Potency Assurance Strategy - Bridging Theory and Practice

Matthias Heemskerk
CASSS

Galápagos

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We've all heard that in Cell Therapy,

~~the Process = the Product~~

the Process + Control strategy = the Product

&

Potency = Product of the Process + Control strategy

In cell therapy, you don't just test potency,
you need to build it into the process

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Potency Assurance Strategy

"A comprehensive approach to help ensure that every lot of a product will have the potency necessary to achieve the intended therapeutic effect" FDA

- The FDA's draft guidance, "Potency Assurance for Cellular and Gene Therapy Products," provides a comprehensive framework for developing a robust strategy to ensure the potency of advanced therapeutic products.
- Quality risk management approach and ICH terminology
- Science-based and risk-based framework for discussing potency
- It highlights the importance of potency as a Critical Quality Attribute (CQA)
- It advocates for integrating multiple measures, ranging from process design to validated potency assays, throughout the product lifecycle.

Potency Assurance Strategy

Aspect	Potency Assay Matrix	Potency Assurance Strategy
Definition	A set of assays designed to measure product potency	A comprehensive system to ensure each lot consistently achieves intended potency
Focus	Measurement of product's biological activity	Control and maintenance of potency across the lifecycle
Components	- Functional assays - Surrogates - Orthogonal methods - Validated MoA-linked endpoints	- Assay matrix - Critical Process Parameter (CPP)/Critical Material Attribute (CMA) control - Material quality - In-process controls - Manufacturing design - Risk mitigation
Timing	Built over development, validated by start of Phase 3	Begins preclinical, refined continuously
Goal	Enable product release and consistency testing	Ensure every lot is potent, not just tested as potent
Regulation	ICH Q14, ICH Q2, ICHQ6B, FDA potency guidance, EMA potency guidance	FDA draft guidance on Potency Assurance (2023), ICH Q8/Q9/Q10

In short,

A potency assurance strategy is a multifaceted approach that reduces risks to the potency of a product

through manufacturing process design,

manufacturing process control, material control, in-process testing, and potency lot release assays.

The goal of a potency assurance strategy is to ensure that every lot of a product released will have the specific ability or capacity to achieve the intended therapeutic effect.

Risk assessment and risk reduction

1. Identify what might go wrong during manufacturing to harm potency – assess likelihood and severity of the risks
2. If risk is high, reduce risk by improving the manufacturing process and/or the controls

Manufacturing process design

The manufacturing process should be designed to consistently produce a potent product

Control strategy

Potency release assays are just the final check – they are not the entire control strategy

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Start with understanding the potency-indicating characteristics of your product

- Define the Quality Target Product Profile (qTPP) and map (proposed) mechanism of action (MoA):

Product type	Clinical Intent (qTPP)	Key MoA Elements	Therapeutic Goal
Autologous CAR T-cells	Eliminate tumor cells in specific patient population	Antigen recognition, T-cell activation, target cell killing	Durable anti-tumor response
Stem cell derived β-cells	Restore glucose-responsive insulin production	Engraftment, glucose responsiveness, insulin secretion	Long term metabolic control

Start with understanding the potency-indicating characteristics of your product

- Identify (potential) Potency-indicating attributes, i.e. direct biological relevance to MoA.

Product type	(p)CQA	MoA relevance
Autologous CAR T-cells	Viability	Required for cell function
	CAR expression	Antigen recognition
	Cytokine release	T cell activation
	Cytolytic activity	Direct potency
	…	…
Stem cell derived β-cells	Viability	Required for cell function
	GLUT2 expression	Glucose responsiveness
	Insulin secretion	Direct potency
	…	…

Potency assay matrix

Map (p)CPPs and (p)CMAs across the process

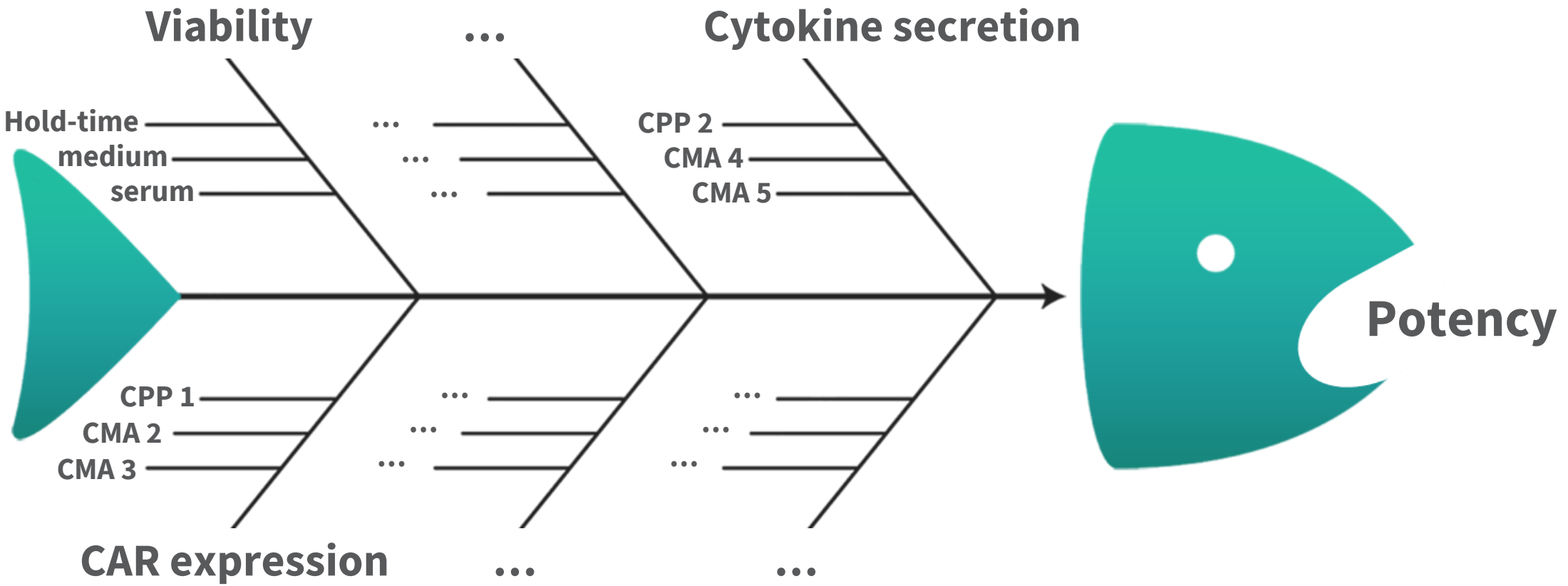
Product type	Process step	Example (p)CPPs	Example (p)CMAs	Linked (p)CQA(s)
Autologous CAR T-cells	Starting Material	Hold time	Apheresis cell quality	Viability
	Activation	Activation duration	Activation reagent	CAR expression, Cytokine release, Cytolytic activity
	Expansion	Culture duration, cell density	Activation reagent, Cytokines; media composition	Viability, CAR expression, Cytokine release, Cytolytic activity
	…	…	…	…
Stem cell derived β-cells	Stem Cell Expansion	Passage number; density	Media composition	Viability
	Differentiation	Stage timing, temperature	Growth factors, glucose	GLUT2 expression, insulin secretion
	Harvest	Dissociation method	Enzyme lot, buffer composition	Viability, GLUT2 expression
	…	…	…	…

Risk Assessment for Potency-Indicating (p)CQAs

Viability, CAR expression, Cytokine release, Cytolytic activity, …

Product type	(p)CQA	(p)CPP / (p)CMA	Rationale	Severity	Uncertainty	Score	Risk Category
Autologous CAR T-cells	Viability	Starting Material	Impacts cellular fitness	4	2	8	Critical
		Hold time	Impacts cellular fitness	2	3	6	Major
		Culture duration	Impacts cellular fitness	3	3	9	Critical
		Cytokines	Impacts cellular fitness	3	2	6	Major

Outcome



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Control strategy for potency-indicating (p)CQAs

Viability, CAR expression, Cytokine release, Cytolytic activity, …

(p)CPP / (p)CMA	Risk Category	Rationale	(Preliminary) Control strategy			
			Control of materials	Manufacturing process design	In-process testing	Lot characterization / release testing
Starting Material	Critical	Impacts cellular fitness				
Hold time	Major	Impacts cellular fitness				
Culture duration	Critical	Impacts cellular fitness				
Cytokines	Major	Impacts cellular fitness				
…	…	…				

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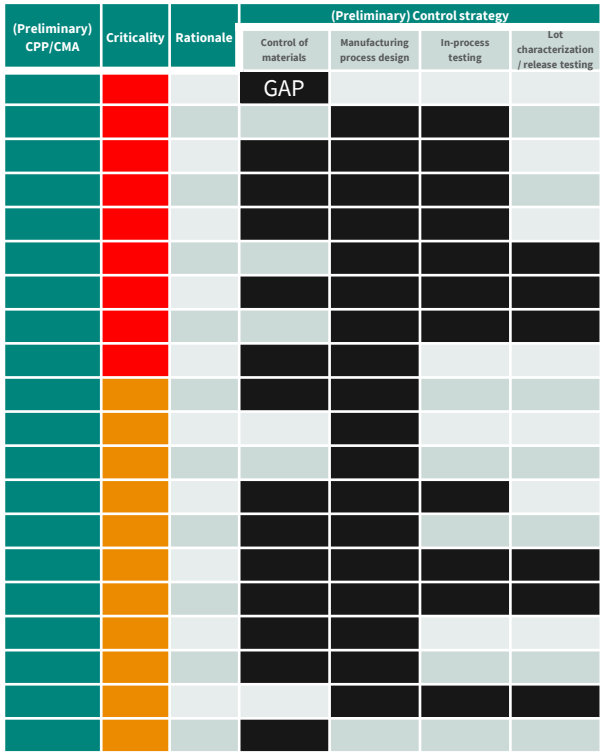
Evolution of the potency assurance strategy

Phase 1



Process design	Clinical-grade process established
Potency Assay Matrix	Fit-for-purpose assay(s)
CPP/CMA assesment	Preliminary identification
PARs	Start gathering data

Potency Assay Matrix

Product type	Assay	MoA Element Addressed	Phase 1	Phase 2	Phase 3
Autologous CAR T-cells	Viability testing	General cell function	Release	Release	Release
	CAR expression	Target recognition	Release	Release	Release
	Cytokine release	T-cell activation	Exploratory	Supportive	Supportive
	Cytolytic activity	Effector function	Exploratory	Phase-appropriate spec	Tightened spec
	…	…			

Fit-for-purpose

Qualified

Validated

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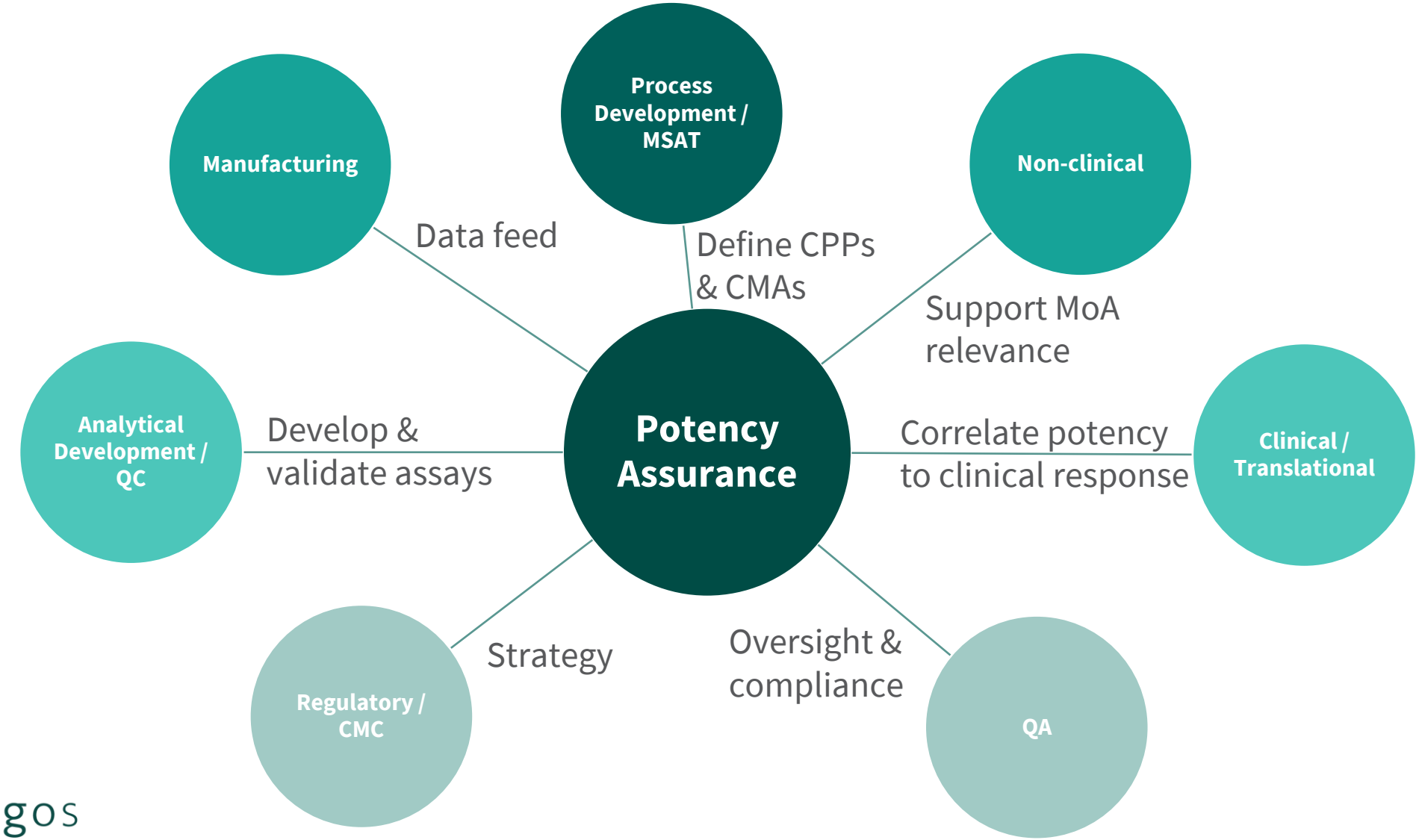
Recognizing and Overcoming Key Barriers

- Lack of product understanding (MoA, CQAs, CPPs, CMAs)
- No single assay reflects complex MoA
- High product variability
- Assay reproducibility issues

- Siloed teams
- Limited resources / assay dev timelines
- Rapid process evolution vs slow assay readiness

- New concept means little existing experience
- Unclear regulatory expectations for novel products
- Changing guidance / evolving standards
- Bridging early surrogate to validated assays

Potency Assurance Requires Cross-Functional Ownership and Coordination



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Start Early, Potency Assurance is a Lifecycle Strategy

This means now!

“Before beginning clinical investigations, you should identify initial potency-related CQAs for your product, and you should perform a risk assessment and develop a strategy for reducing risks to these CQAs”

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My Vision for the Future of Potency Assurance

Potency assured by design, not confirmed by test

Imagine a control strategy where:

- All CPPs are controlled through robust process design or adaptive manufacturing via Process Analytical Technology (PAT)
- All CMAs are assured through stringent incoming goods performance testing
- Biological fitness of apheresis starting material is confirmed through functional performance testing

Then, potency testing at release becomes a redundant check ?

Take home message

Potency Assurance

A lifecycle strategy

Multifaceted

Starts early

Risk-based

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