Design of a Process Qualification and Continued Process Verification Program within an Enhanced Development Framework

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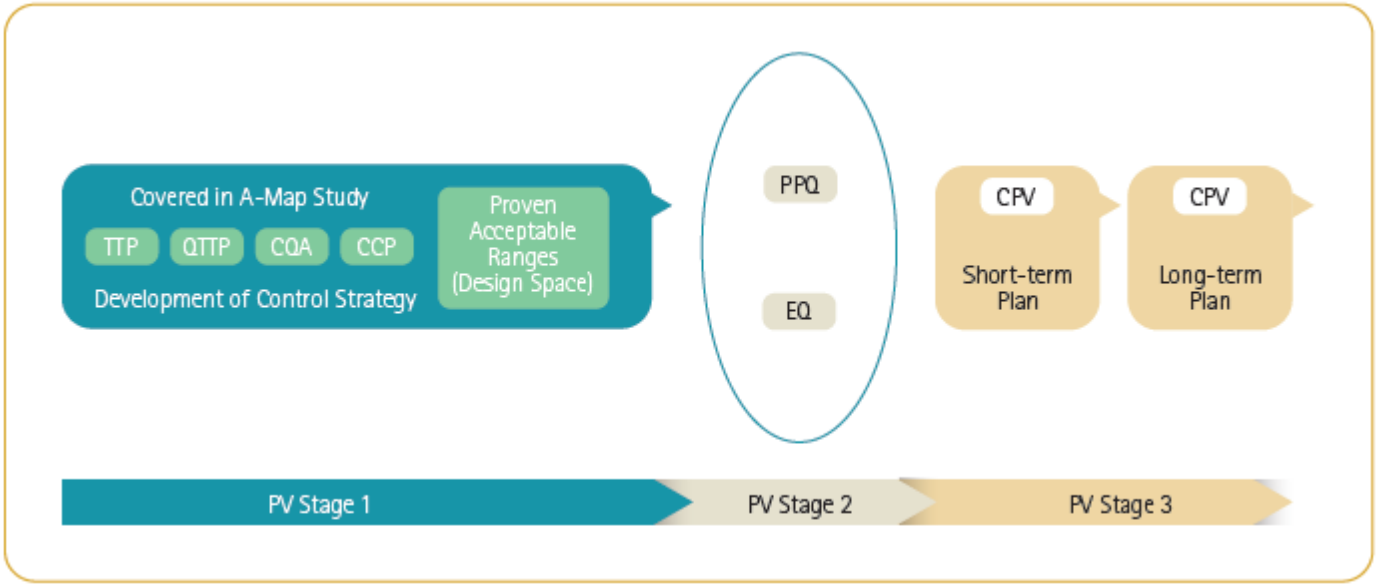
Eli Lilly & Co.

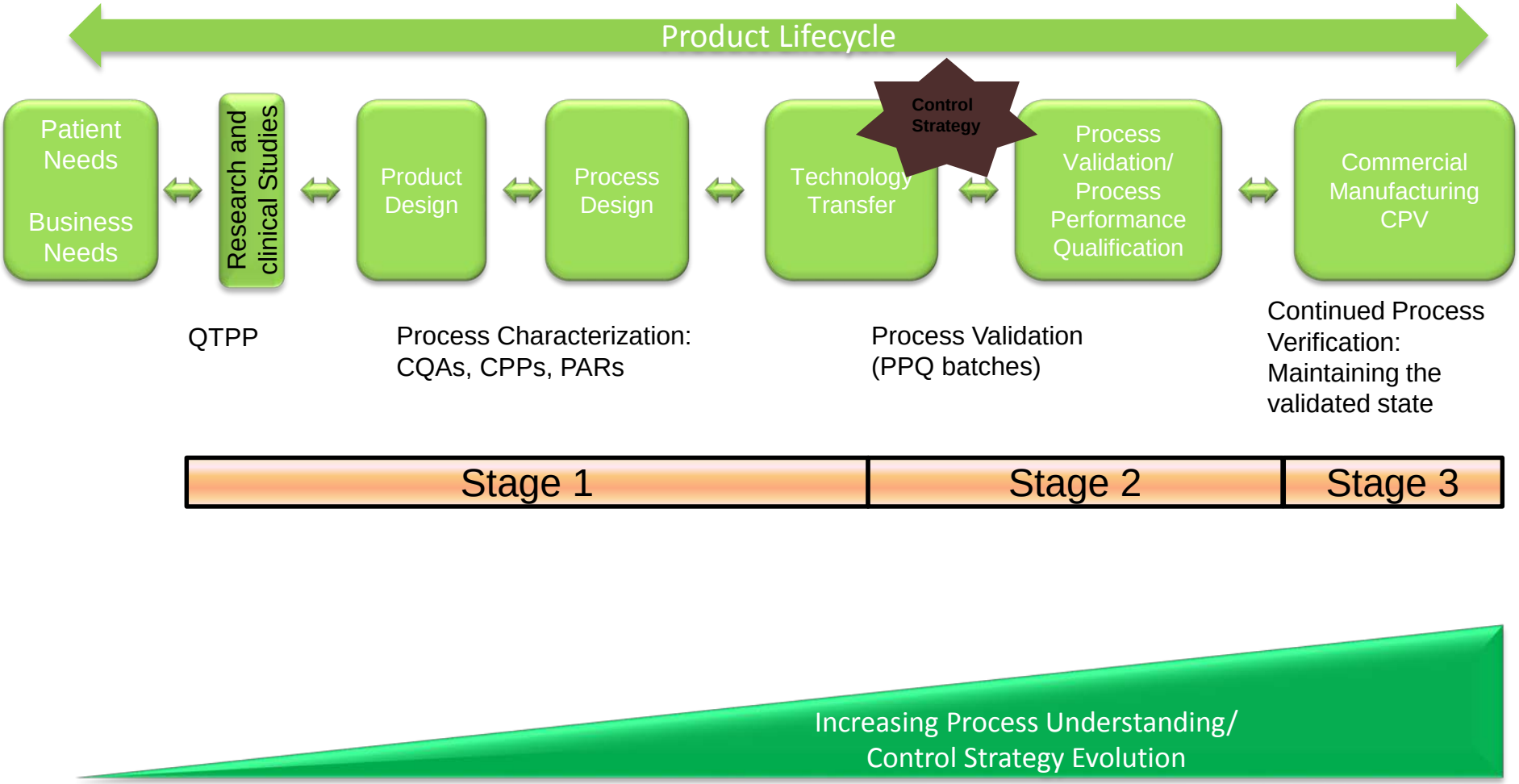
Overview

- Control Strategy Development: enhanced process understanding
- PPQ Approach
- Continuous verification/ monitoring
- Summary
- Questions

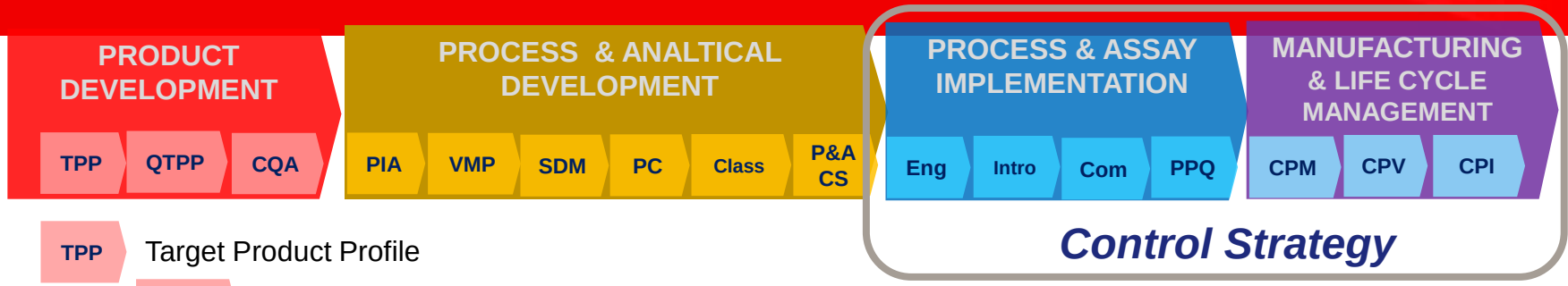


***BioPhorum Operations Group: Paper on Continuous Process Verification: An Industry Position Paper with Example Plan**

Stage 1: Control Strategy Evolution



QbD Work Flow Leading to Control Strategy and CPV



TPP Target Product Profile

QTPP Quality Target Product Profile (QTPP)

CQA Product Quality Attribute Assessment (Identification of CQAs) → CQAs

Process Parameter Impact Assessment — PIA VMP Process Development and Validation Master Planning

SDM Scale-down Model Development and Characterization

PC Process Characterization) → PARs/MARs

Class Parameter (Criticality) Classification → CPPs

Product-specific Control Strategy — PCS → IPCs

Engineering Design — Eng

Process Introduction — Intro

Equipment Commissioning/Validation — Com PPQ Process Performan Qualification

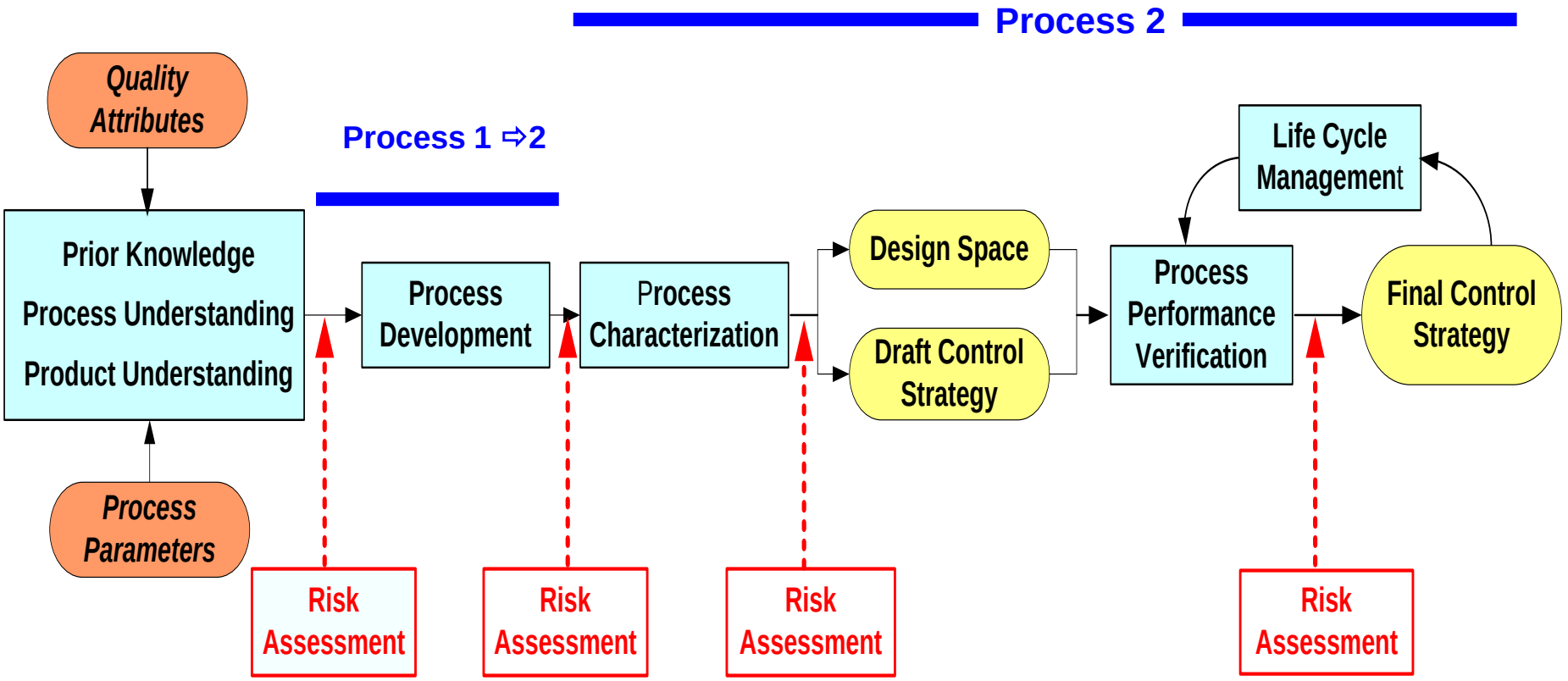
Continuous Process Monitoring — CPM

Continued Process Verification — CPV

Continuous Process Improvement — CPI

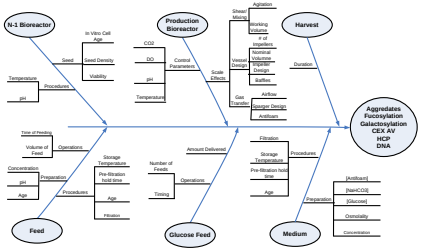
Science and Risk Based approach to develop comprehensive control strategy.....

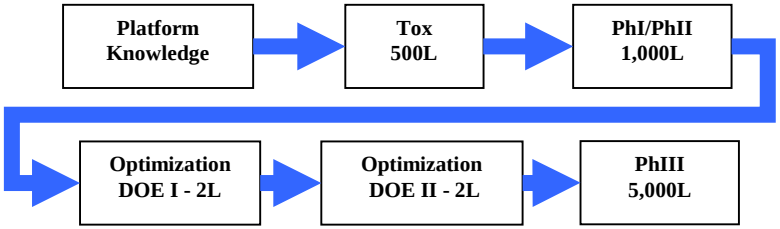
Process Development and Characterization Scheme

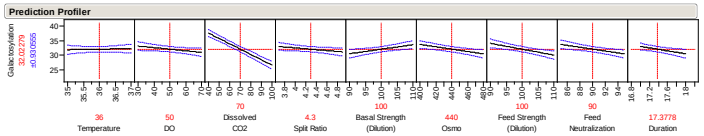


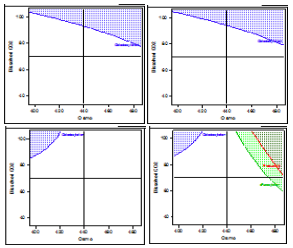
A-mAb Systematic Approach

1. Use of prior platform knowledge and process risk assessments to identify those steps that need additional experimentation
2. Demonstration that laboratory scale models are representative of the full-scale operations
3. DOE to determine parameter criticality
4. Linkage of process parameters to product Quality Attributes to create a Design Space
5. Use of statistical tools to model data
6. Final risk assessment and categorization of process parameters to develop control strategy

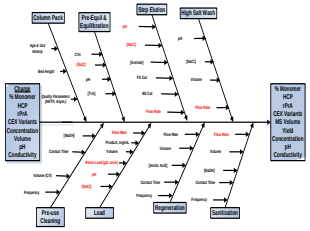


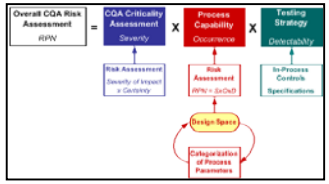


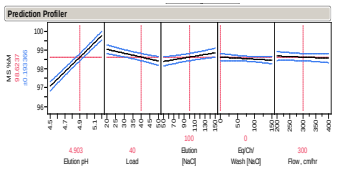


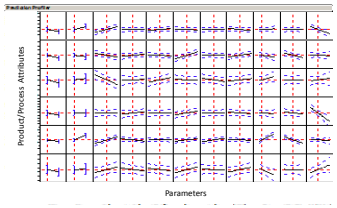


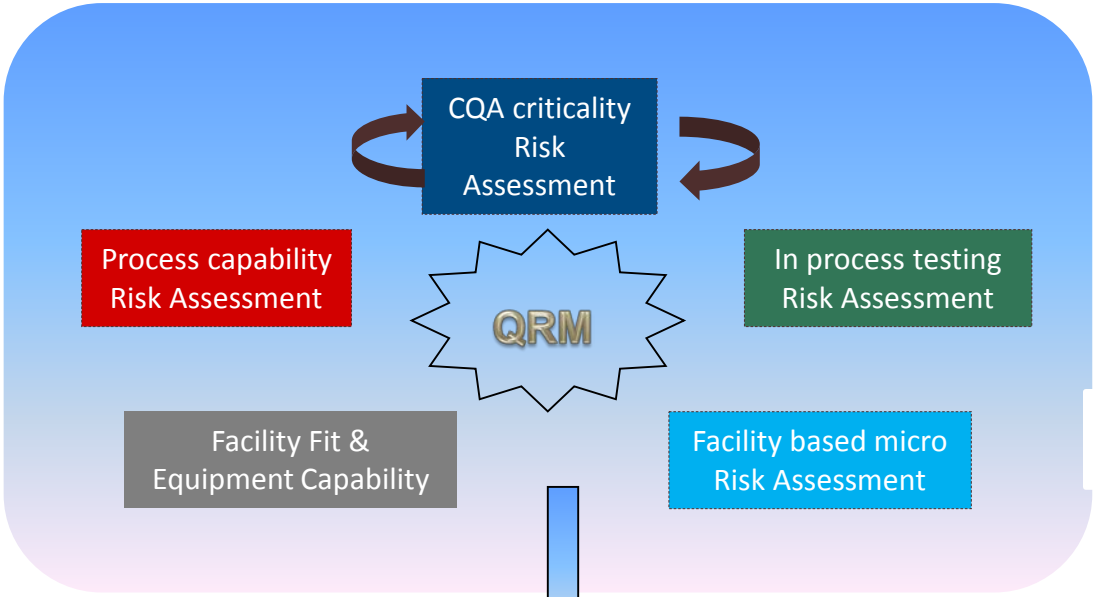
Holistic Process Control Strategy Forms the Basis for Process Validation

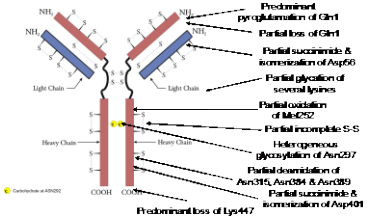


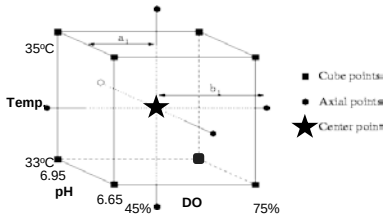


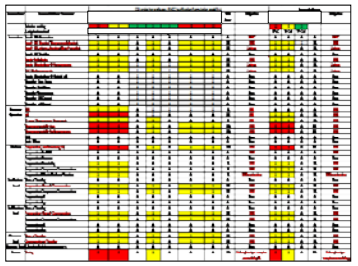












Process Control Strategy

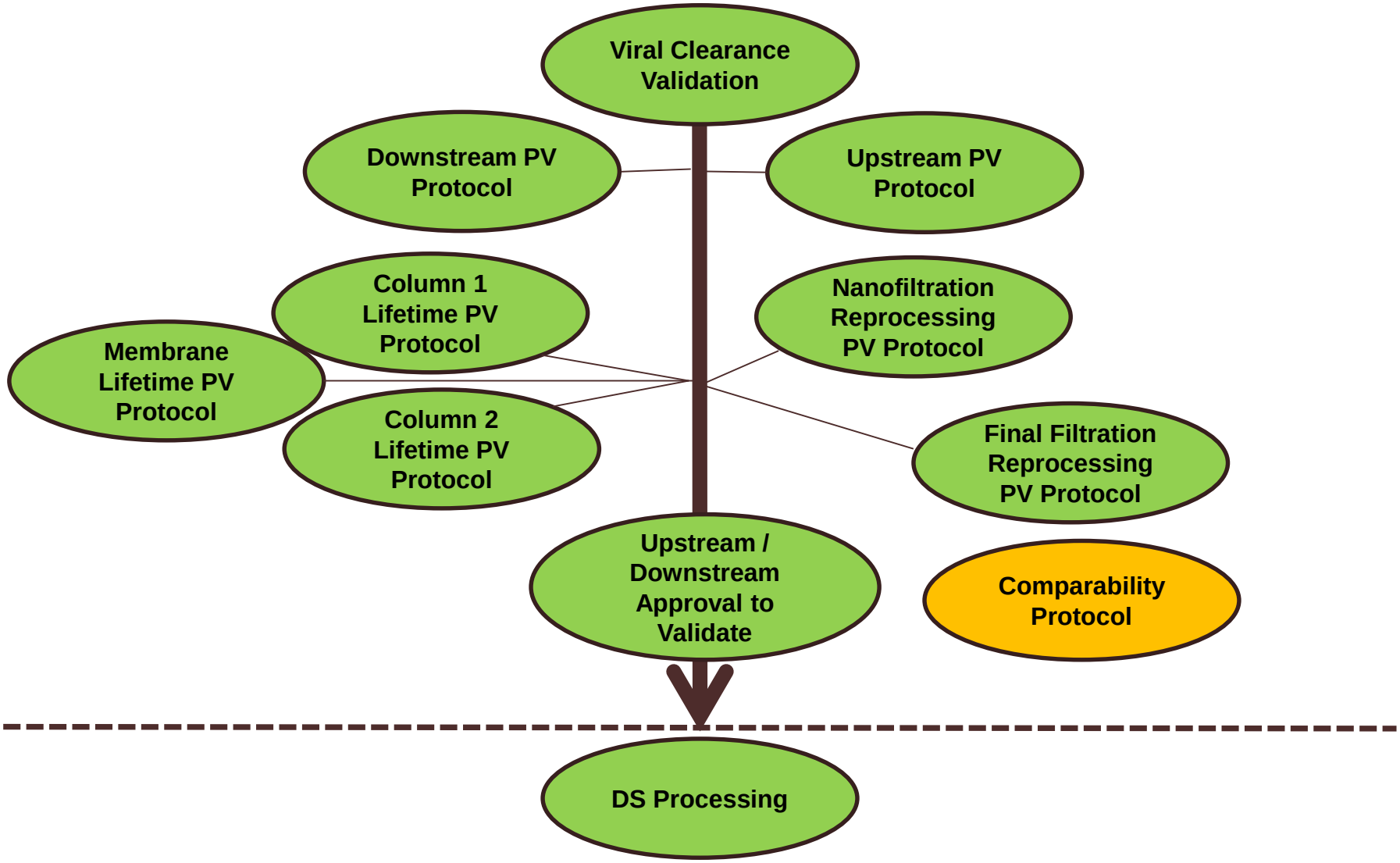
- CQAs and rationale
- Parametric controls: CPPs/ OPPs/ IPCs/ KPIs
- Microbiological and viral controls
- Testing strategy: in-process, release, stability
- Resin/ membrane lifetime, hold times, etc…

Control Points Matrix: Defines the PPQ validation strategy……

Product Quality Attribute	CQA	Production Bioreactor	Protein A	Low pH/VI	CEX	AEX	Nanofiltration	UF/DF	Compounding	Filtration	Filling, stopper, cap	Testing elements
Aggregate	Yes	Form	Remove	Form	Remove	Remove			Form		Form	LR
Deamidated isoforms	No	Form										PM
Oligosaccharide	Yes	Form										PM
CHO HCP	Yes	Form	Remove	Remove	Remove	Remove						PM
DNA	No	Form				Remove						None
Protein A	No		Form		Remove	Remove						None
Viral safety	Yes			Inact		Clear	Clear					Biorx. IPC

- Unit Operation functional claims
- Parametric Controls: CPPs/ OPPs
- In-process hold times
- Testing Strategy
  - IPCs and validation limits
  - Biochemical testing
  - Microbiological testing
  - IP Specifications
  - Release specifications
- Demonstrate consistent process performance over 3-5 consecutive lots

Other Elements to Stage 2……

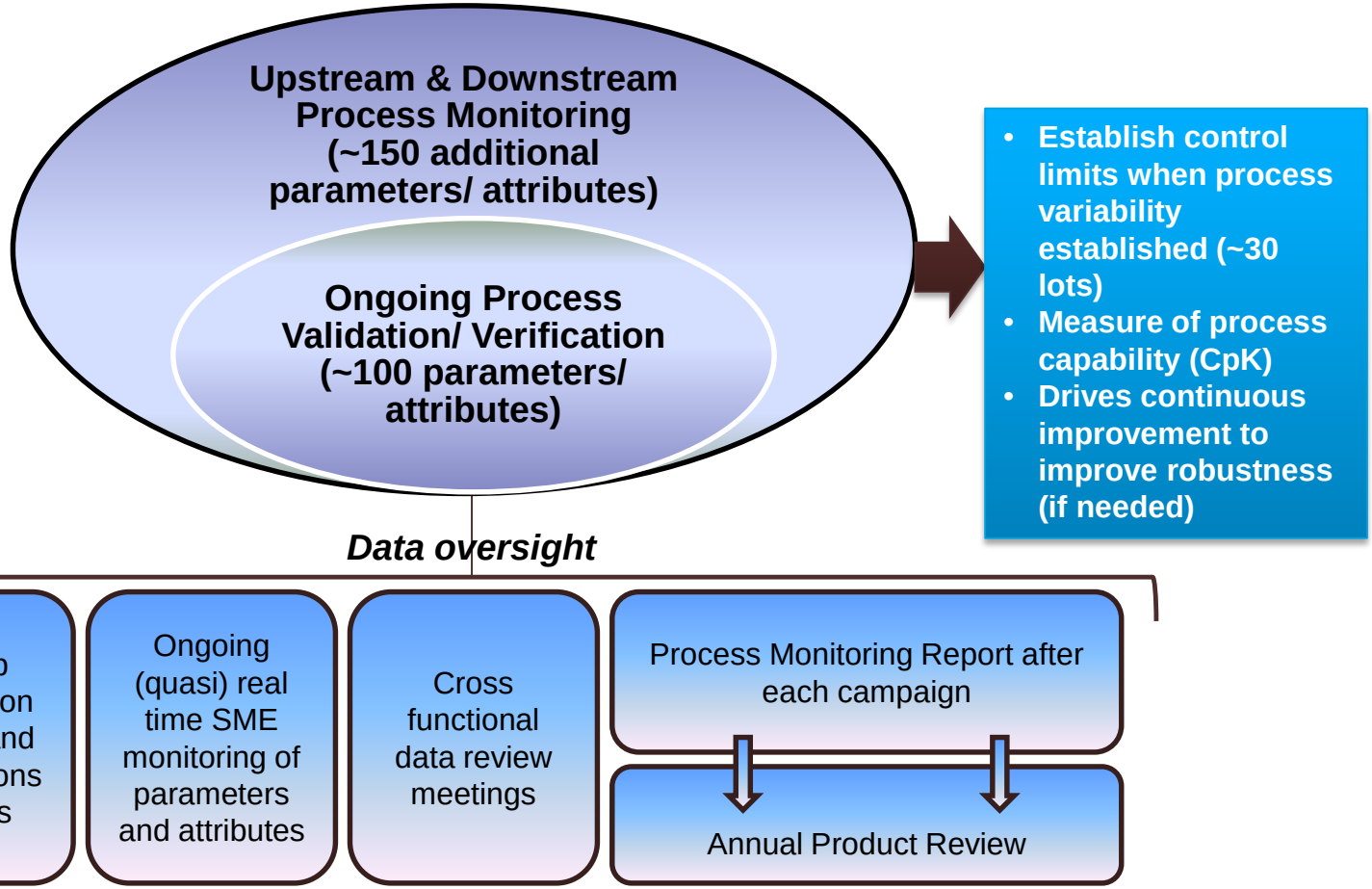


Stage 3: CPV Program Overview

<u>Objective:</u> Demonstrate ongoing assurance that process remains in state of control for commercial manufacturing

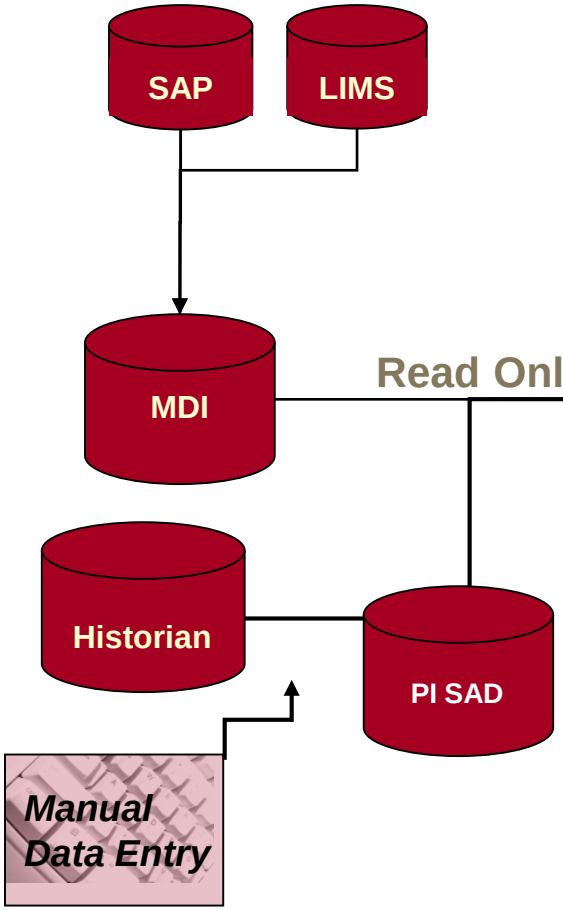
Orthogonal/ leading indicators of process performance

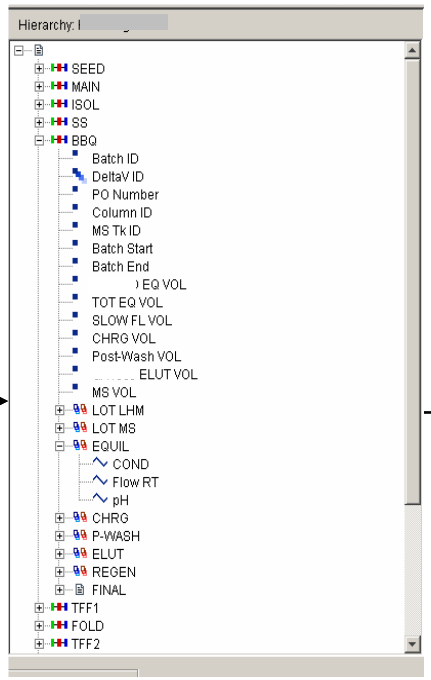
Critical parameter and process consistency indicators: trending and assessment of state of control



Process Data acquisition and analysis

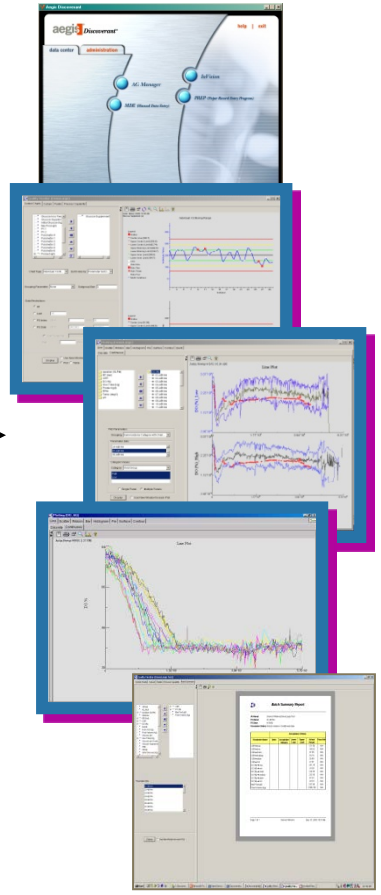
Source Systems



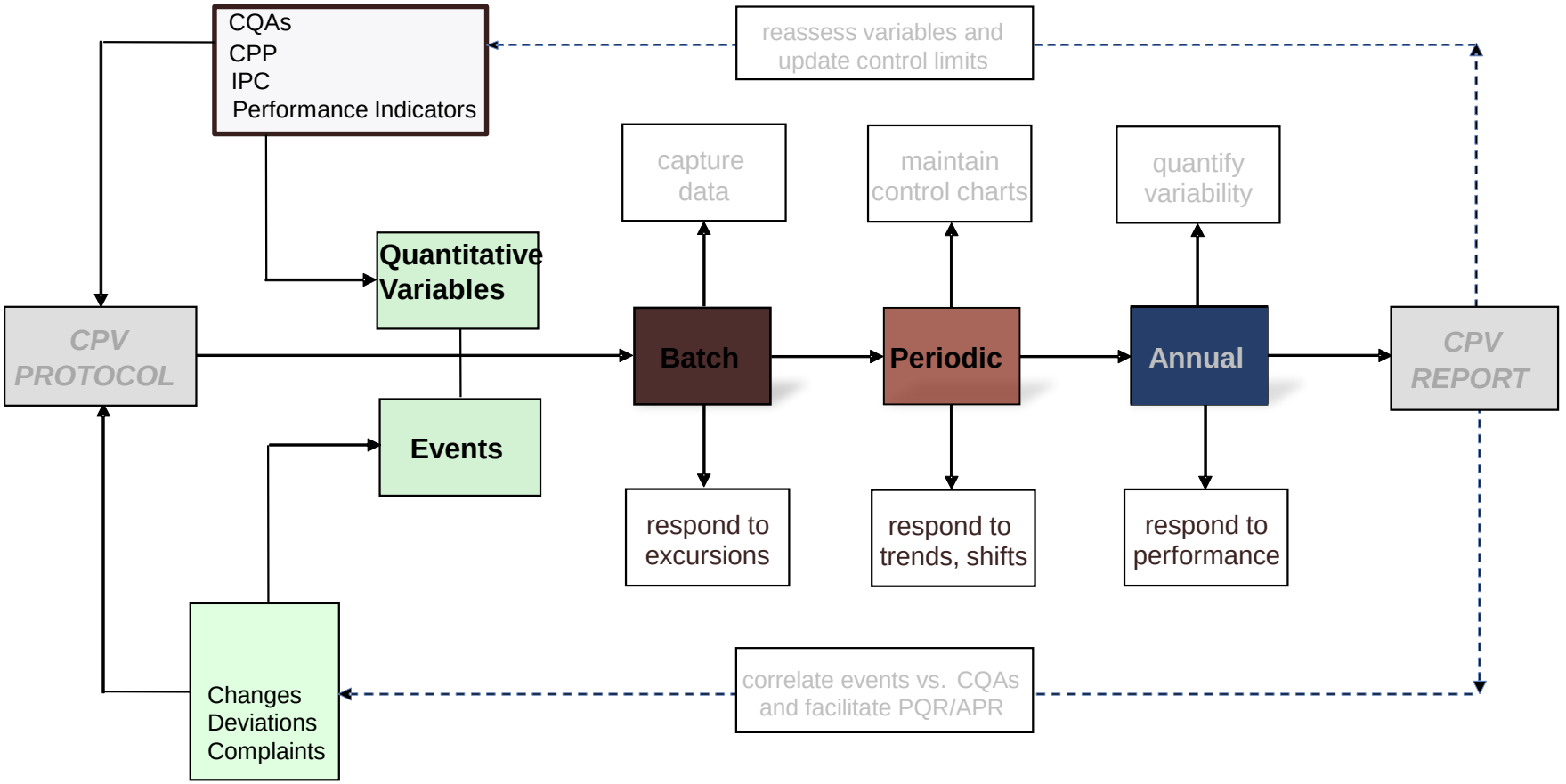


Hierarchy
Process Driven

Analysis / Results



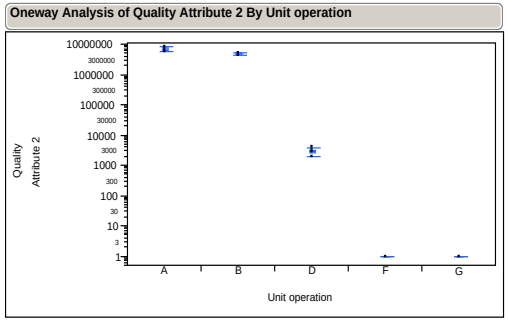
Roadmap for CPV



Stage 3a and 3b: reduced testing once variability established

Stage I	Stage II	Stage III
Development	**Validation: PPQ**	**Commercial Mfg: CPV**

IIIa	IIIb
Heightened Sampling & Testing until variability established	Routine Monitoring Program

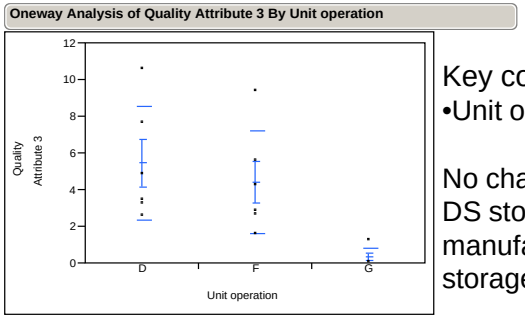


Key control points:
- Unit operation D
- Unit operation F

No change during DS storage or DP manufacturing and storage

	Spike	Residual
Unit Operation F	2x	<LOQ
	5x	<LOQ
Unit Operation G	2x	<LOQ
	5x	<LOQ

Remove from in-process and DS analytical testing after variability established



Key control point:
- Unit operation G

No change during DS storage or DP manufacturing and storage

	Spike	Residual
Unit Operation G	2x	<LOQ
	5x	>LOQ

Remove from in-process analytical testing after variability established

Include in enhanced DS analytical testing program

Integration within the Quality System key to maintain the validated state…….

Preventative Maintenance and Calibration
Ensures equipment and systems are maintained in a qualified state.

Annual Product Review
Monitor, measure and analyse manufacturing processes and products, using statistical techniques, on a routine basis to evaluate trends over time.

Change Control
All changes proposed for a manufacturing system, equipment, method or process are evaluated to assess the impact on validation/ qualification.

Deviation management
Provides a structured risk-based approach to the investigation, determination of the root cause, documentation, identification and implementation of any resultant corrective action and preventive actions (CAPAs) for all departures

Periodic Review of Facilities, Utilities, Equipment and Computer Systems
Evaluate trends, compare data with historical information to determine shifts and assess the state of control of the facility, utility, equipment and computer system.

Process Change Management

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- Process changes can result from following:
  - Low process capability
  - Special cause variability
  - Monitoring program detects process shift/ trend
  - Process optimization to improve yields
  - Raw material supplier change or second source
  - New working cell bank
  - Equipment changes
  - Scale-up or Qualification of second site
- Changes assessed based on risk and science, controlled via change management system
  - Small scale model data may be required to support
  - Assess impact to control strategy and validated state
  - Assess regulatory reporting category based on registered commitments and impact to control strategy

Summary

- Enhanced development program results in well understood, holistic and robust control strategy development
- PPQ program demonstrates process performance consistency prior to commercial manufacture
- CPV program and quality systems ensure process remains in state of control and continuous improvement opportunities identified and implemented appropriately

Results in a well understood and controlled process that produces high quality medicine over the lifecycle of the product

Lessons Learned….

- Excellent feedback from regulators on control strategy and validation approach
  - Strong regulatory and business drivers to adopt QbD approach
- Strong data packages will allow for some regulatory relief
  - Testing strategies: validate out process-related impurities
- Learning and open questions
  - Non-CPPs expected as commitments in 2.2 and 2.4
    - What parameters to pick?
    - 2 tier parameter classification system does not line up with this approach
    - Significant variability in these requirements exist between regulatory bodies
  - Requirements emerging for additional data/ risk assessments: examples raw materials, extractables and leachables
  - Release specifications: balance between manufacturing history and clinical history
    - Common cause variability at time of filing may not be completely understood: examples: raw material variably and impact charge and glycosylation variants
  - PALM plan: consider including elements in filing: address in Q12

Acknowledgements

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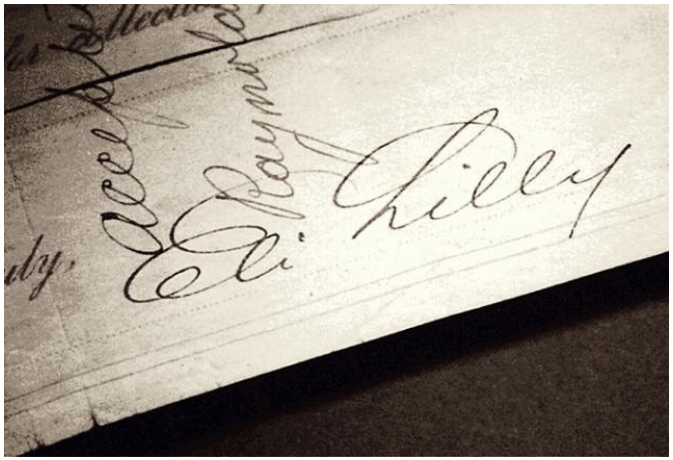

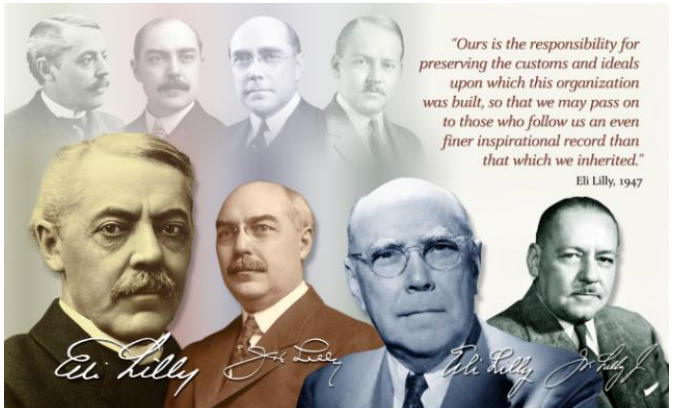
"Ours is the responsibility for preserving the customs and ideals upon which this organization was built, so that we may pass on to those who follow us an even finer inspirational record than that which we inherited."
Eli Lilly, 1947

Lilly