Platform Analytical Method Lifecycle: Trends, Strategies, and Case Study Through the Lens of mRNA Vaccines

CASSS WCBP 2023

25 January 2023

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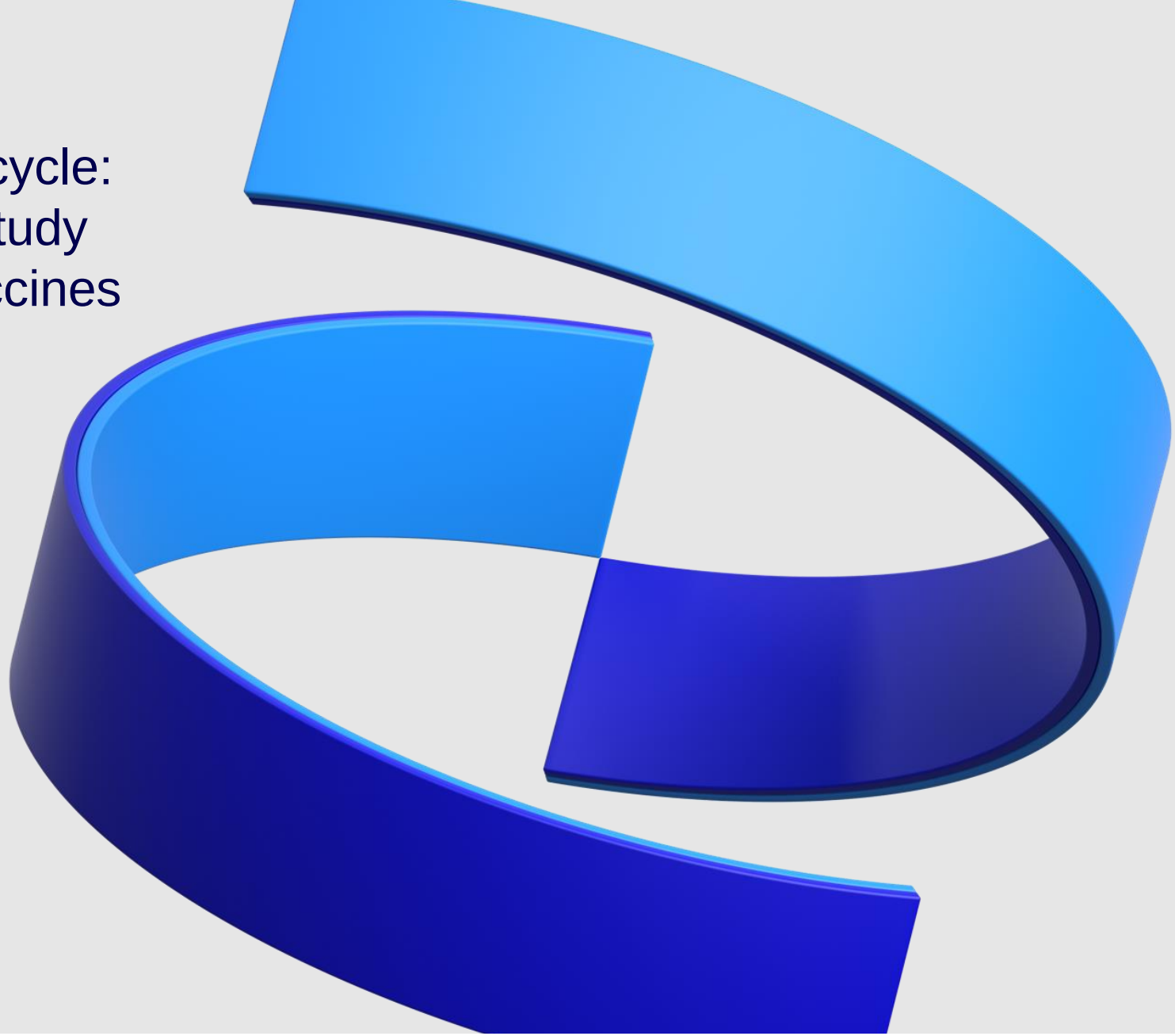
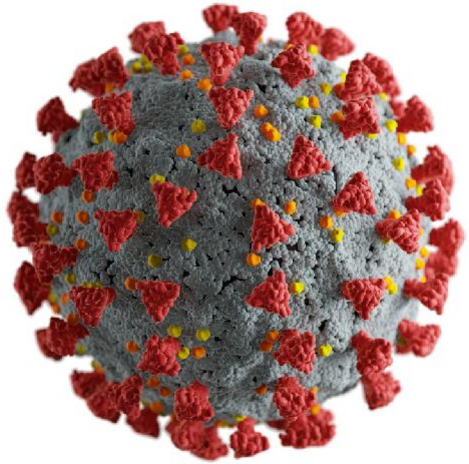


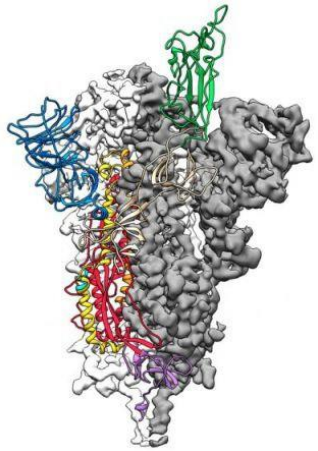
Outline

- COVID-19 Vaccine Analytical Toolbox
- Importance of Platform Strategy to Enable Acceleration
- Validation Strategy & Application to New Variants / Programs

Pfizer-BioNTech Collaboration to Develop BNT162b2

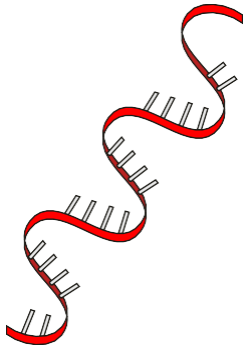


SARS-COV-2 (3D Model)

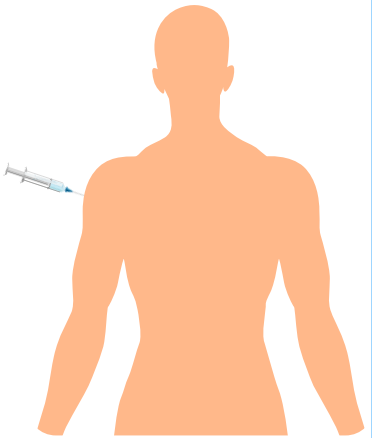


SARS-COV-2 Spike Protein 3D Structure

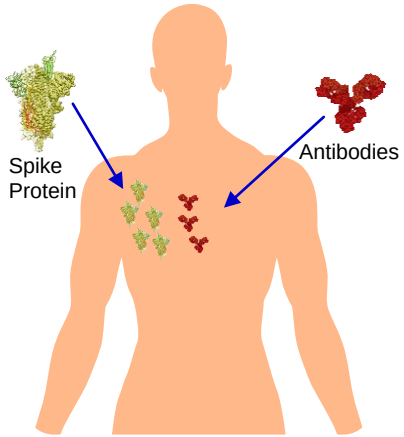
(Wrapp et al., 2020, Science)



mRNA for spike protein of coronavirus



mRNA is injected into muscle



The vaccine triggers production of the spike protein and antibodies specific to it

March 17, 2020
PFE/BNT Letters of Intent

November 18, 2020
Phase 3 Study Meets All Endpoints

December 2020
Temporary authorization for emergency use in UK & US
Conditional authorization in EU

Feb 2021
Japan exceptional approval
特例承認

Aug 2021
BLA Approved

Oct 2021
EUA for Pediatric (5-11 years)

June 2022
EUA for Infant (6m-4 years)

Sep 2022
EUA for BA.4/5 Bivalent Booster

Oct 2022
EUA for Pediatric BA.4/5 Bivalent Booster

Dec 2022
EUA for Infant BA.4/5 Bivalent Booster

* Authorized or Approved in 98 countries as of October 19, 2021

** Emergency Use Authorization (EUA) granted for individuals 65 years of age and older, and individuals ages 18 through 64 within certain high-risk groups

Margaret & Sandra Get Vaccinated

Manufacture and Testing of BNT162b2 Vaccine

Bioreactor

Quality Testing

Plasmid DNA Template

In vitro

Transcription

Quality Testing

RNA

Purification

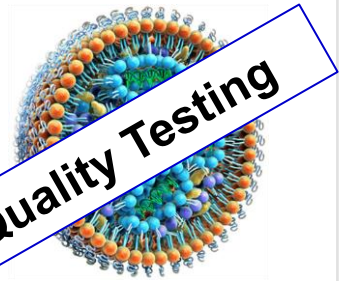
Quality Testing

Drug Substance

Mixer

Quality Testing

Lipids



Quality Testing

Lipid Nanoparticle

Purification

Quality Testing

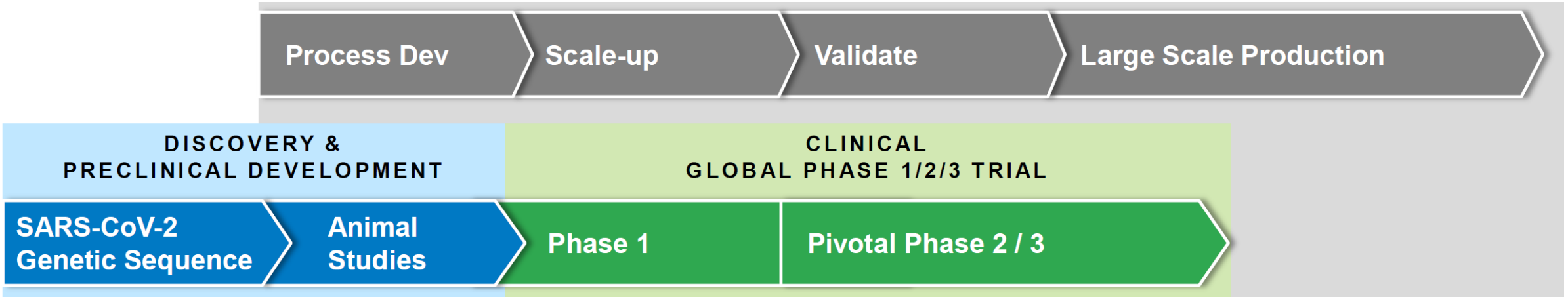
Bulk Drug Product

Fill and Finish

Quality Testing

Drug Product

BNT162b2 Vaccine Analytical Development Timeline



Rapid implementation of platform assays to enable Phase I start

Support process development, product characterization, and multi-site PV/PPQ for DS and DP

Product lifecycle support

Develop & validate novel QC assays for DS and DP

QC release and stability testing with industry-leading cycle times

Define control strategy

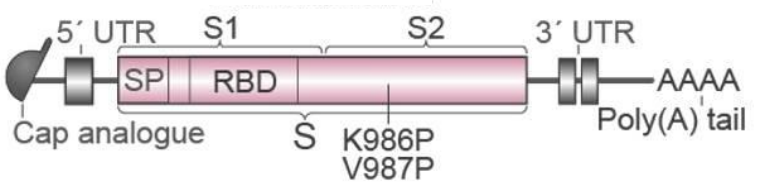
Validation of platform assays across multiple sites for DS and DP

Establish dedicated QC labs to enable rapid vaccine launch

Expand QC network to support global manufacturing & supply demand

BNT162b2 messenger RNA Drug Substance Quality Control Strategy

mRNA Encoding Spike Protein



5' – Cap attributes by LC/MS & LC/UV

Poly(A) Tail attributes by PCR and LC/UV-MS

Platform QC Assays

- Compendial methods
- Purity by Capillary Gel Electrophoresis
- Concentration by UV spectroscopy
- Identity, Impurities by PCR-based methods
- Purity by Immunoblot

Characterization Assays

- NextGen Sequencing (NGS)
- Nucleoside/tide and Oligonucleotide mapping LC-MS/MS
- Higher Order Structure by Circular Dichroism (CD)
- Protein Expression Western Analysis

BNT162b2 Lipid Nanoparticle Drug Product Quality Control Strategy

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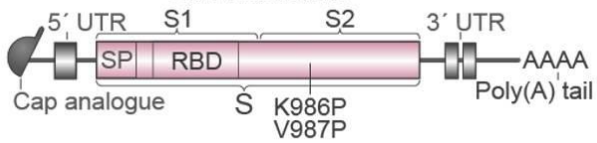
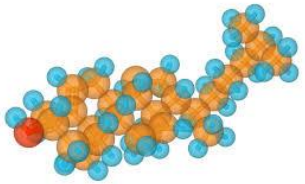
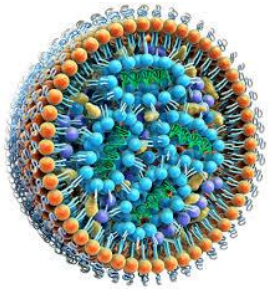


Four Functional & Structural Lipids





Lipid Nanoparticle

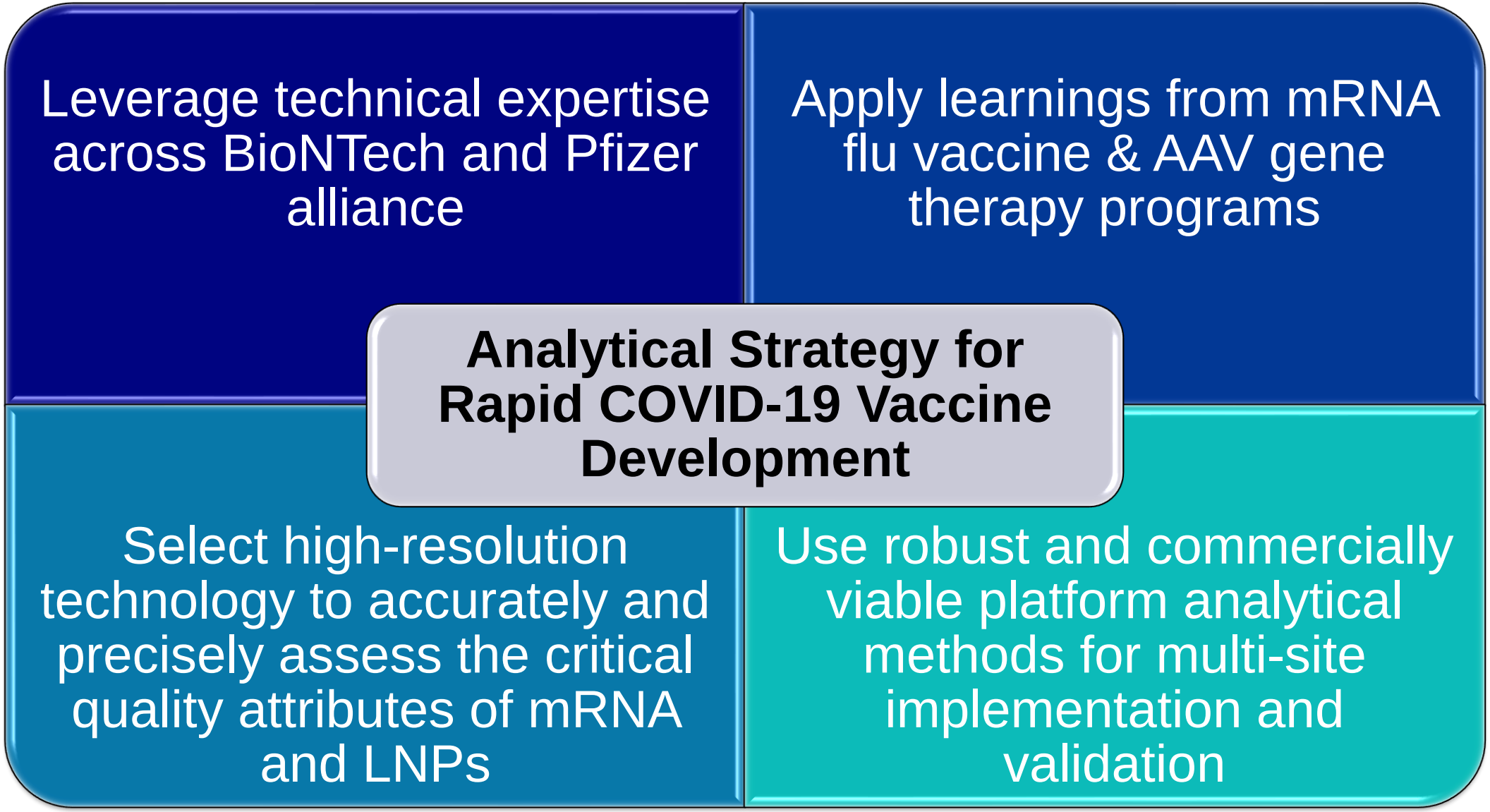
Lipid ID and Content by LC-CAD
LNP Size and Polydispersity by DLS
In Vitro Expression by Cell-based FACS

Platform QC Assays

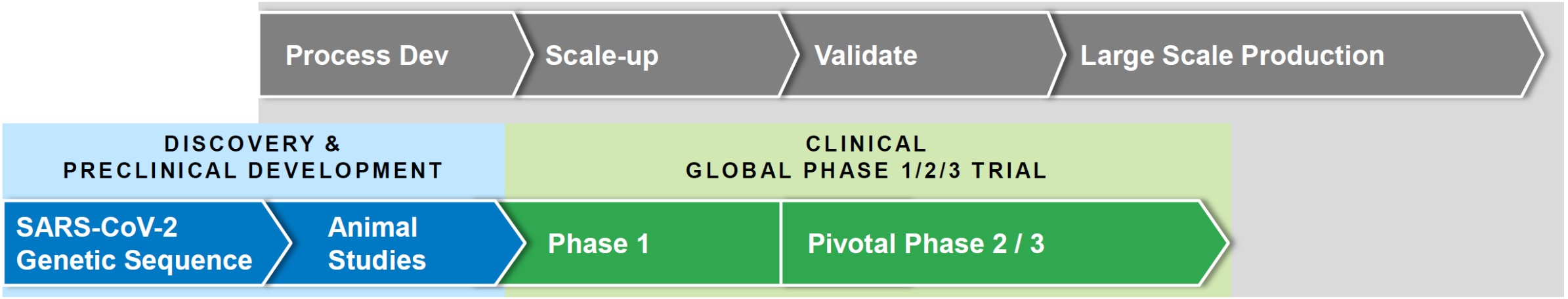
- Compendial & Safety methods
- Purity by Capillary Gel Electrophoresis
- Content, RNA Encapsulation by Fluorescence Assay
- Identity by PCR-based method

Characterization Assays

- Lipid ID and content by LC-MS
- LNP surface properties by high-field NMR
- LNP surface charge by Zeta potential
- Orthogonal size measurements


Leverage technical expertise across BioNTech and Pfizer alliance
Apply learnings from mRNA flu vaccine & AAV gene therapy programs
Analytical Strategy for Rapid COVID-19 Vaccine Development
Select high-resolution technology to accurately and precisely assess the critical quality attributes of mRNA and LNPs
Use robust and commercially viable platform analytical methods for multi-site implementation and validation

BNT162b2 Vaccine Analytical Development Timeline



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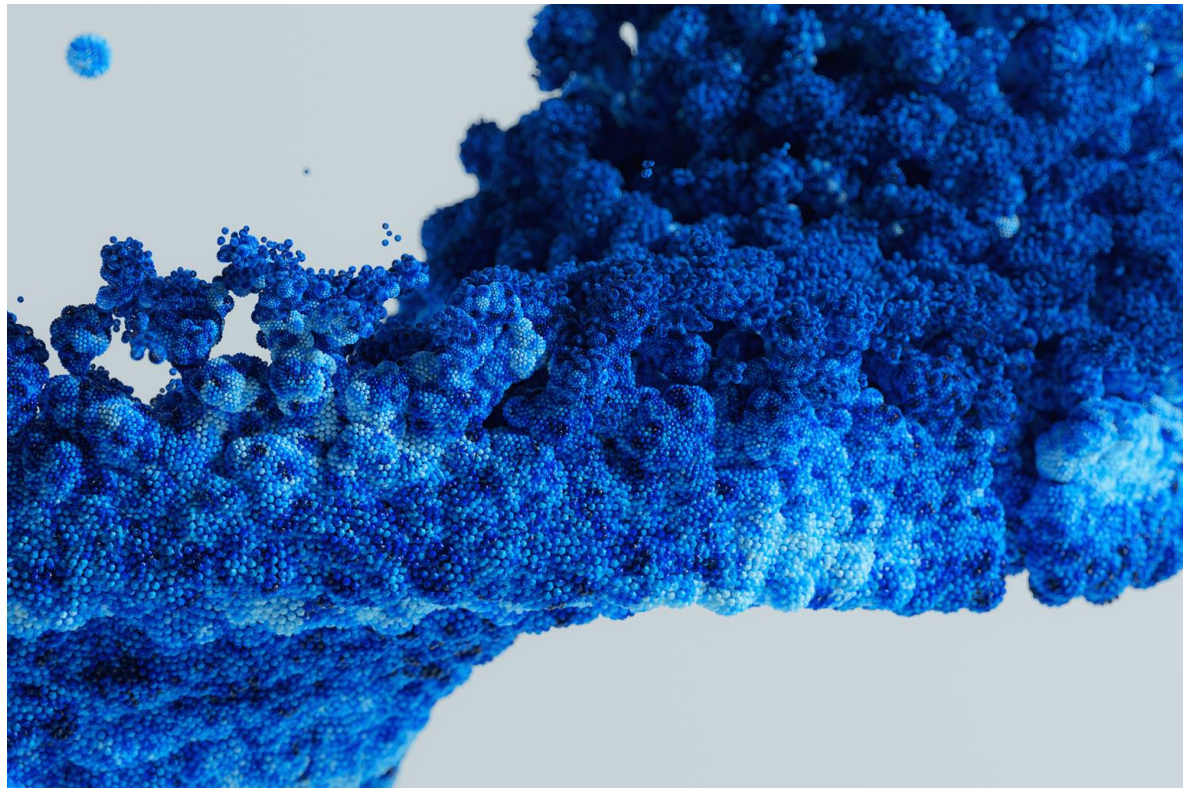
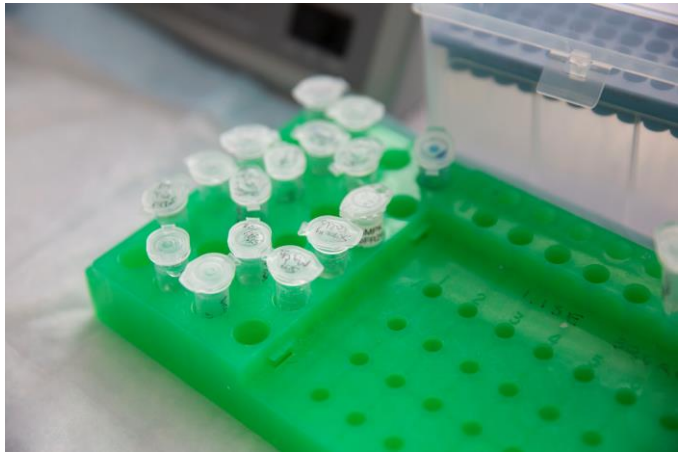
Pfizer

Product Lifecycle Support - Toolbox to Accelerate mRNA Therapeutics

- Industry alignment for mRNA therapeutics
- Platforming analytical methods
- mRNA validation strategy
- Leverage big data
- Collaboration and innovation for future platform technology



Industry Alignment for mRNA Therapeutics



- Evolving USP draft for mRNA
- mRNA quality attribute alignment across industry
- Focused menu of successful analytical tools to monitor CQAs
- Accelerate product development & regulatory confidence
- Industry, academia, and government to shape guidance, Pfizer joining effort

Platforming Analytical Methods

- Platform definition:
  - ICH Q2 (R2) draft guidance

505 **PLATFORM ANALYTICAL PROCEDURE**

506 A platform analytical procedure can be defined as a multi-product method suitable to test
507 quality attributes of different products without significant change to its operational conditions,
508 system suitability and reporting structure. This type of method would apply to molecules that
509 are sufficiently alike with respect to the attributes that the platform method is intended to
510 measure. (ICH Q2)

- Apply robust methods to highly similar/identical attributes
- Enable rapid analytical support for variants and new products

mRNA Validation Strategy For Variants and Follow-on Constructs

- Strategic pathway to apply original validation to new mRNA strain
  - Platform method requires no/minor operational changes
  - Conditional verification activities may be required

Example of application….

mRNA Validation Strategy For Variants and Follow-on Constructs

Extension of Validation

Scientific Rationale

- Attribute measured unaffected by sequence change
- Justification to waive additional laboratory verification
- Document rationale

Laboratory Verification

- Confirm expected results under real laboratory conditions
- Under protocol
- Predefined acceptance criteria
- Document rationale and data

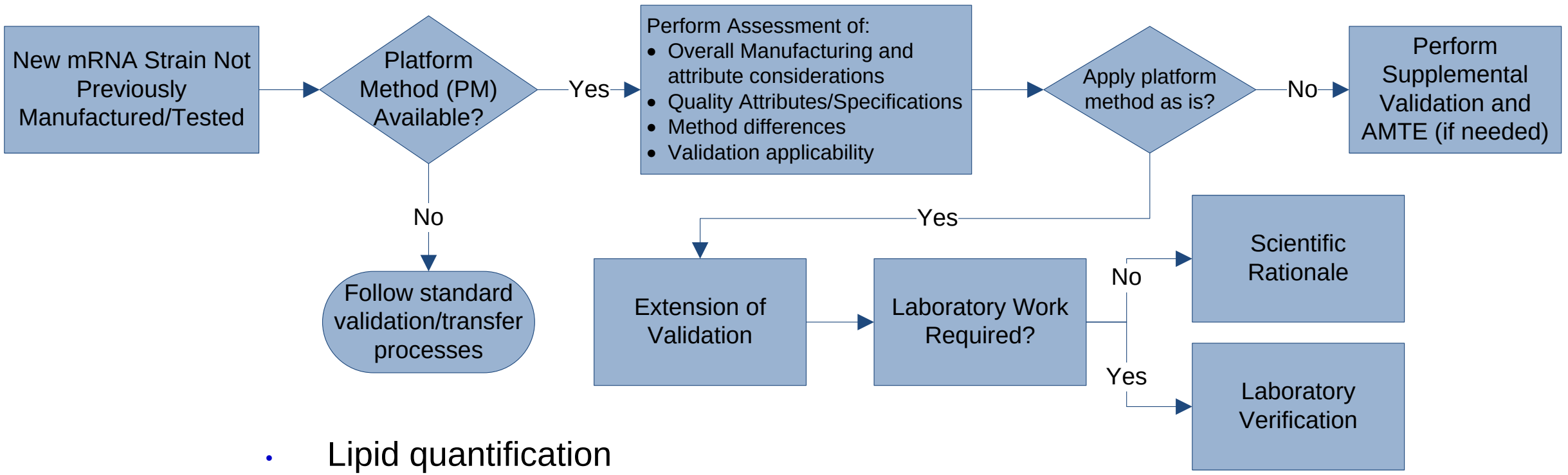
Supplemental Validation

- Challenge of additional ICH Q2 (R1) characteristics
- Under protocol
- Predefined acceptance criteria
- Document rationale and data

New Methodology/New Attribute

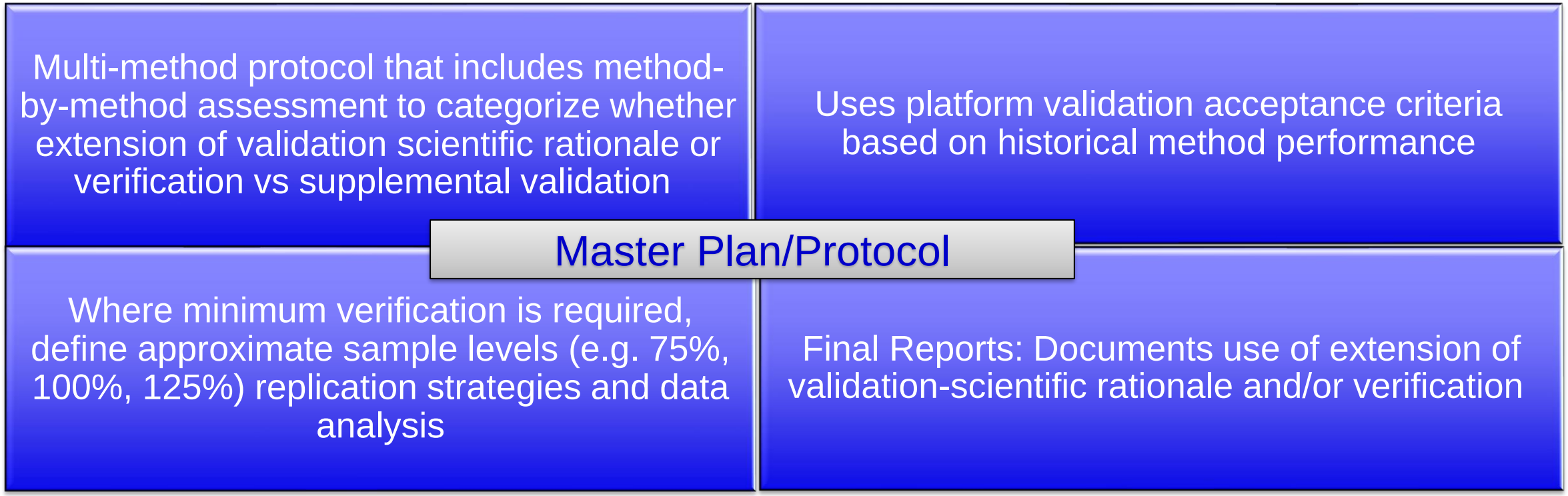
- New validation required
- New protocol
- Pre-defined acceptance criteria
- Documented in new validation report

mRNA Validation Strategy Flow Chart



- Lipid quantification
  - Extension of validation via scientific rationale
- RNA integrity
  - Extension of validation via laboratory verification

How to Manage Document Workflow
Putting the Pieces Together



Regulatory Filing Strategy For Platform Analytical Procedures

- Full description of validation strategy provided in the M3 3.2.S.4.3 and 3.2.P.5.3 Validation of Analytical Procedures - Overviews covering details on the various validation scenarios
- Provide platform method validation data and any additional data supporting the specific validation scenario for new product or strain
- Critical reagent details specific to a product or strain are left out of 3.2.S.4.2 and 3.2.P.5.2 Analytical Procedures and refer to validation section (i.e. Identity)

Case Study: Filing Strategy for Platform Methods

Table 3.2.S.4.3-1. Summary of Product Analytical Procedure Validations				
Analytical Procedure	**Quality Attribute**	**Mode of Validation**	**Platform Validation**	**Source Document**
UV Spectroscopy	Concentration	Extension of Validation	Report XXX	3.2.S.4.3 Validation of Analytical Procedures – Concentration by UV Spectroscopy
PCR	Identity	Validation	NA	Report XXX
Capillary Gel Electrophoresis	Purity	Supplemental Validation to include new kit	Report XXX	Report XXX

Platform validation directly linked unless procedure is fully validated for product XXX

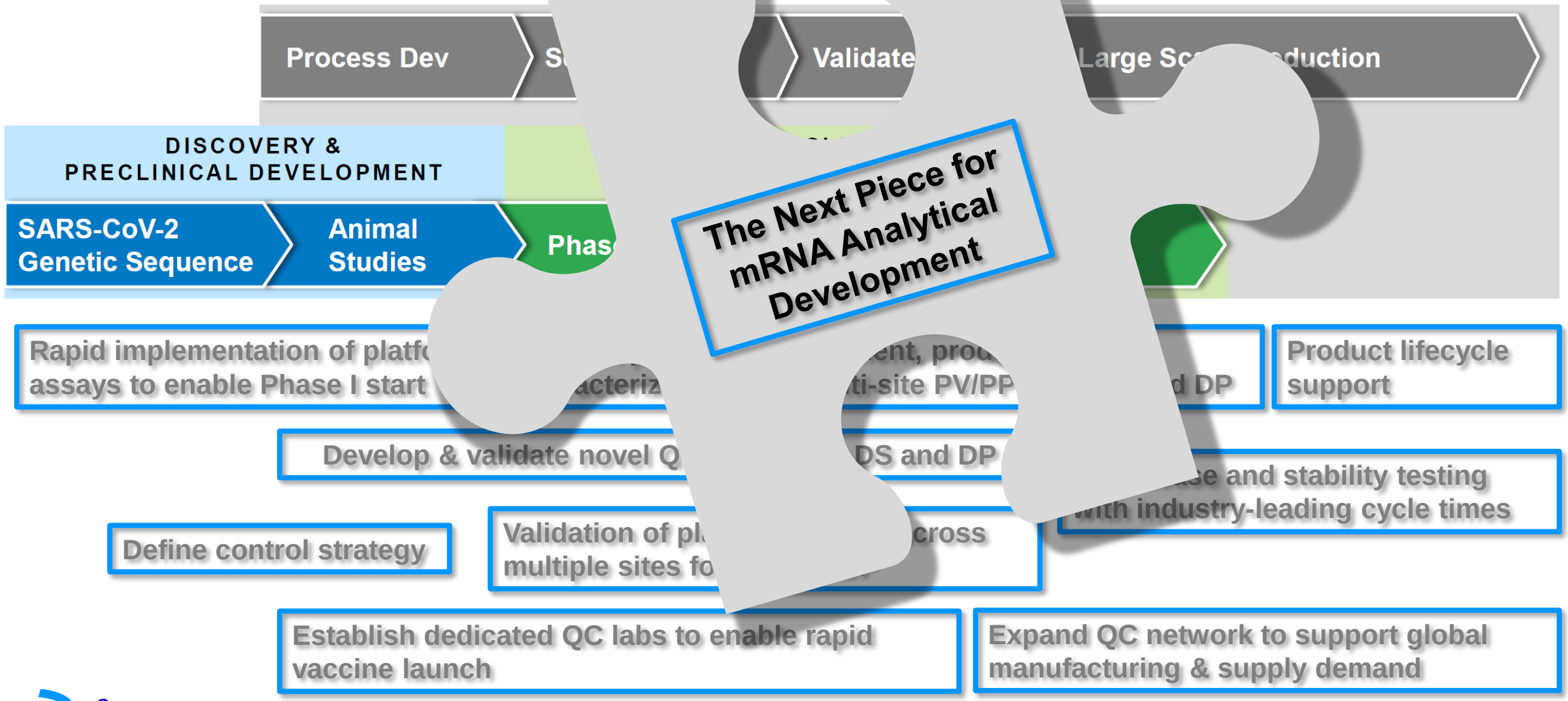
An S.4.3 specific to the procedure is only provided for scientific rationale

Critical reagent details found in these reports, not in S.4.2

Analytical Regulatory Filing Strategies to Reduce Life-Cycle Management Submissions

- Provide an analytical method transfer protocol in 3.2.S.4.3 and 3.2.P.5.3, where possible
  - Allows path for quick and efficient onboarding of future network testing sites
    - Needed for testing flexibility as the pipeline changes/progresses

BNT162b2 Vaccine Analytical De ent Timeline



Blaze A Trail to New Platform Analytics!

What worked, and what can be improved?

Where are more precise instruments needed?

What industry trends will challenge analytics?

Build on success of partnerships

Forge new alliances and consortiums

Vendors, Industry, Academia

Closer to Home!

Thank you!

To an incredible cross-functional team too large to list individually:

BioNTech:

- BioNTech SE (Mainz, Germany)
- BioNTech RNA Process Development
- BioNTech RNA Analytics
- BioNTech IMFS (Idar-Oberstein, Germany)

Pfizer:

- Pfizer Vaccine Research Division (Pearl River, NY)
- Pfizer Pharmaceutical Sciences (Chesterfield, MO and Andover, MA)
- Analytical Research & Development
- Bioprocess Research & Development
- Pharmaceutical Research & Development
- Pfizer Global Supply (Andover, MA; Grange Castle, Ireland; Kalamazoo, MI; Puurs, Belgium)

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