Analytical Comparability of mRNA Vaccines: Supporting the Global Rollout of Comirnaty® and Streamlining the Strategy for the mRNA Vaccine Pipeline

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Pfizer
Research & Development

Overview

01 Introduction to Analytical Comparability

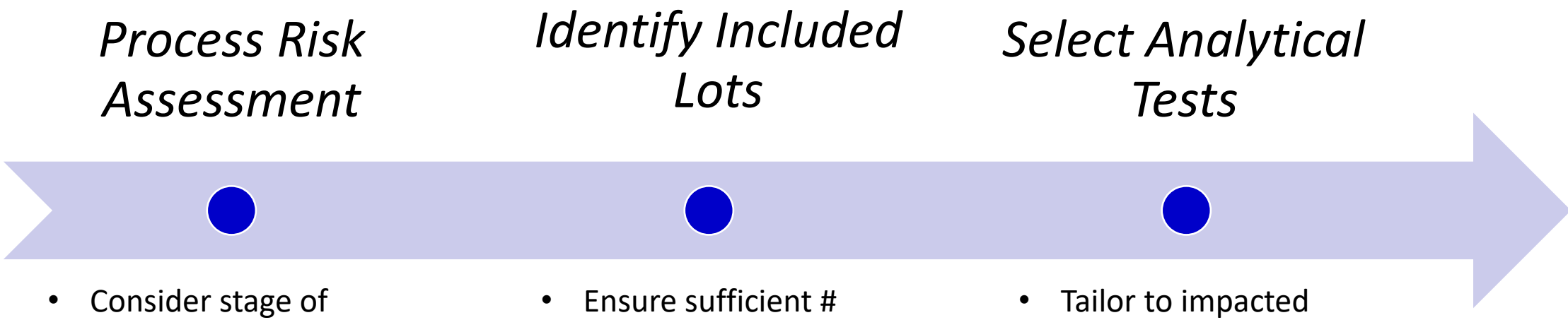
02 Comirnaty® Analytical Control Strategy

03 Comirnaty® Comparability Examples

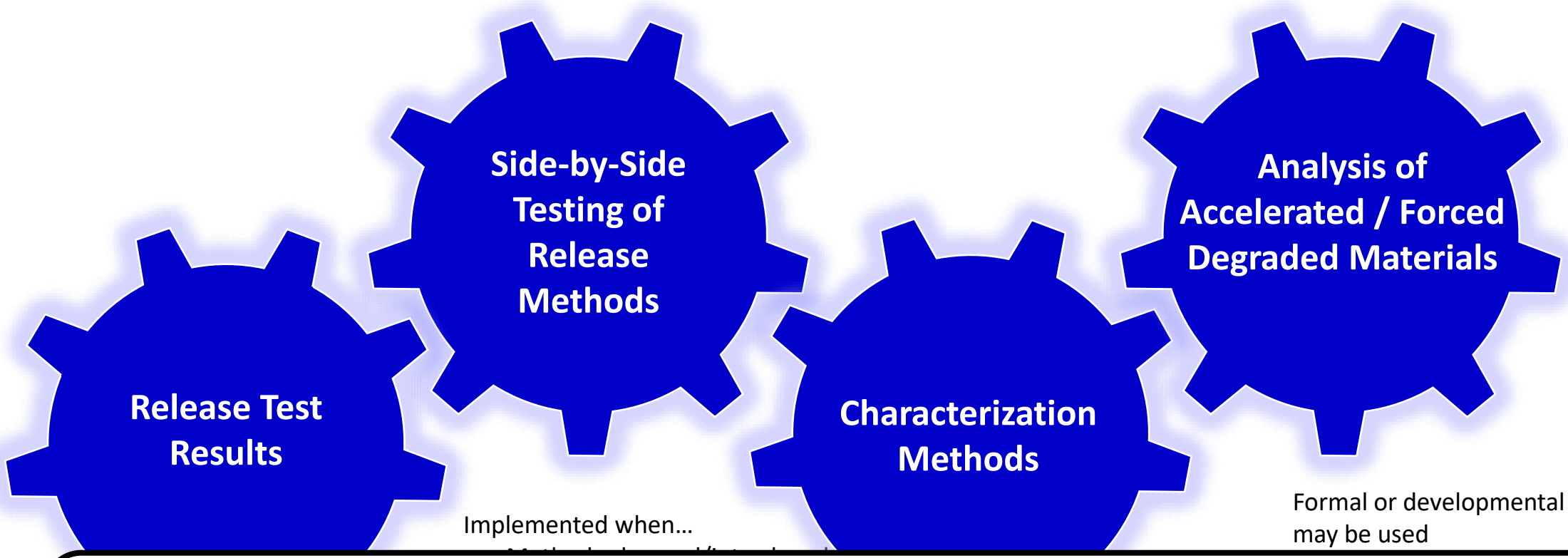
04 Extending to Another mRNA Vaccine

Introduction to Analytical Comparability

Objective (ICH – Q5E): "Demonstrate that quality attributes of the pre-change and post-change product are ***highly similar,*** and that existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have ***no adverse impact upon safety or efficacy*** of the drug product."



Components of Analytical Comparability Testing



Implemented when…

Formal or developmental data may be used

A risk-based approach should be used to identify which components of the analytical comparability exercise should be included. Depending on the nature of the change, some or all components may be needed.

Include
clinical,

Target attributes potentially impacted by change

Comparability Study Design

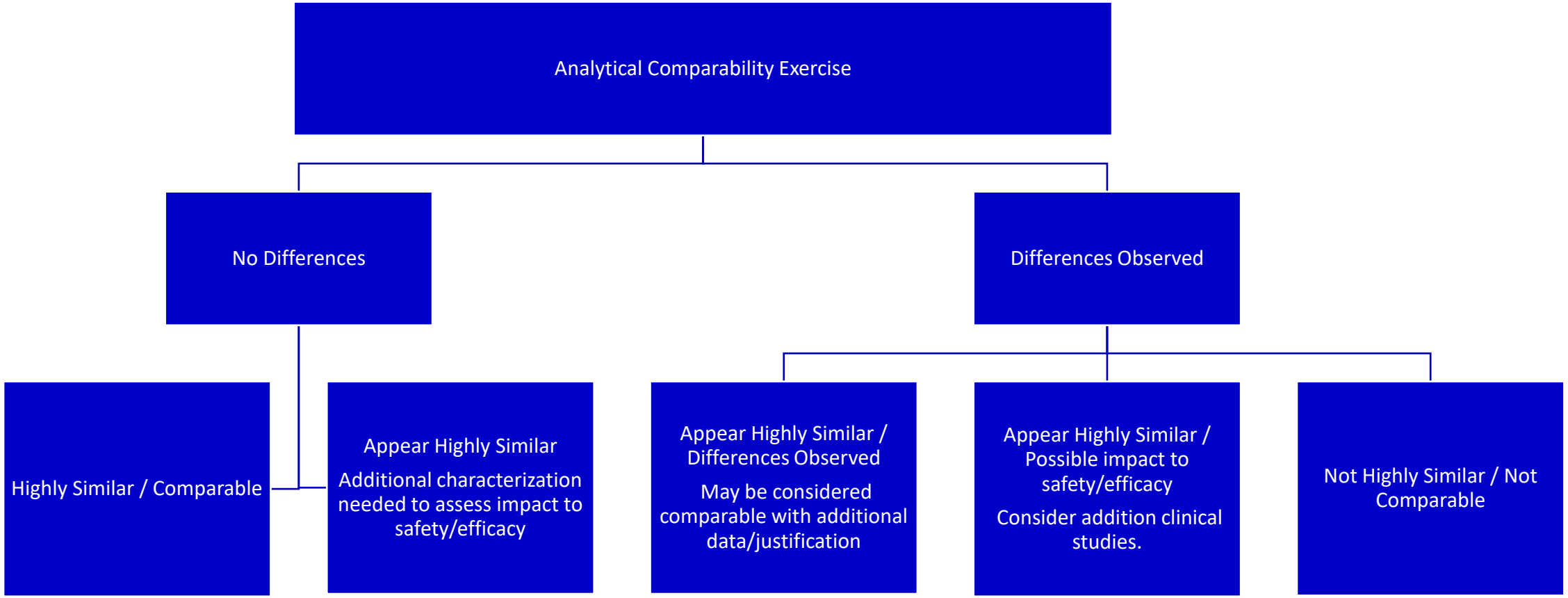
Risk Assessment of Process Changes and Impact on Comparability Study Design

	Early/Mid Development	Late-Stage Development	Post Pivotal Development
Minor Change	Low Risk	Medium Risk	High Risk
Moderate Change	Medium Risk		
Major Change	Medium Risk		
Strain Change	Low Risk		

Impact of Manufacturing Stage on Comparability Study Design

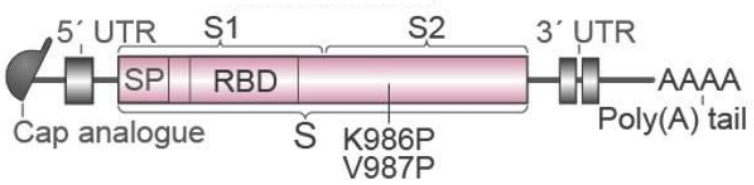
	Early/Mid Development	Late-Stage Development	Post Pivotal Development
Components used for comparability testing	Primarily Release Panel	Release Panel with other analytical components to demonstrate comparability	

Comparability Outcomes (ICH Q5E)



Comirnaty® mRNA DS Quality Control Strategy

mRNA Encoding Spike Protein (DS)



GMP Release

Composition and Strength	
Clarity / Color	Appearance
pH	Potentiometry
Content (RNA Concentration)	UV Spectroscopy

Purity	
RNA Integrity	CGE
5’-Cap	RP-HPLC
Poly (A) Tail	ddPCR
Poly (A) Tail Length	IP-RP-HPLC

Identity	
Identity of Encoded RNA Sequence	PCR

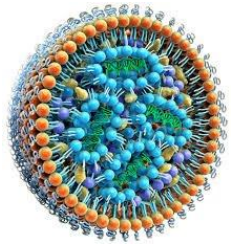
Process / Product Impurities	
Residual DNA	qPCR
dsRNA	Immunoblot

Safety
Endotoxin
Bioburden

Characterization	
5’-Cap	LC – UV/MS
Oligonucleotide Mapping	LC – MS/MS
Higher Order Structure	Circular Dichroism
Protein Expression	Western Analysis

Comirnaty® mRNA Drug Product Quality Control Strategy

mRNA Encapsulated
Lipid Nanoparticle (DP)



GMP Release

Composition and Strength	
Clarity / Particulates	Appearance
pH	Potentiometry
Osmolality	Osmometry
RNA Content / Encapsulation	Fluorescence
Lipid Content	HPLC-CAD
LNP Size / Polydispersity	DLS

Identity	
Identity of Encoded RNA Sequence	PCR
Lipid ID	HPLC-CAD

Purity	
RNA Integrity	CGE

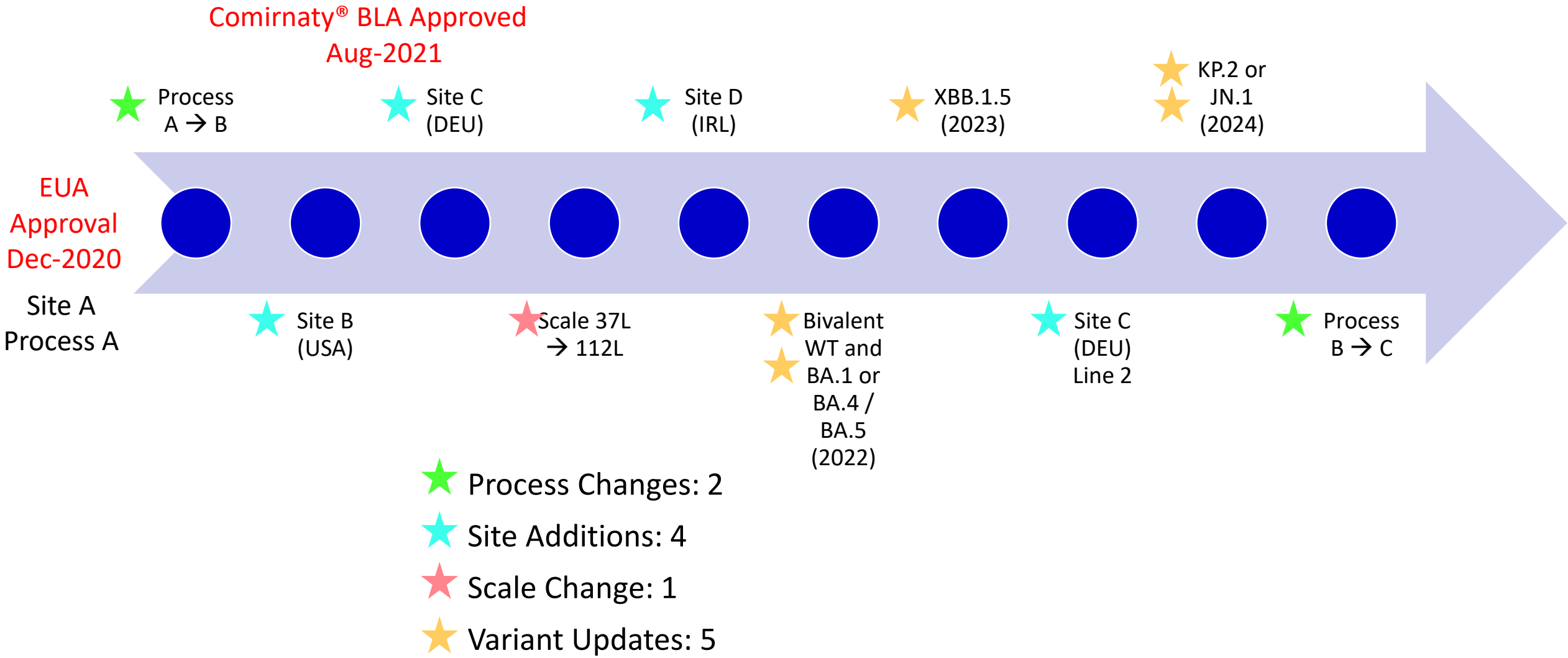
Potency	
In-Vitro Expression	Cell-based FACS

Safety
Endotoxin
Sterility

Characterization	
Lipid ID / Content	LC-MS
LNP Surface Properties	High-Field NMR
LNP Surface Charge	Zeta Potential
Size Distribution / Shape	AF4
5’-Cap	RP-HPLC
Poly (A) Tail	ddPCR
Poly (A) Tail Length	RP-HPLC

Pfizer

Comirnaty® Drug Substance Updates



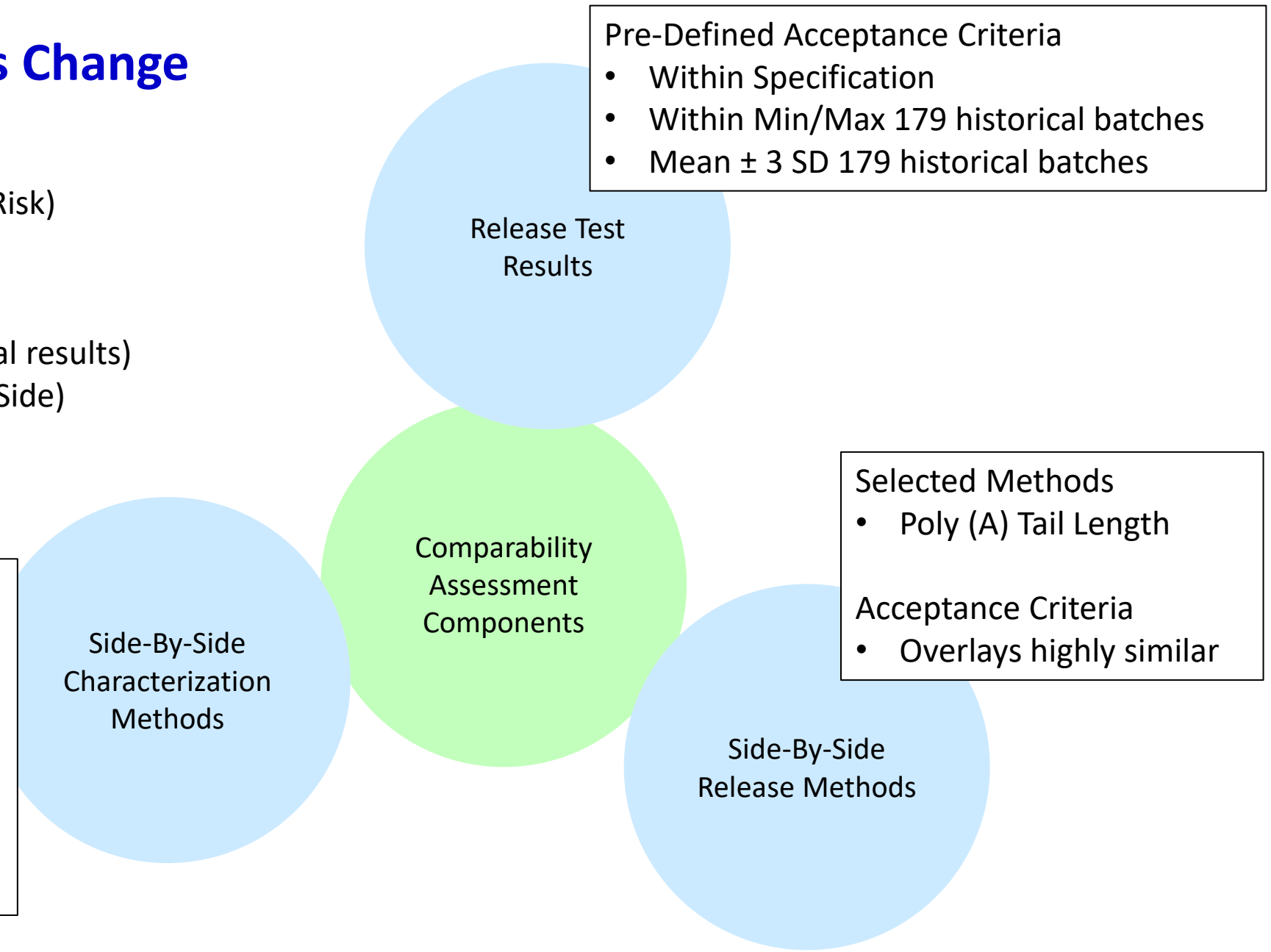
DS Case Study: Process Change

Process Risk Assessment

- Late Stage / Post Approval (High Risk)
- Fine Tuning Process Parameters

Batch Selection

- 179 Pre-Change Batches (historical results)
- 1 Pre-Change RM Batch (Side-by-Side)
- 6 Post-Change Batches



Pre-Defined Acceptance Criteria
- Within Specification
- Within Min/Max 179 historical batches
- Mean ± 3 SD 179 historical batches

Selected Methods
- 5′-Cap (LC-UV/MS)
- Oligonucleotide Mapping
- Circular Dichroism
- Western Analysis

Acceptance Criteria
- Overlays highly similar

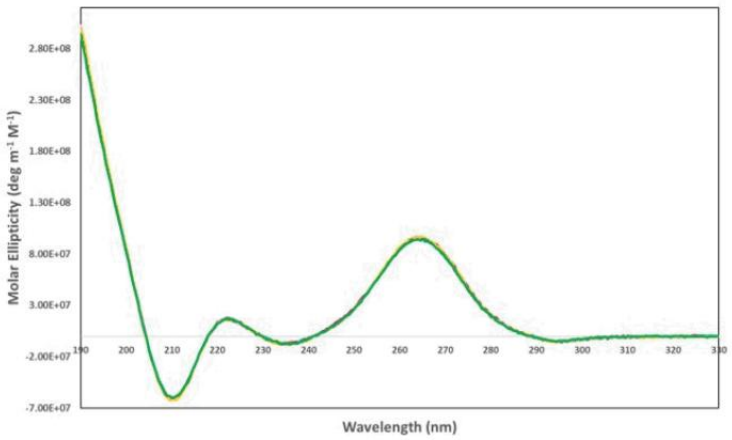
Selected Methods
- Poly (A) Tail Length

Acceptance Criteria
- Overlays highly similar

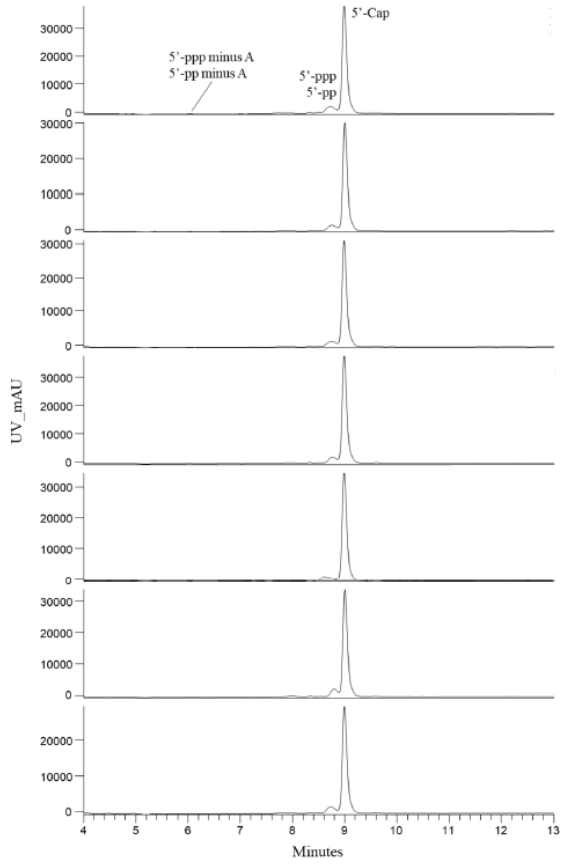
Successful DS Comparability Assessment

- ***Release Test Results*** → Met All Comparability Acceptance Criteria
- ***Side-By-Side Release*** → Chromatographic overlays found to be highly similar
- ***Side-By-Side Characterization*** → Pre- vs. Post- change batches found to be highly similar

Circular Dichroism



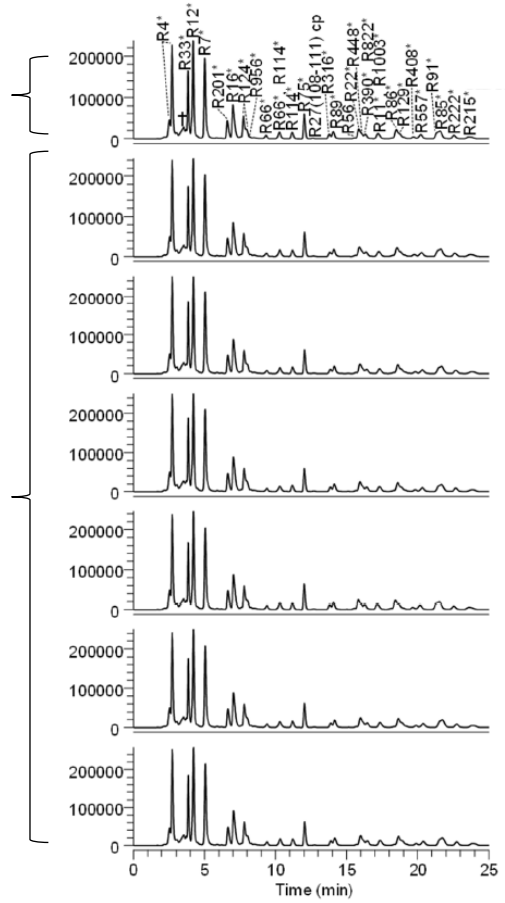
5′-Cap: LC/UV



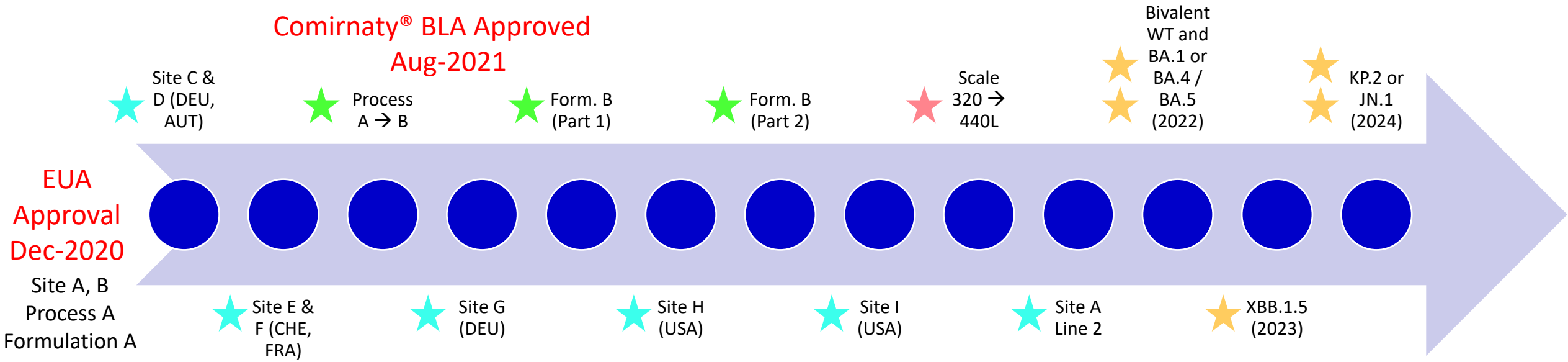
Pre-Change

Post-Change

Oligonucleotide Mapping



Comirnaty® Drug Product Updates



★ Process / Formulation Changes: 3

★ Site Additions: 8

★ Scale Change: 1

★ Variant Updates: 5

DP Case Study: Formulation

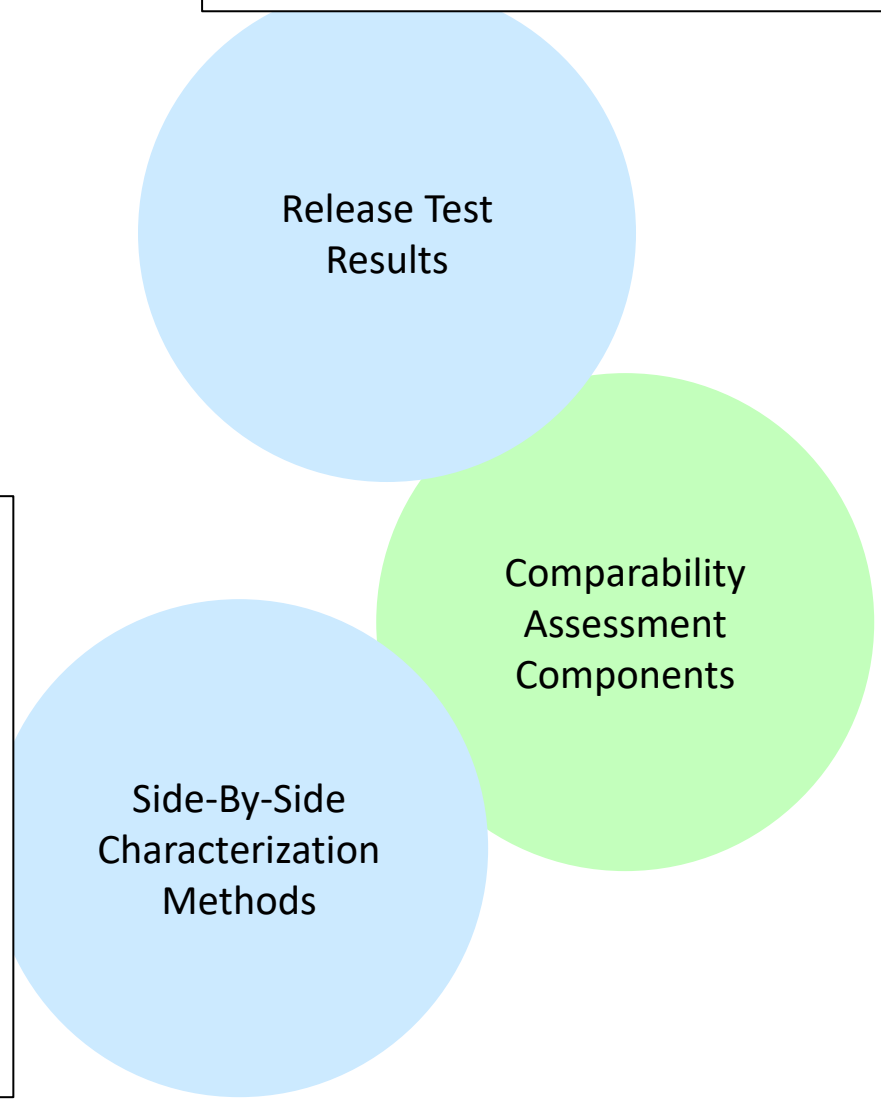
Process Risk Assessment

- Late Stage / Post Approval (High Risk)
- New DP Formulation Introduction

Batch Selection

- 94 Pre-Change lots (historical results)
- 1 Pre-Change RM lot (side-by-side)
- 3 Post-Change lots (side-by-side)

Pre-Defined Acceptance Criteria
- Within Specification
- Within Min/Max 94 historical batches



Selected Methods
- Zeta Potential
- Size / Shape AF4
- Surface PEG Characterization (NMR)
- 5′-Cap (RP-HPLC)
- Poly (A) Tail (ddPCR)
- Poly (A) Tail Length (RP-HPLC)

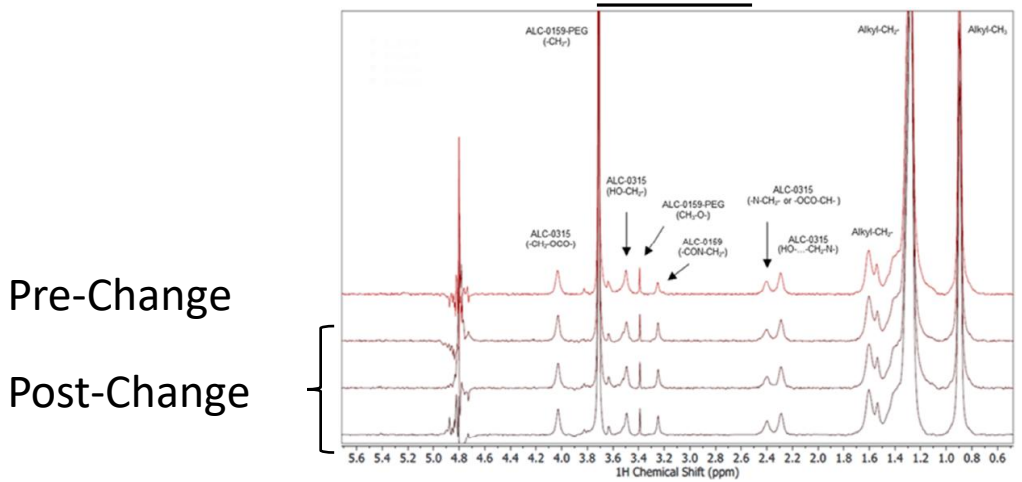
Acceptance Criteria
- Overlays highly similar

Successful DP Comparability Assessment

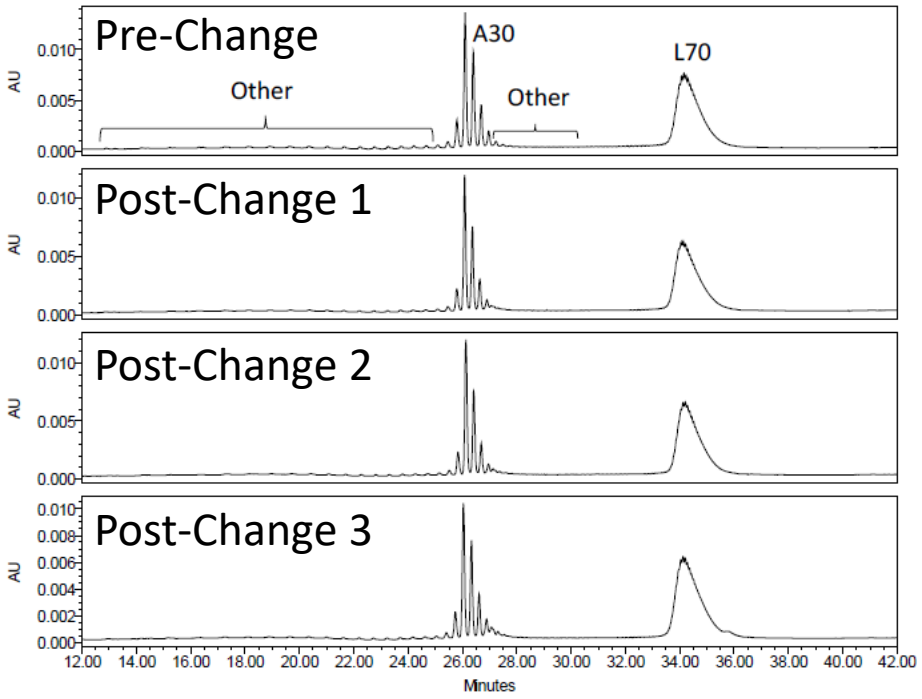
Release Test Results → Met
All Comparability Acceptance Criteria

Side-By-Side Characterization →
Pre- vs. Post- change batches found to be highly similar

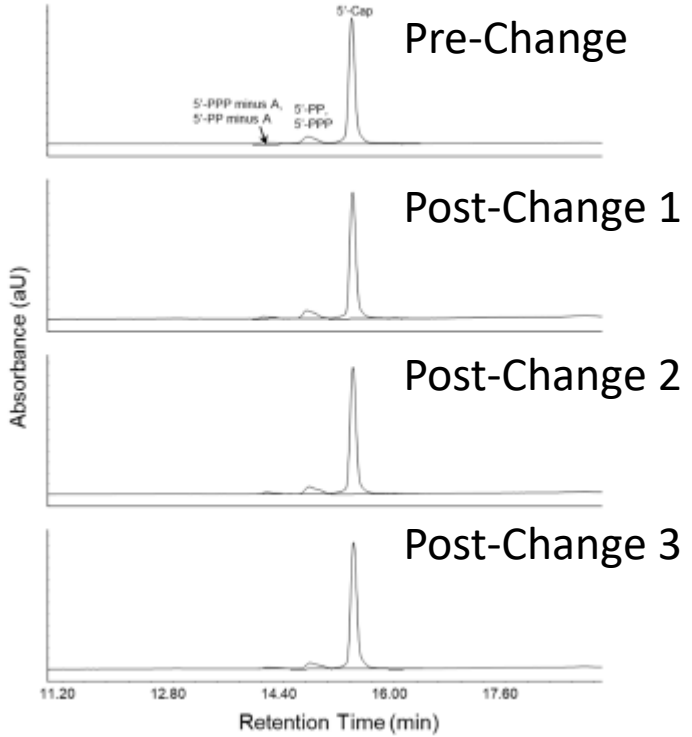
^{1}H NMR



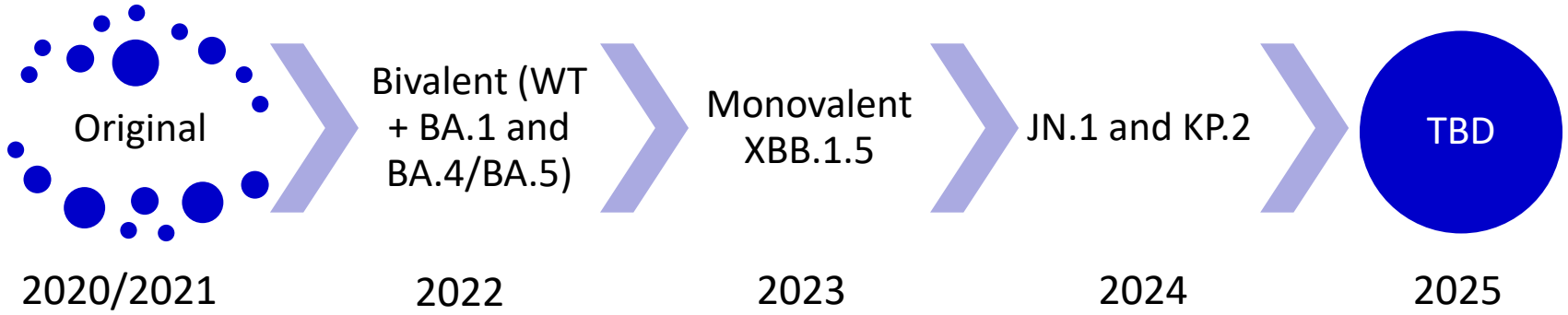
Poly (A) Tail Length RP-HPLC



5′-Cap (RP-HPLC)



Comirnaty® Seasonal Strain Change

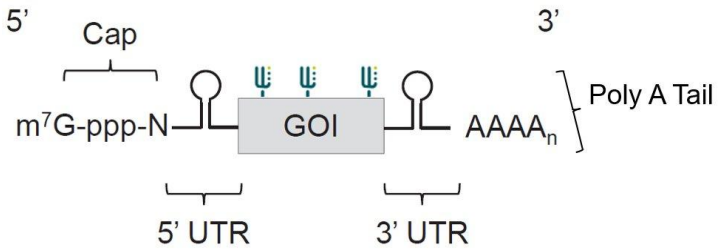


Unchanged

- Manufacturing Process
- 5′-Cap, UTRs, Poly(A)Tail
- Lipid composition
- LNP characteristics
- Formulation
- Container closure
- Supply chain

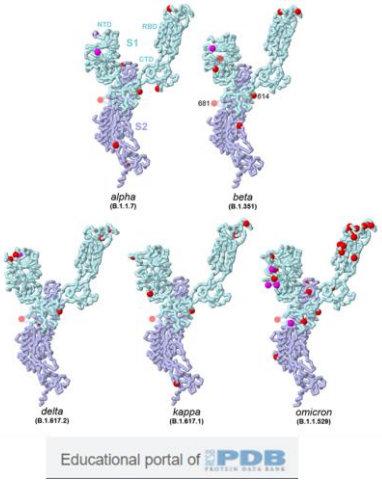
Highly Similar

- Nucleic acid length (mRNA length)
- A, U, G & C composition
- Molecular weight



Updated

•Nucleic acid sequence



Comirnaty Seasonal Strain Change

Original | Bivalent (WT | Monovalent | KP.2 | TBD

Comparability Assessment (DS and DP)

- ✓ Release Specifications Identical
- ✓ Batch Analysis – Meets Specification
- ✓ Characterization

Unchanged

- Manufacturi
- 5'Cap, UTRs,
- Lipid compos
- LNP characte
- Formulation
- Container closure
- Supply chain

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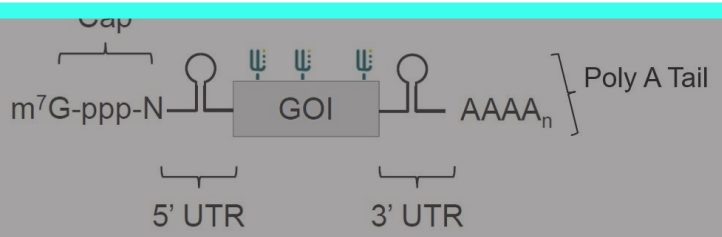
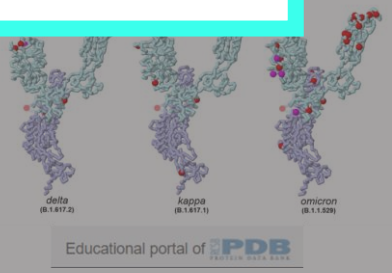
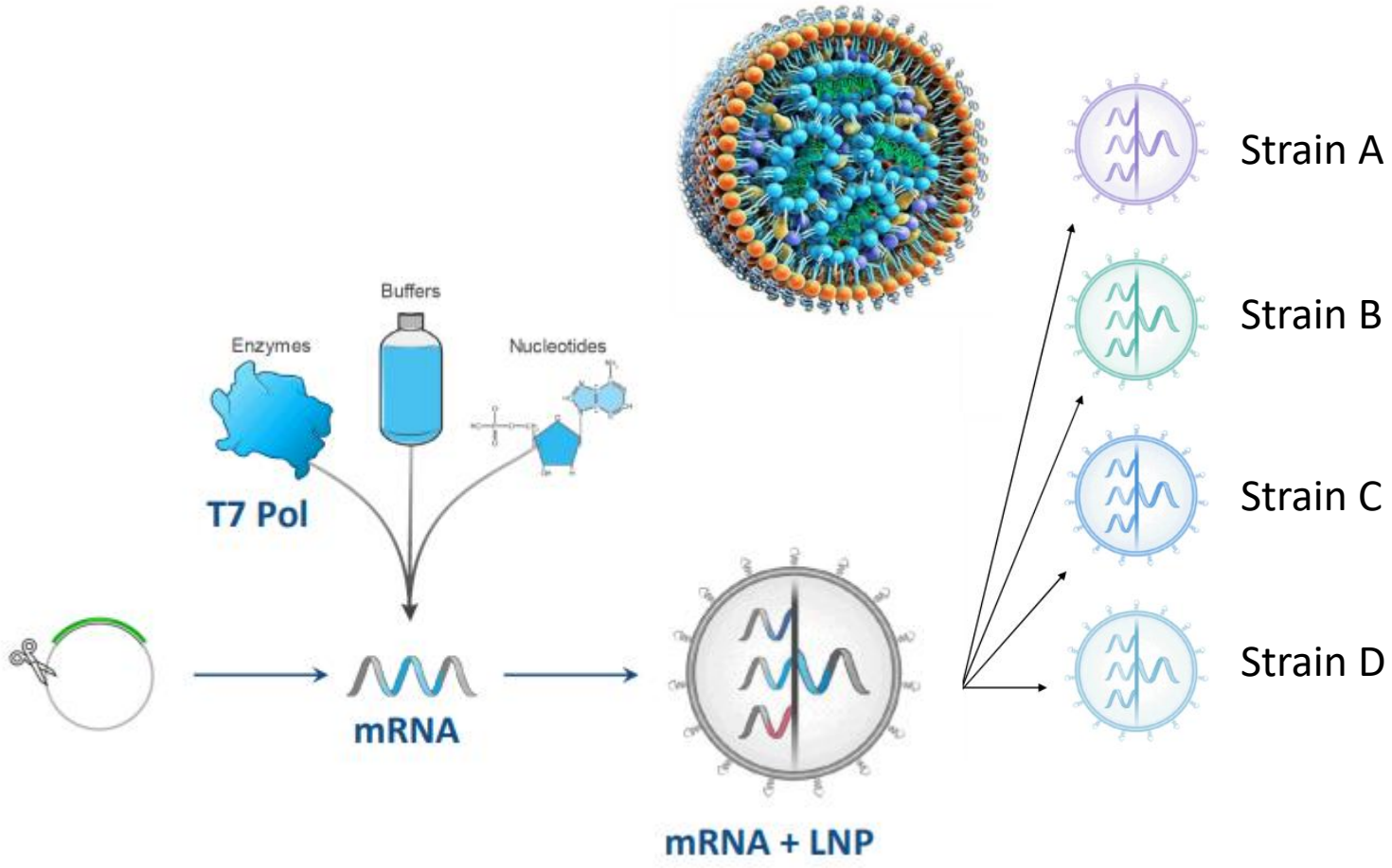




Pfizer

Beyond Comirnaty® – Comparability of multi-valent mRNA vaccine



DS Control Strategy

- Same attributes

DP Control Strategy

- Same attributes
- Strain Ratio by ddPCR

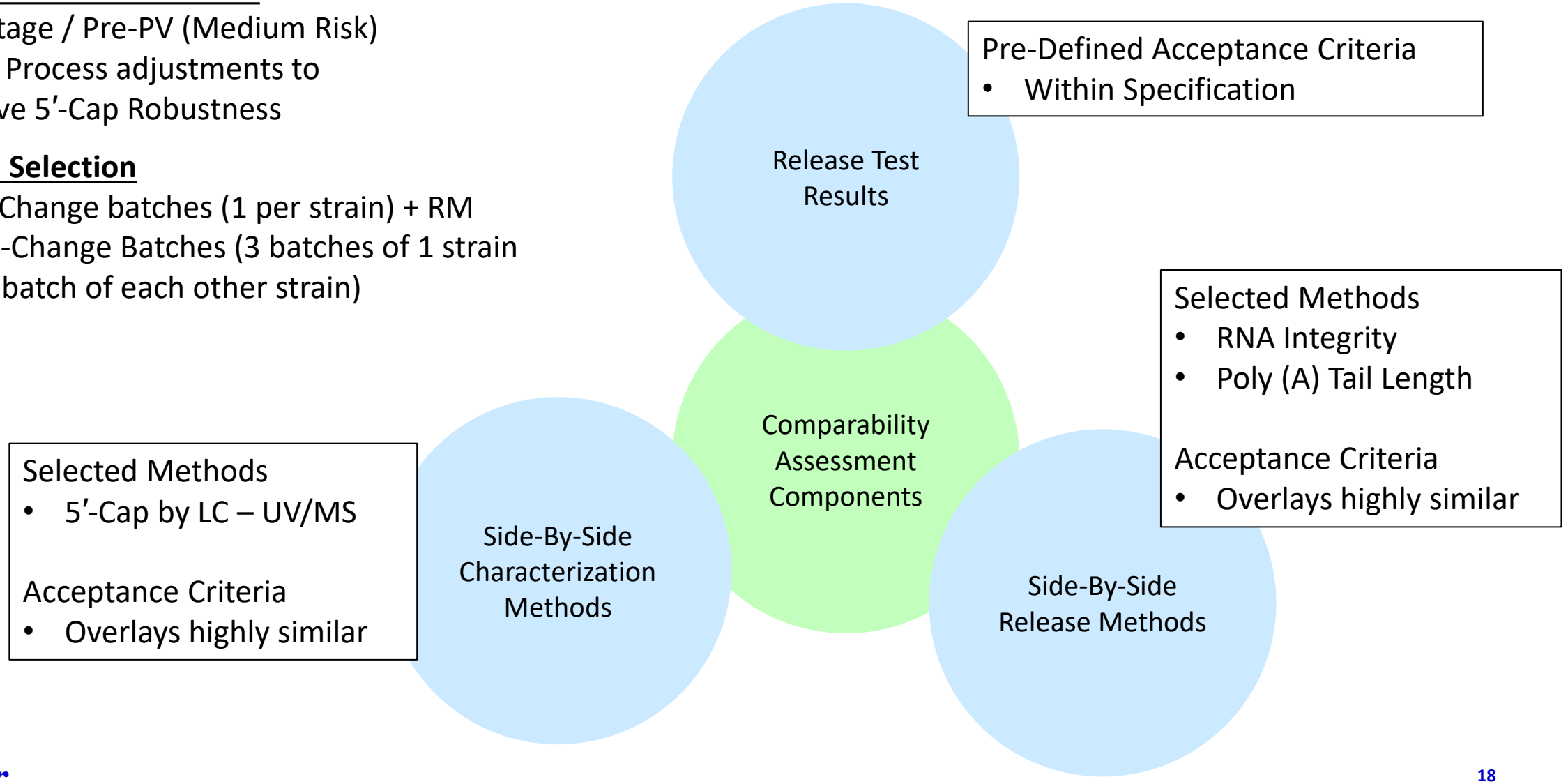
Multi-Valent Vaccine Comparability: Process Improvements

Process Risk Assessment

- Late Stage / Pre-PV (Medium Risk)
- Minor Process adjustments to improve 5′-Cap Robustness

Batch Selection

- 4 Pre-Change batches (1 per strain) + RM
- 6 Post-Change Batches (3 batches of 1 strain and 1 batch of each other strain)



Successful DS Comparability Assessment

Release Test Results

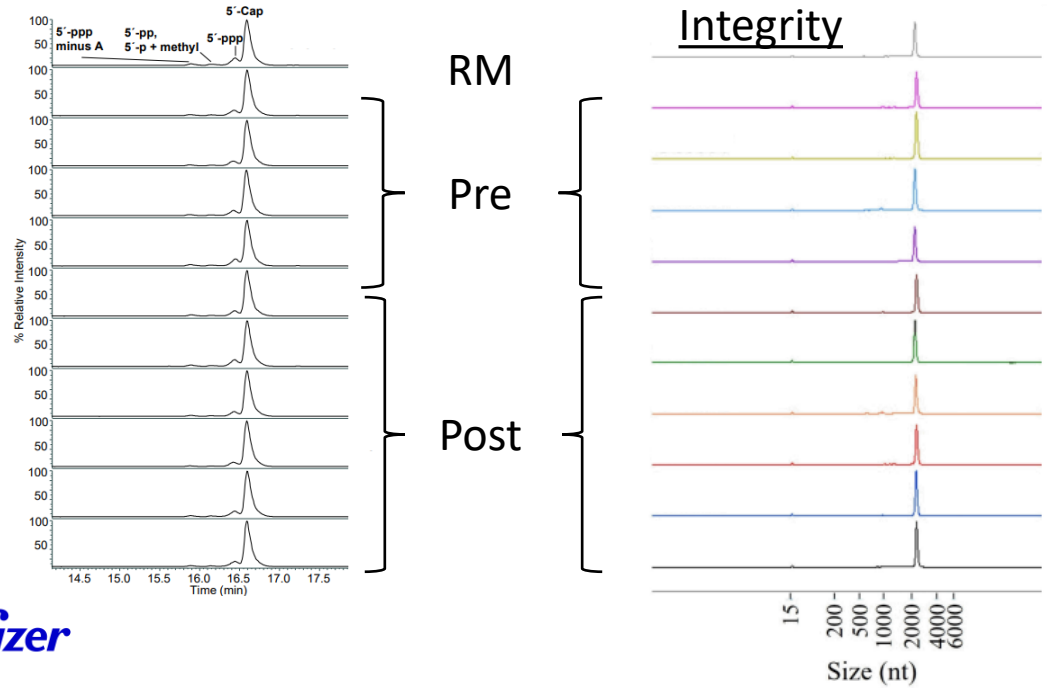
→ Met Acceptance Criteria

→ Improvement to impurity profile

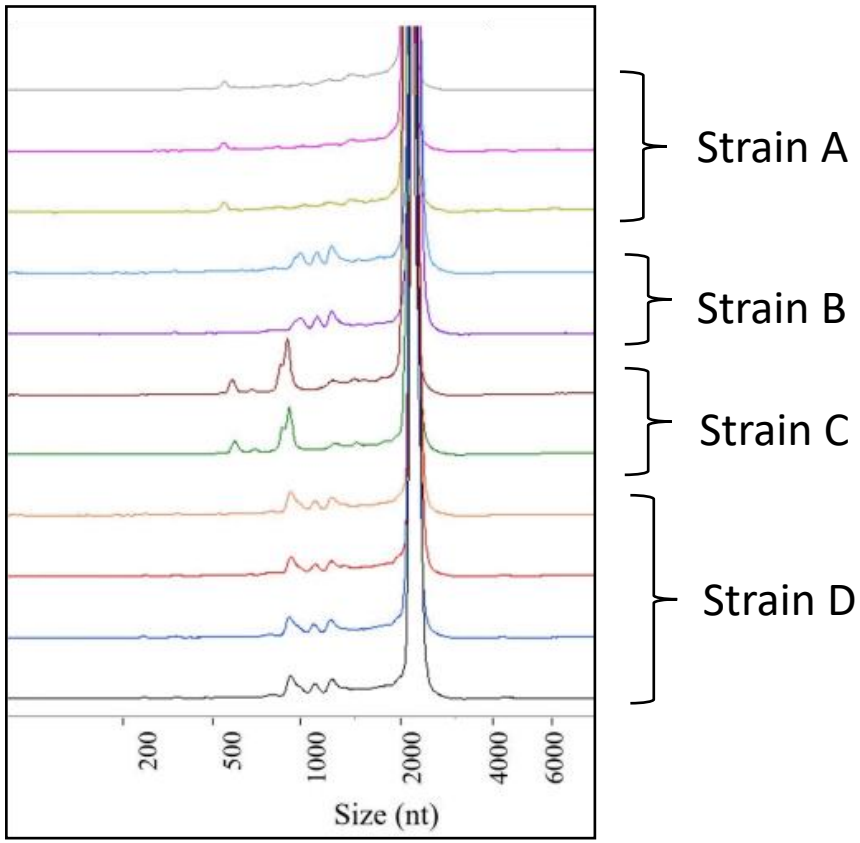
Side-By-Side Characterization →

Pre- vs. Post- change batches found to be highly similar

5′-Cap



Integrity (organized by strain)



Key Takeaways and Overall Conclusion

- No one-size fits all to comparability
  - Comparability assessment should be tailored to potentially impacted CQA's using a risk-based approach.
  - Exception to seasonal strain change activities.
- Elements of analytical comparability work together to provide a comprehensive assessment of comparability
  - Release test results
  - Side-by-side testing
  - Characterization testing
  - Forced degradation studies
- Multiple comparability criteria can be used to assess data. Comparability criteria selection may depend on the number of available batches, the nature of the study, and the specific attribute/procedure.
  - Statistical criteria
  - Acceptance criteria
  - Qualitative evaluations

Acknowledgements

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