most of available discounts when you register as a team of 10 or more or if you register yourself for all nine webinars!

CONNECTING PEOPLE SCIENCE AND REGULATION®

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Additional Resources of Interest

PDA Parenteral Drug Association
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Recent articles on managing risk and uncertainty

- **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

- **How Military Thinking Can Improve Pharma Decision Making Under Stressful Conditions**
  https://www.bioprocessonline.com/doc/how-military-thinking-can-improve-pharma-decision-making-under-stressful-conditions-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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  - Contamination and Cross-Contamination Control
  - Regulatory Compliance
  - Cleanroom design
  - Audits, inspections, and responses
  - Compounding pharmacies