Using Elements of Quality by Design to Manage Variability

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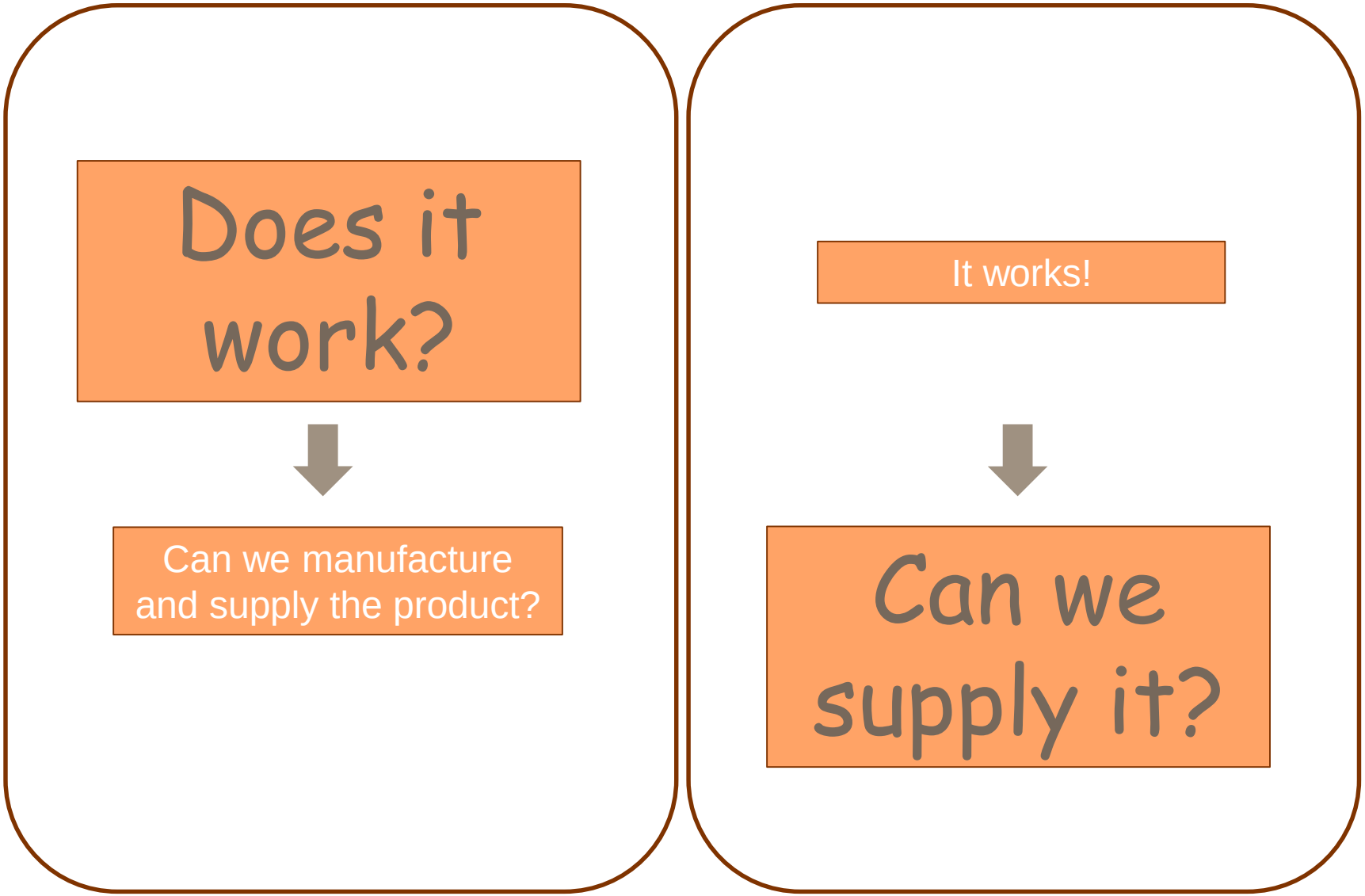
A New Paradigm



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Process Changes as a Source of Variability

- Situation
  - Process changes are inevitable in this space as technology is quickly evolving
  - Analytical method improvements are typically necessary throughout development
  - Change creates variability
  - Variability creates complexity in an already complex medicinal product
- Target
  - Implement process and analytical improvements that will provide greater process robustness and enhanced product quality while minimizing the impact of changes
- Proposal
  - Use elements of Quality by Design to take a science- and risk-based approach

Quality by Design: a systematic **approach to development** that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

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Proposed Science- and Risk-Based Approach to Managing Changes

- Define the Critical Quality Attributes of the Product

CQAs are:

-Product attributes with potential to impact safety or efficacy

- The foundation for managing product quality through all stages of the product lifecycle

CQAs are NOT:

- Analytical methods

-Specifications

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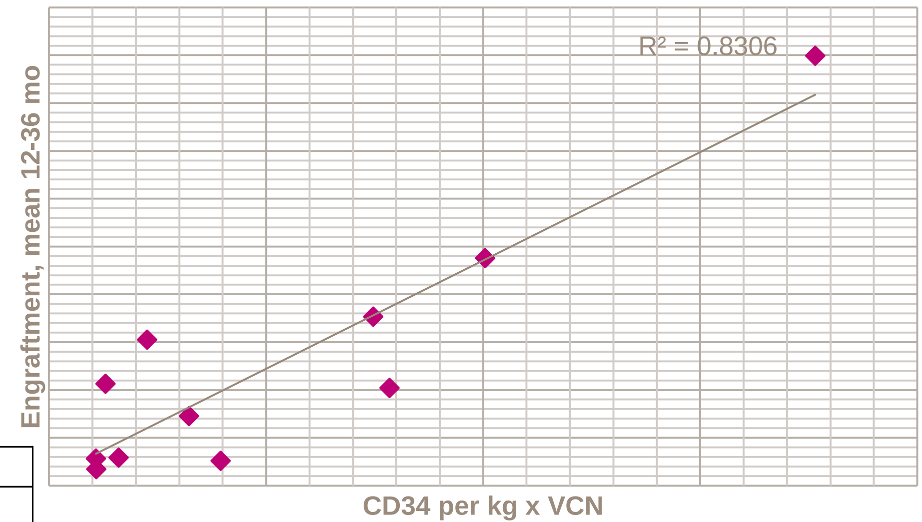
Proposed Science- and Risk-Based Approach to Managing Changes

- Ideally CQA definition is based on data



Product characterisation:	Clinical endpoints							

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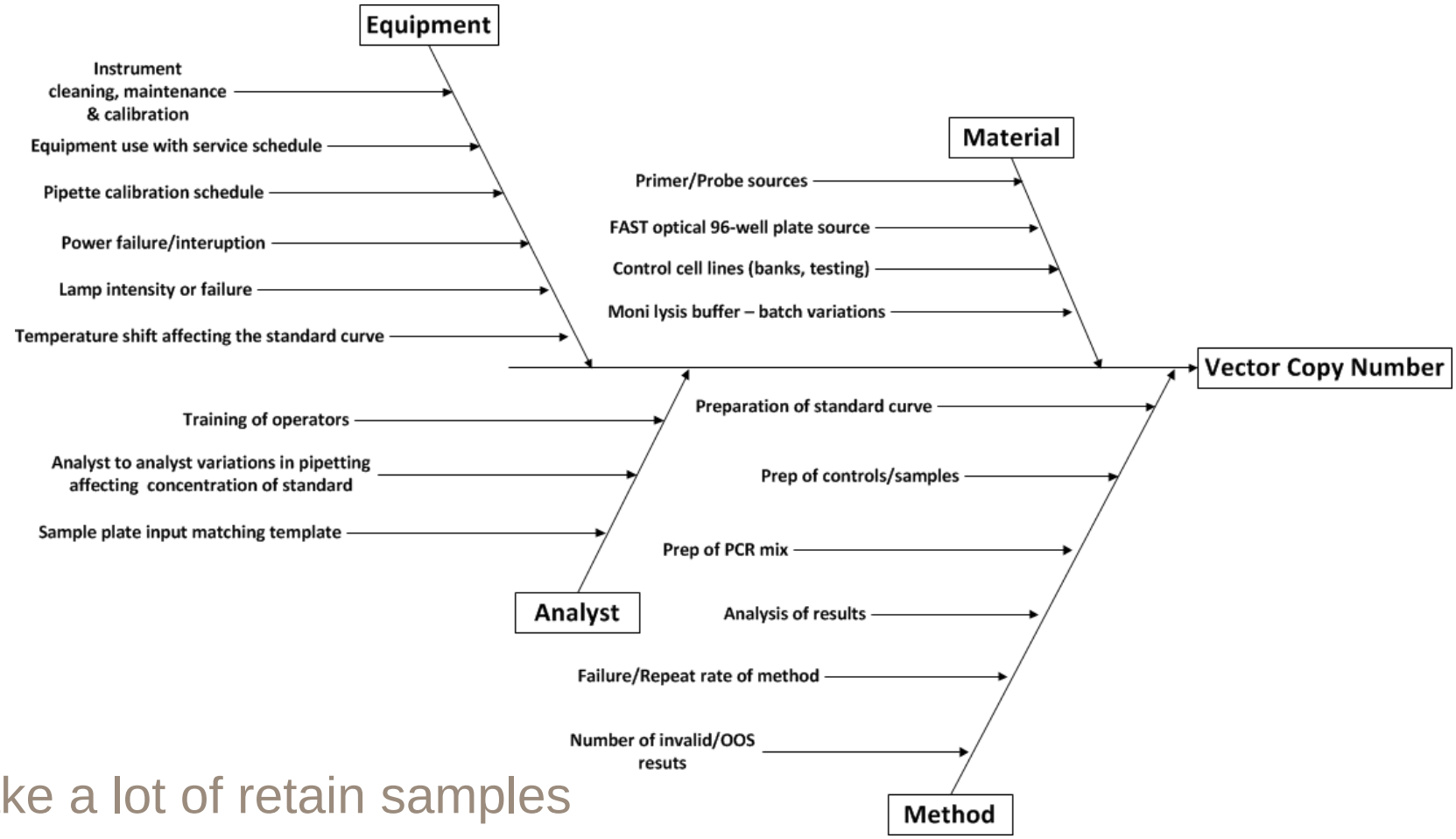
Ensure Consistency of Assay Performance

- Systematic approach based on science and risk management to define sources of variability and implement controls in analytical methods as early as possible in development



- Take a lot of retain samples

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Potential Process Changes

Manufacturing Process Component		Process v 1.0	Proposed Process v 2.0	Rationale for Change
Vector Process	Cell expansion	Adherent	Suspension	• Enable treatment of larger population of patients including some older patients • Improve supply chain robustness
Cell Process	Cell manipulation	Manual production	Implementation of automation	
	Final product formulation	Fresh product with 4 hour shelf life	Cryopreserved product.	

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Systematically Assess the Risks Associated with the Process Changes

Vector CQAs	Potential Impact
Infectious viral titer	H
Infectivity	H
Transgene sequence	L
Vector Integrity	L
HCP	H
HC DNA	H
Benzonase	L
Microbiological Control	L
mycoplasma	L
endotoxin	L
Adventitious virus	L
Plasmid DNA	M
RCL	L

Cell Product CQAs	Potential Impact of Vector Change	Potential Impact of automation	Potential Impact of cryopreservation
Percent CD34+	L	H	H
Vector copy number	H	H	M
CD34+ Stem Cell Potential	L	H	H
Enzyme Activity	H	H	M
Cell Viability (%)	L	M	H
Transduction efficiency	H	H	L
Endotoxin	L	L	L
Mycoplasma	L	L	L
Microbiological control	L	L	L
RCL	L	L	L
Adventitious virus	L	L	L
HCP	H	L	L
Plasmid DNA	M	L	L
Host Cell DNA	H	L	L
Residual cytokines	L	L	L

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Proposed Science- and Risk-Based Approach

- Use the risk assessment to
  - Drive development and generate data
  - Define the comparability strategy
  - Determine the required product characterization
  - Document rationale