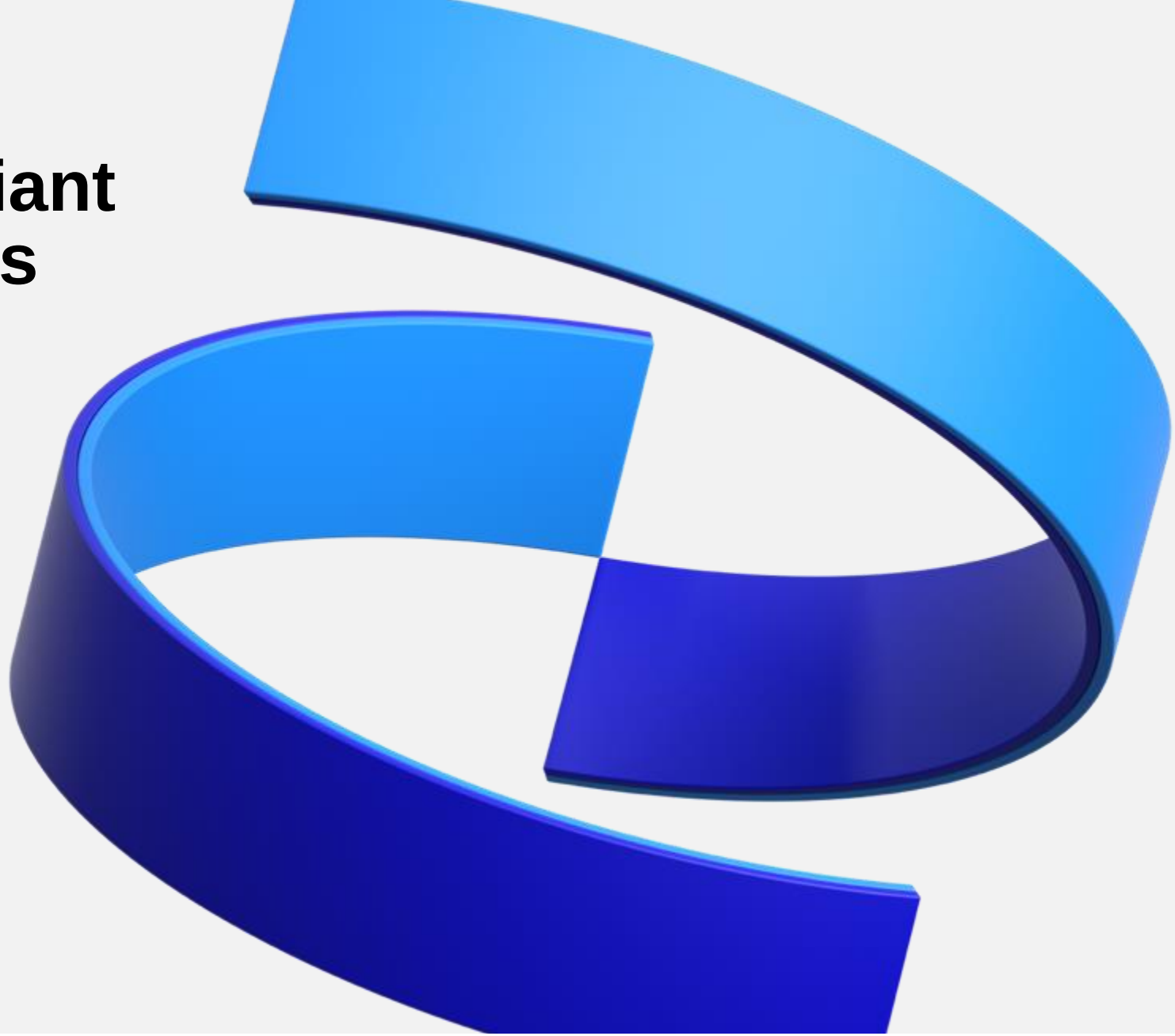
Delivering COVID Variant Vaccines in ≤ 100 days



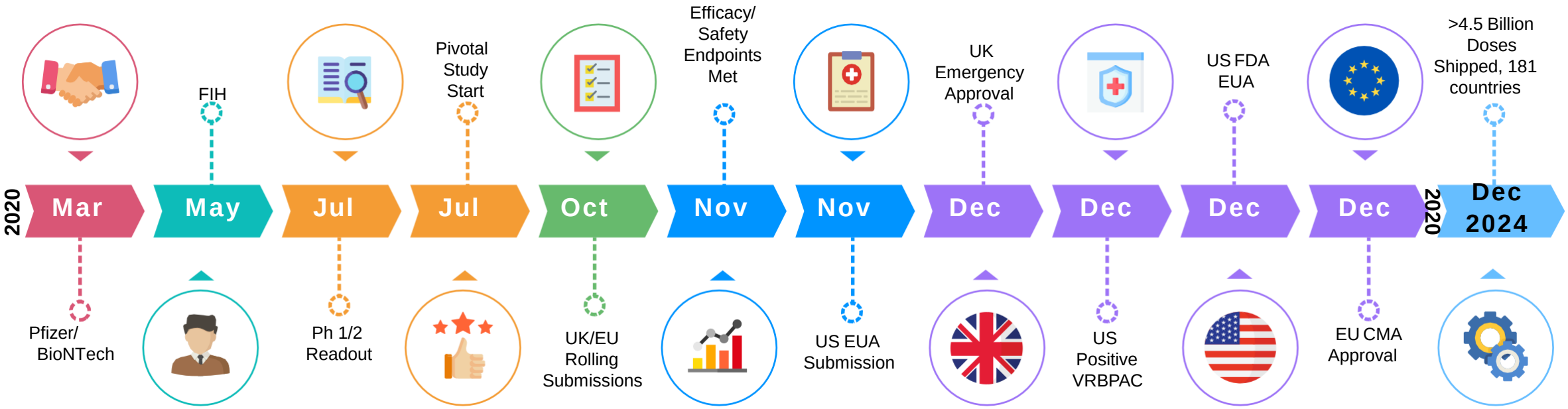
Carly Daniels
On behalf of the entire team

Analytical R&D
Biotherapeutics Pharm. Sci
Pfizer Inc., Chesterfield, MO

Outline

1. Background
2. Variants of Concern
3. Adapting the COVID Platform
4. Bivalent Vaccines
5. Conclusions

Global Pandemic to Initial Vaccine Authorization



VRBPAC (Vaccines and Related Biological Products Advisory Committee); FIH (First in Human); CMA (Conditional Marketing Authorization); EUA (Emergency Use Authorization)

Global Pandemic to Initial Vaccine Authorization

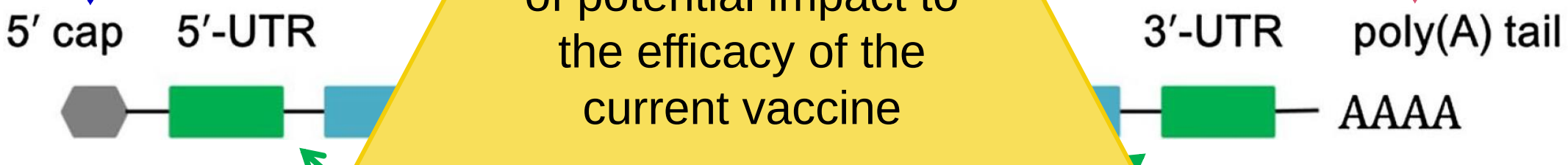
COVID Variants

- Variants of concern (VOC)
  - Increased transmissibility
  - Increased virulence
  - Decreased effectiveness of public health measures
    - Current vaccine:

5’ cap
Capping efficiency, cap structure innate sensing, protein synthesis
STABILITY ↑

Poly(A) tail
Tail elongation (length) impacts the stability and translational efficiency
STABILITY ↑

Mutations to the Spike protein in a VOC require an assessment of potential impact to the efficacy of the current vaccine



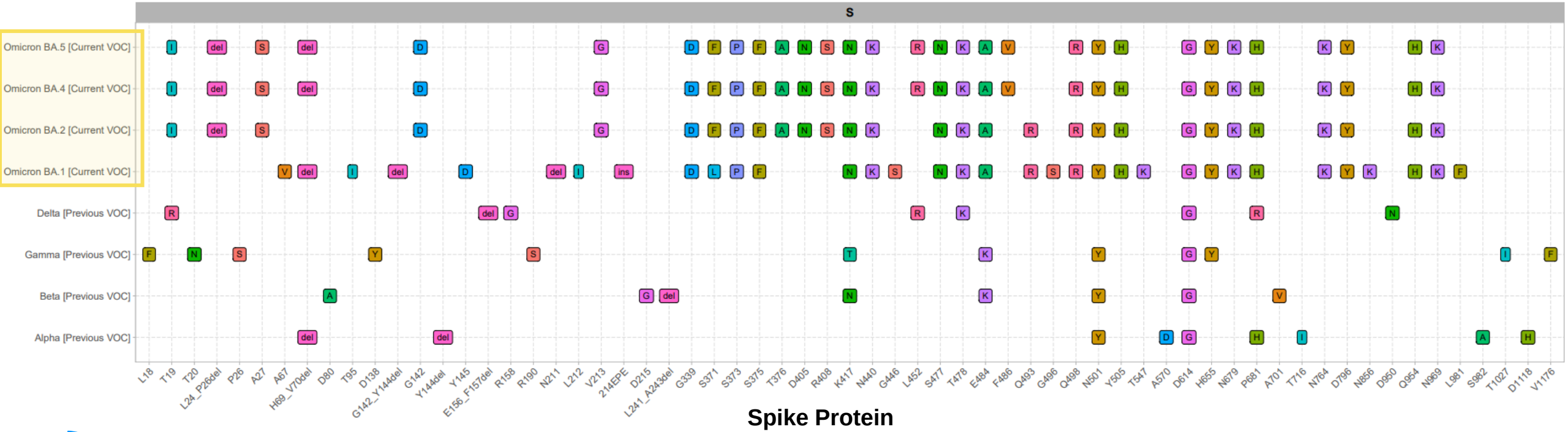
Regulatory elements modulate the translation efficiency with their length and structure

Wrapp et al., 2020, Science.

Adapted from Molecular & Cellular Toxicology (2022) 18:1–8
https://doi.org/10.1007/s13273-021-00171-4

COVID Variant Lineages

- 5 main genetic lineages that WHO has tracked:
  - Alpha
  - Beta
  - Gamma
  - Delta
  - Omicron
- Omicron is the most prevalent, and several genetic sublineages of Omicron have become VOCs



COVID Variant Lineages

- 5 main genetic lineages that WHO has tracked:
  - Alpha
  - Beta

Data analysis shows omicron variant less severe, better at evading vaccines

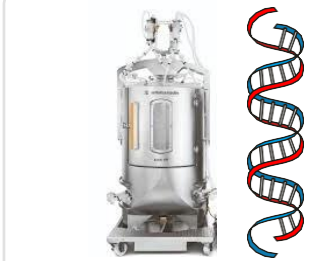
Health Dec 14, 2021 10:34 AM EST

Developing a 100-Day Plan

- Critical to leverage as much historical knowledge, experience, and data as possible
- Teams focused across the entire Pfizer/BioNTech network
- All work done proactively/at-risk
- Early, high-level feedback from regulators

An mRNA Platform

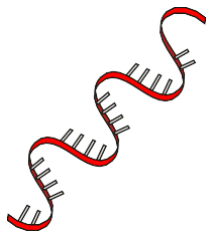
Bioreactor



Plasmid DNA Template

In vitro

Transcription

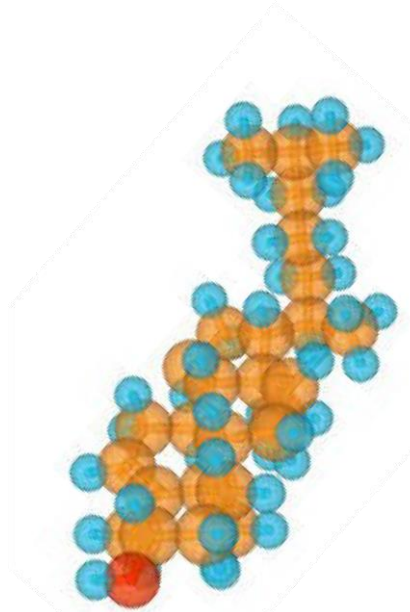


RNA

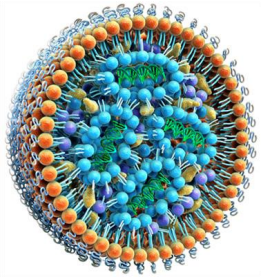
Purification

Drug Substance

Mix



Lipids



Lipid Nanoparticle

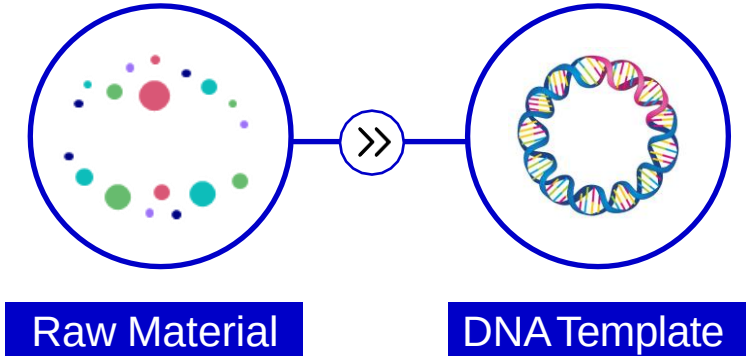
Purification

Bulk Drug Product

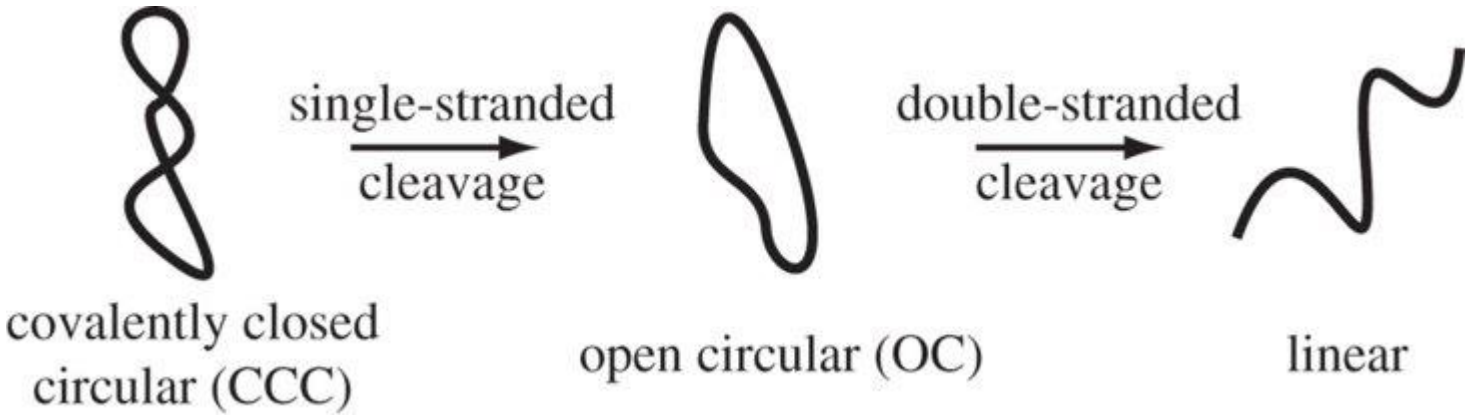
Fill and Finish

Drug Product

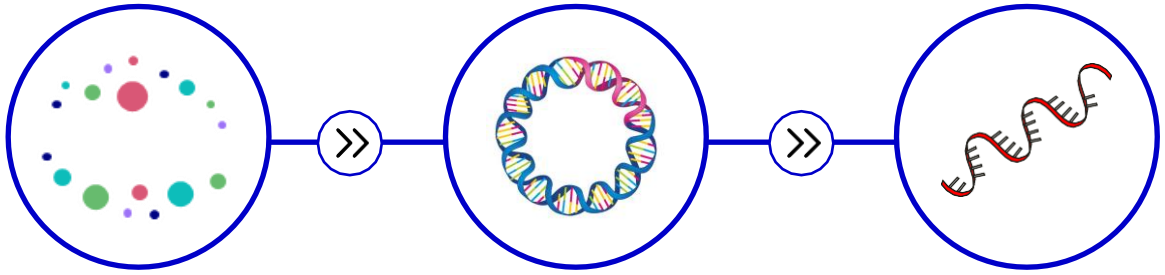
mRNA Platform: Plasmid



- With mutations in the COVID virus Spike protein, the plasmid DNA starting template was adapted to match the mutated variant Spike protein
- The original COVID vaccine leveraged Pfizer's internal pDNA platform expertise built for gene therapy programs
- This pDNA platform was utilized for the quickly evolving variant vaccines, allowing for rapid progression from raw material to DNA template

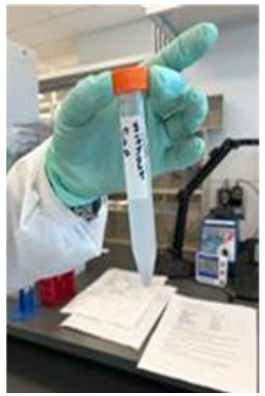


mRNA Platform: Drug Substance



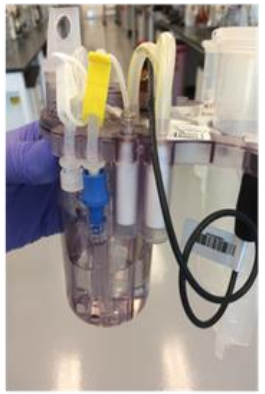
- Pfizer/BioNTech began an mRNA influenza collaboration in 2018, which enabled the rapid development of the COVID vaccine
- The influenza and COVID mRNA experience led to a robust, platform mRNA synthesis process using in vitro transcription (IVT)
- The adapted pDNA containing the COVID variant Spike protein mutations was processed through the platform IVT process

5 mL



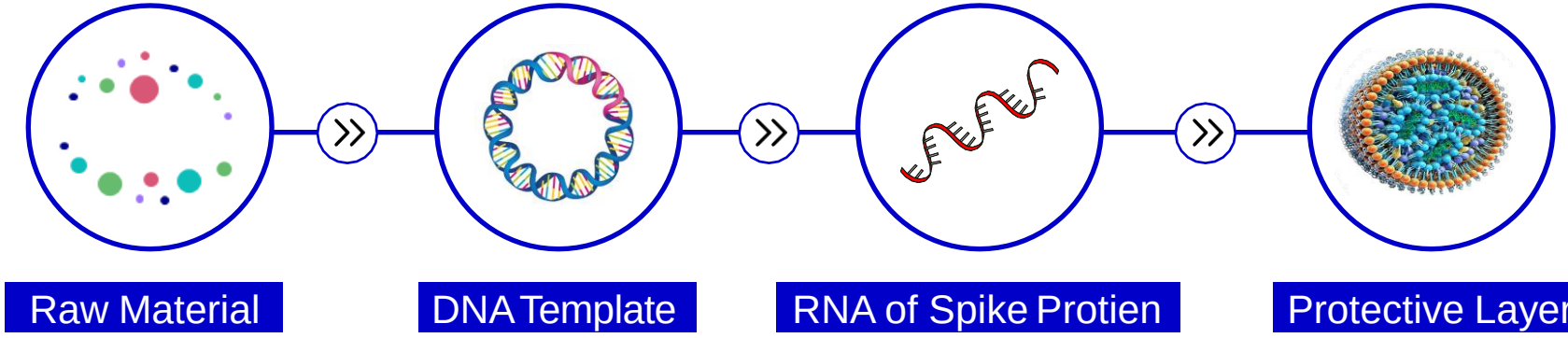
15 mL

250 mL



Commercial Scale

mRNA Platform: Drug Product



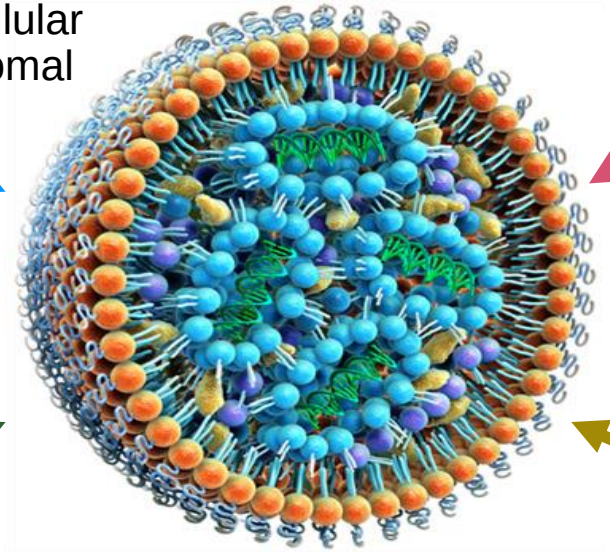
- Lipid nanoparticle (LNP) formation process was established through development of the Original COVID vaccine
- COVID variant vaccine utilized the same formulation and process, which allowed for leveraging of historical knowledge, experience, and data

Ionizable Cationic Lipid

Regulates particle formation, cellular uptake, fusogenicity and endosomal release of RNA

PEG-Lipid

Provides a protective hydrophilic layer for LNP colloidal stabilization and control of circulation and cellular uptake



Structural Lipid #1

Provides structural stability and facilitates endosomal escape

Supports optimal size, encapsulation, and stability properties

Structural Lipid #2

Provides structural stability and facilitates endosomal escape

mRNA Platform: Analytics

ICH Q2 (R2) Guidance, Implementation Phase 4

From Introduction...

"When an established platform analytical procedure is used for a new purpose, validation testing can be abbreviated, if scientifically justified."

From Glossary Definitions: Platform Analytical Procedure

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

WHO/BS/2023.2442

"A platform would be considered when the elements of the manufacturing methods and/or processes, the mAb protein scaffold, and the compliance with GMP are unchanged. The experience and knowledge gained, data generated (from manufacturing, control, and stability), and the validation of unchanged methods can all be used as supportive data for the more rapid assessment and development of a new mAb product candidate that fits within the boundaries of the platform."

mRNA Platform: Analytics

New mRNA Variant

Applicability Assessment

- Manufacturing process
- Quality attributes
- Platform method operating parameters/differences
- Validation applicability

Extension of Validation

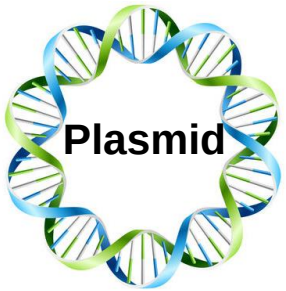
UV Spectroscopy	Capillary Gel Electrophoresis	Critical Parameter Change (Kit, Primer / Probe)
Scientific Rationale	**Laboratory Verification**	**Supplemental Validation**
• Attribute measured unaffected by sequence change • Document scientific rationale	• Confirm expected result under real laboratory condition • Under protocol • Predefined acceptance criteria • Document scientific rationale & data	• Challenge of additional ICH Q2 • Under protocol • Predefined acceptance criteria • Document Rationale & data

Non-platform method will require product-specific full validation

Having common structural elements with only the codon-optimized sequence encoding the target antigen being unique to each new mRNA construct/variant makes mRNA a good candidate to adopt platforming strategy

mRNA Platform: Analytics

- Leveraging the existing platform pDNA process for the COVID variant vaccine limited the impact to analytical methods
- Validated methods, significant process knowledge and product understanding through characterization, process validation, and commercial experience laid foundation for strong analytical platform
- Analytical method impact assessment focused on the changes in pDNA sequence
  - Omicron variant molecular properties were highly similar to the Original vaccine



Compendial methods

Concentration

Identity ----------→ Need to be able to identify the variant sequence

Purity (topology)

Purity (process-related impurities)

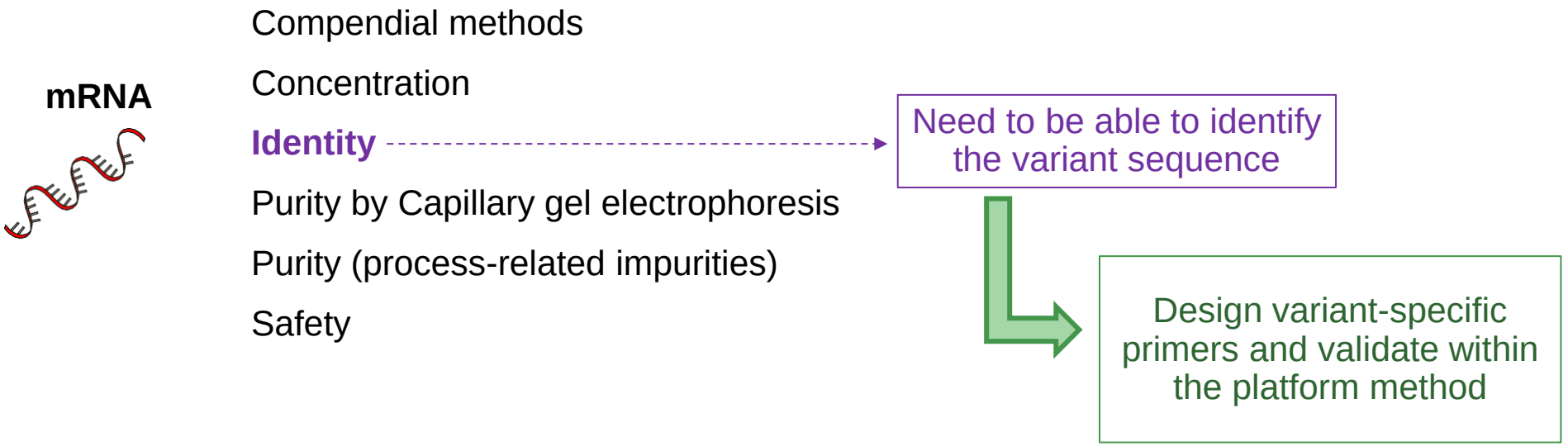
Safety

↓

Design variant-specific primers and validate within the platform method

mRNA Platform: Analytics

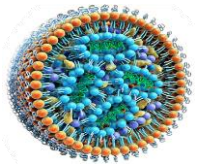
- Leveraging the existing platform mRNA process for the COVID variant vaccine limited the impact to analytical methods
- Analytical method impact assessment focused on the changes in mRNA sequence
  - Omicron variant molecular properties were highly similar to the Original vaccine



mRNA Platform: Analytics

- Leveraging the existing platform LNP process for the COVID variant vaccine limited the impact to analytical methods
- Analytical method impact assessment focused on the changes in mRNA sequence
  - Omicron variant molecular properties were highly similar to the Original vaccine

LNP



Compendial methods

Concentration

Identity ----------→ Need to be able to identify the variant sequence

RNA encapsulation

Potency ----------→ Do mutations in the Spike protein impact detection by the potency assay?

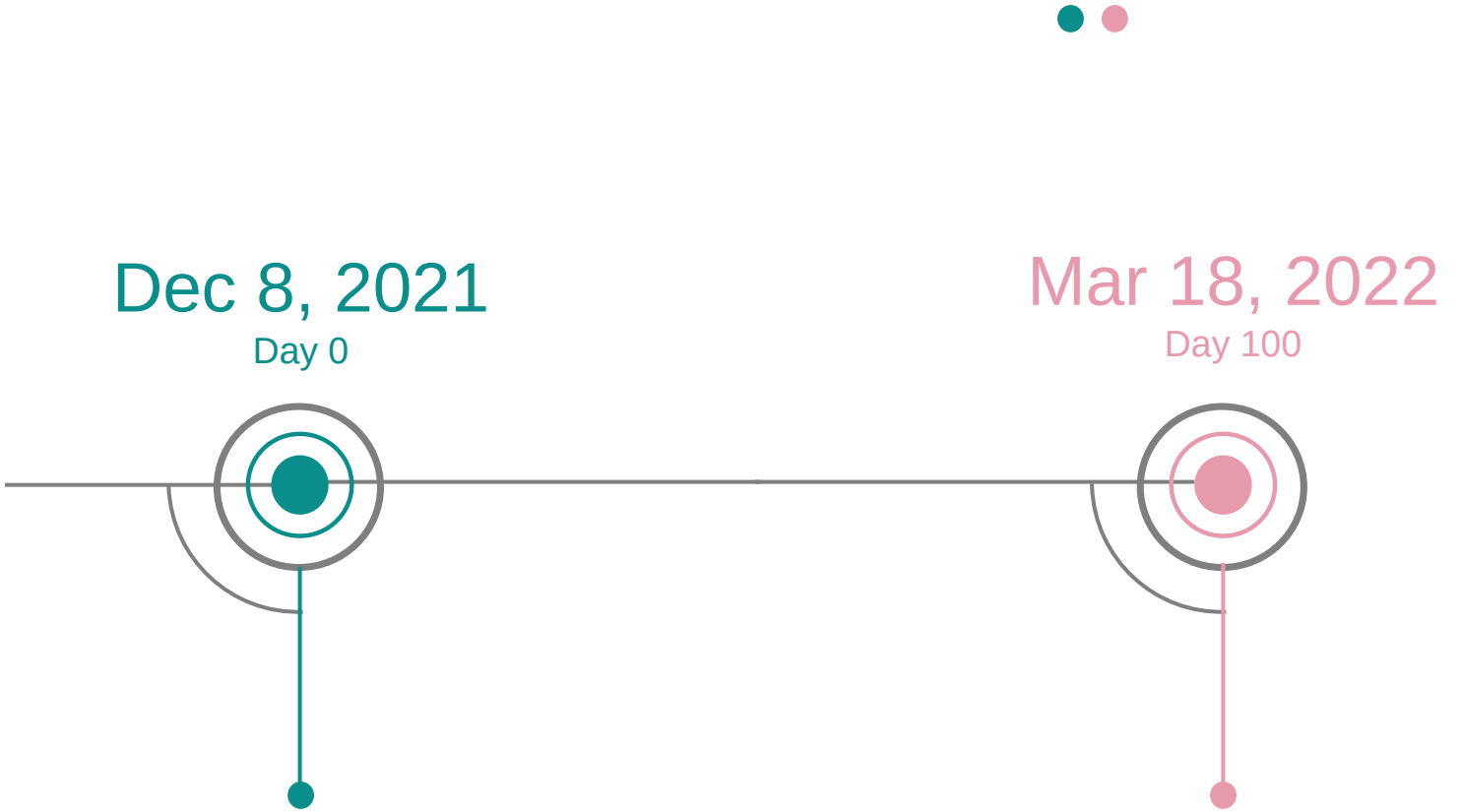
Purity by Capillary gel electrophoresis

Safety

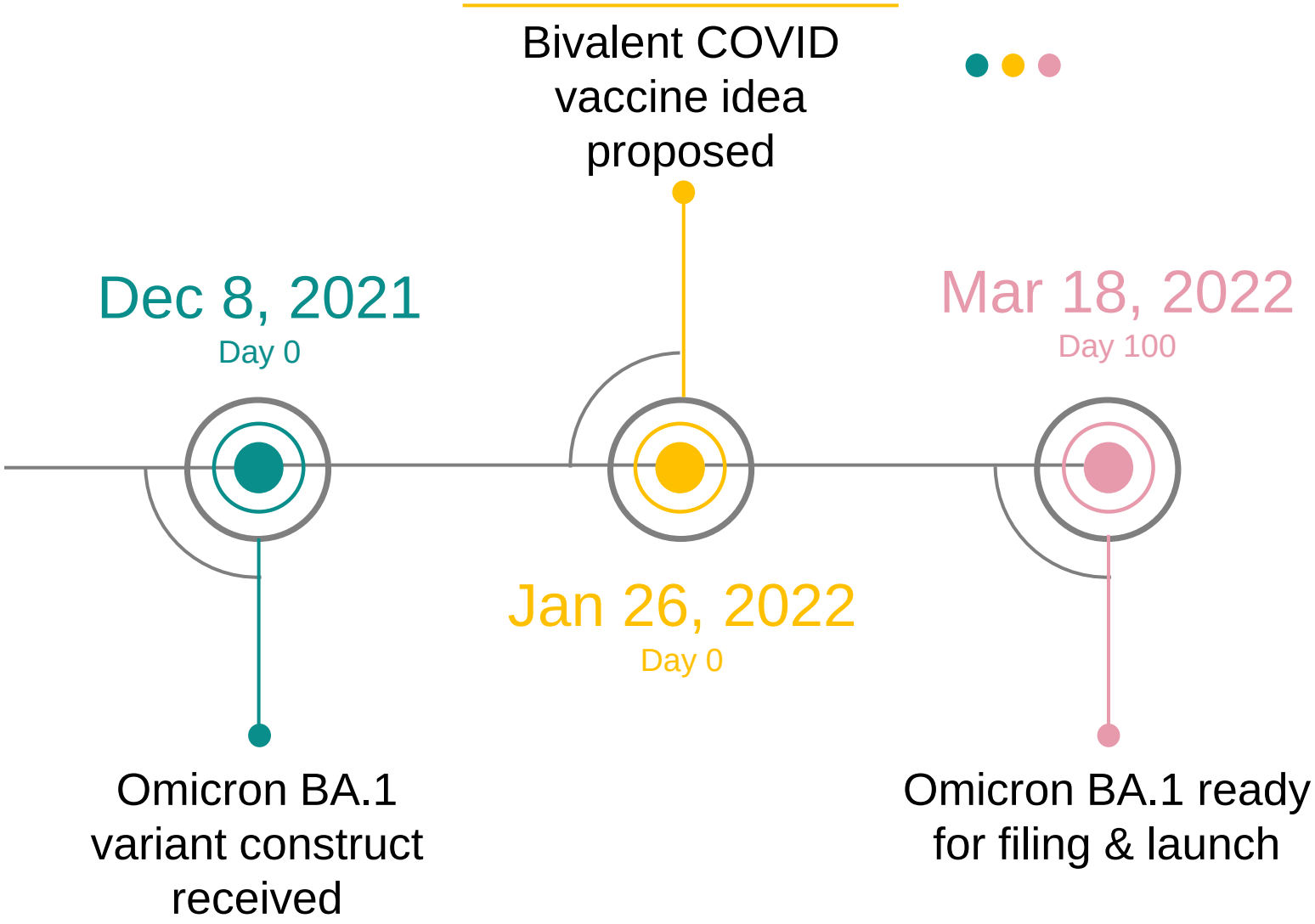
Design variant-specific primers and validate within the platform method

Identify robust antibody and validate within the platform method

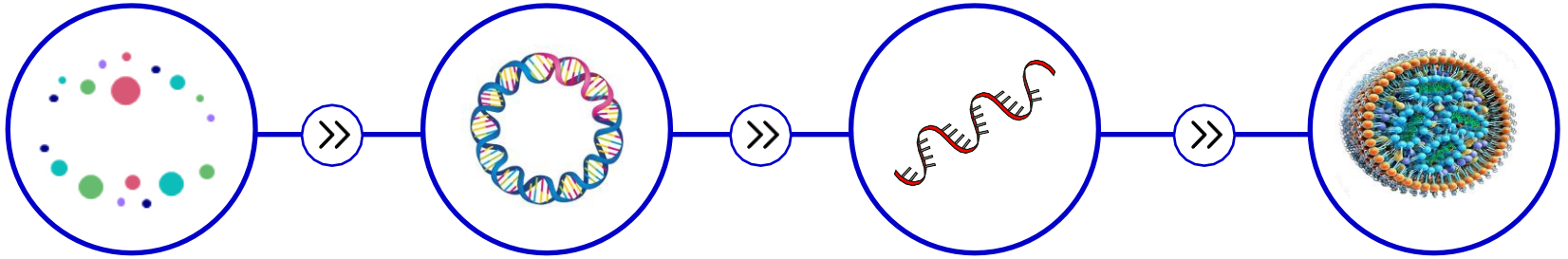
COVID Variant in 100 Days



COVID Variant in 100 Days to Bivalent COVID in 100 Days



mRNA Platform: Bivalent Drug Product



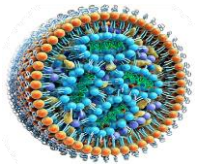
- Team was able to pivot quickly to a bivalent drug product due to:
  - Unchanged formulation
  - Same overall LNP process
  - Final concentration of total mRNA in DP remained unchanged
    - Converted to a 1:1 ratio for the Original and Omicron variant
- Sufficient mixing demonstrated through characterization studies

Lipid Nanoparticle

Bivalent mRNA Platform: Analytics

- Leveraging the existing platform LNP process for the COVID variant vaccine limited the impact to analytical methods
- Analytical method impact assessment focused on the changes in mRNA sequence
  - Omicron variant molecular properties were highly similar to the Original vaccine

LNP



Compendial methods

Concentration

Identity ----------▸ Need to be able to identify both sequences

RNA encapsulation

Potency

Ratio ----------▸ Ensure each sequence is present at the intended level

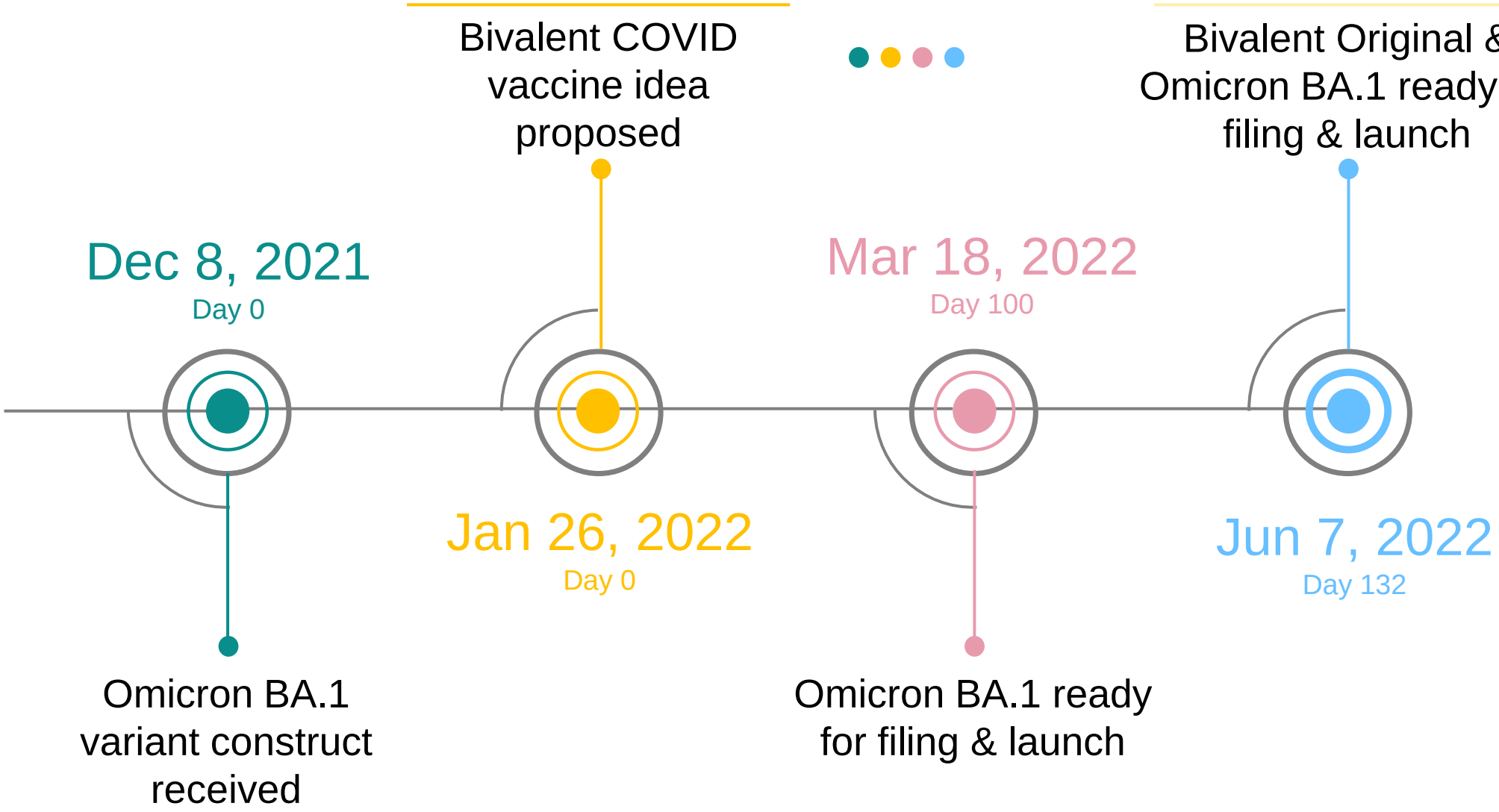
Purity by Capillary gel electrophoresis

Safety

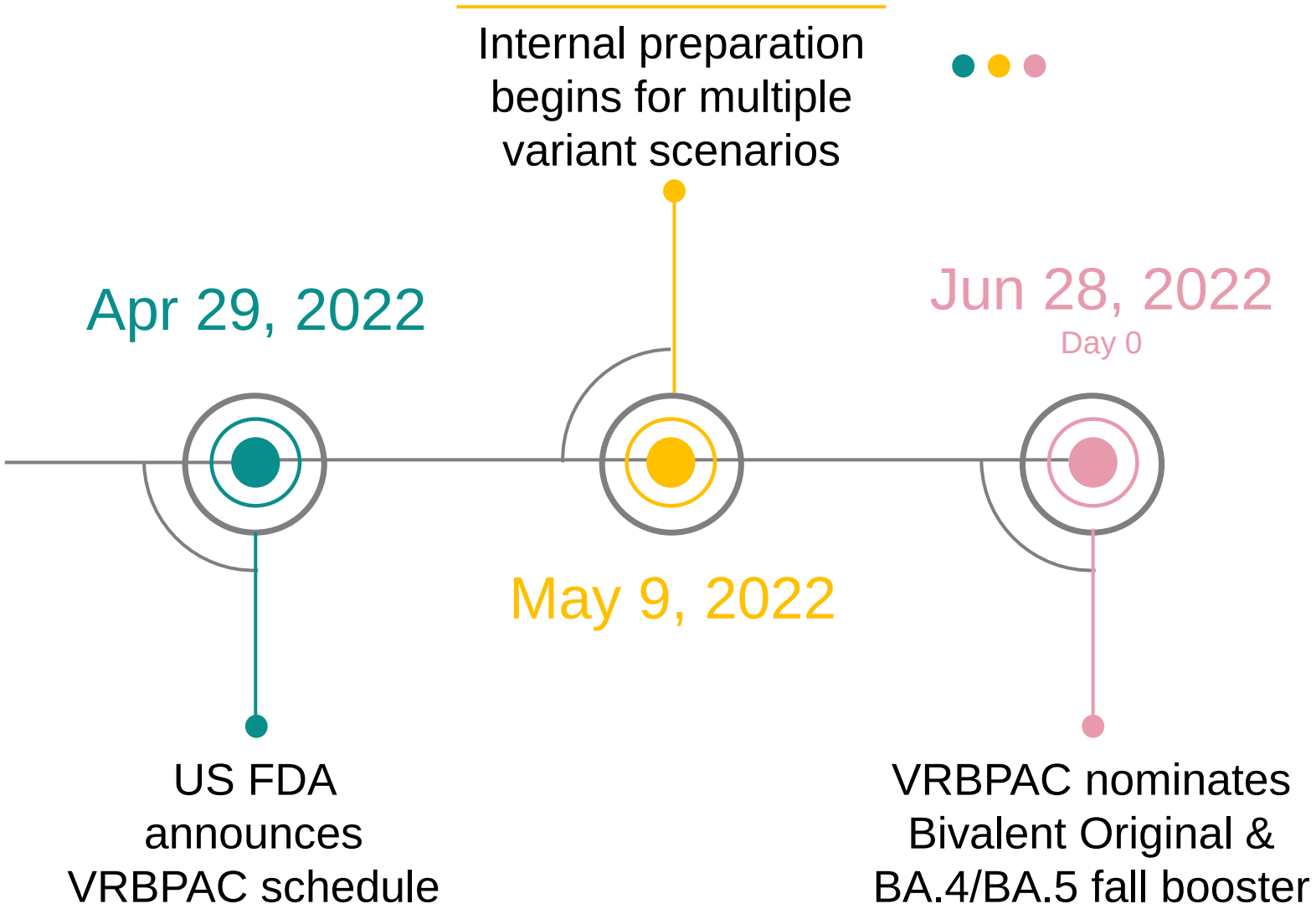
Design variant-specific primers and validate a new method

Design and validate a new method

COVID Variant in 100 Days to Bivalent COVID in 100 Days

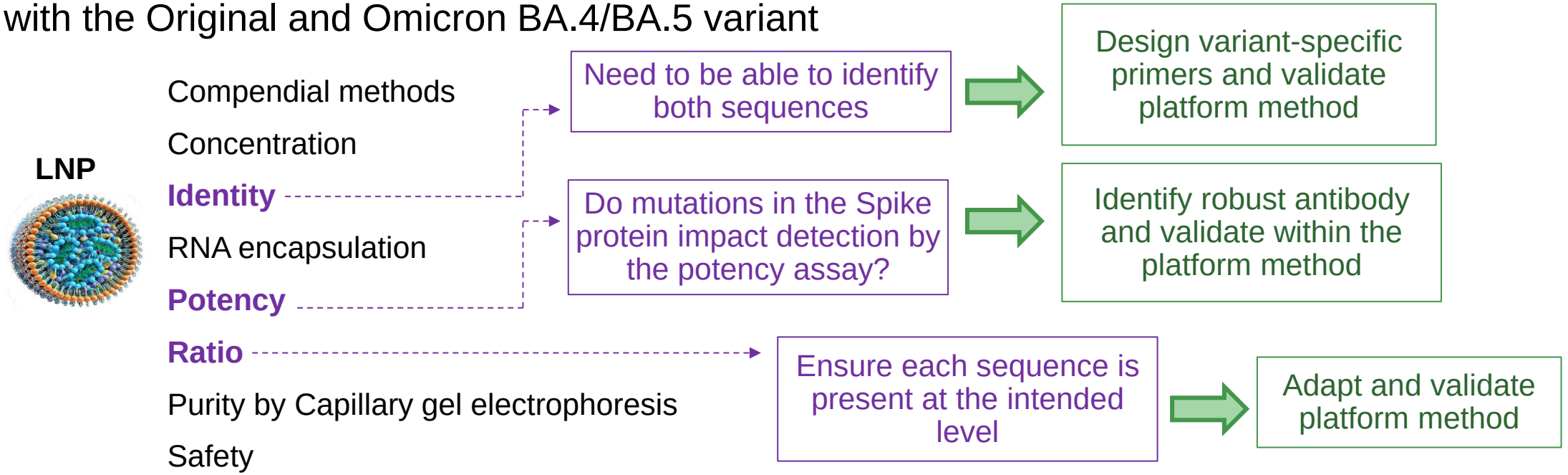


Shifting Variant Landscape

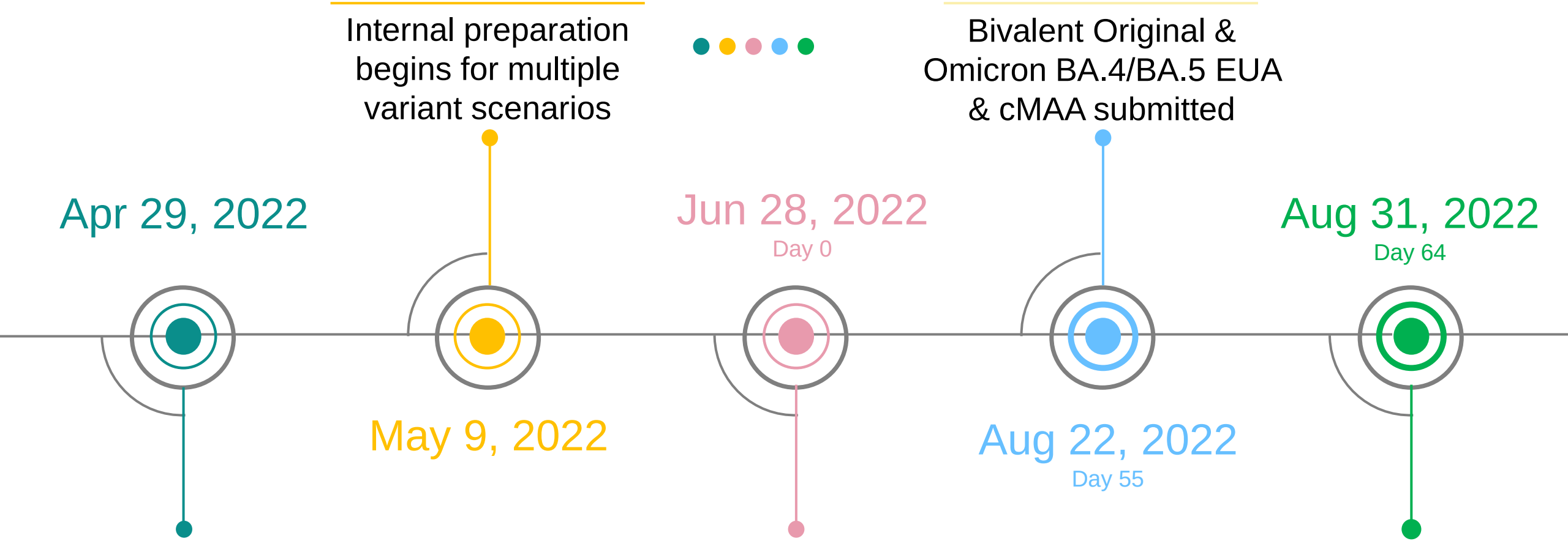


Bivalent mRNA Platform: Analytics

- Prior work focused on the Omicron BA.1 variant
- The global landscape shifted, and the Omicron BA.4/BA.5 sublineage became the predominant variant
- A VRBPAC meeting was held, and the recommendation was made to progress a bivalent fall booster with the Original and Omicron BA.4/BA.5 variant



Delivering a Fall 2022 Booster Vaccine



Key Messages

- Leveraging historical experience and our well-developed platform allowed for rapid response to an evolving variant landscape
- Close collaboration across development and commercial groups enabled ramp up to supplying an adapted vaccine globally
- Clear decisions from health authorities resulted in clear focus area for vaccine adaptation

Thank You

- First responders, healthcare providers and caregivers performing heroic efforts during the pandemic
- Patients, physicians and nurses participating in our clinical trials
- Essential workers, teachers
- Vendors and suppliers who supported us along the way
- Pfizer and BioNTech colleagues and their families

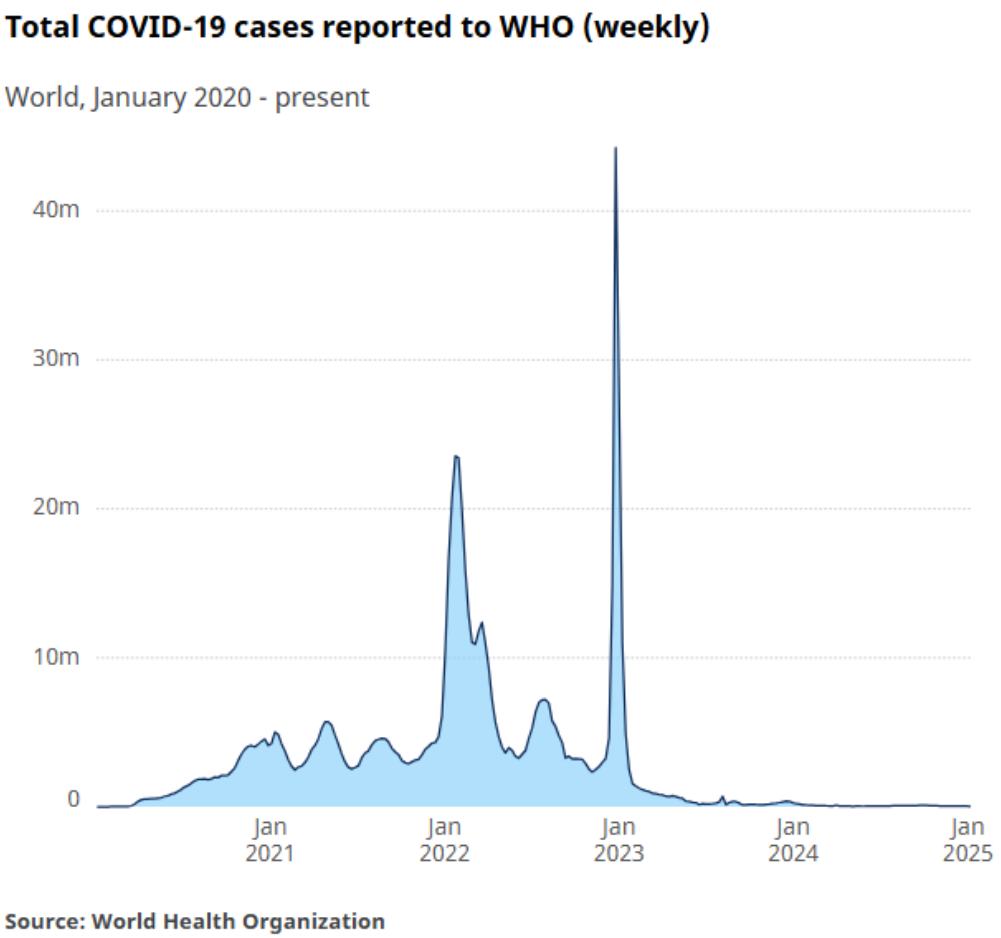
Looking to the Future

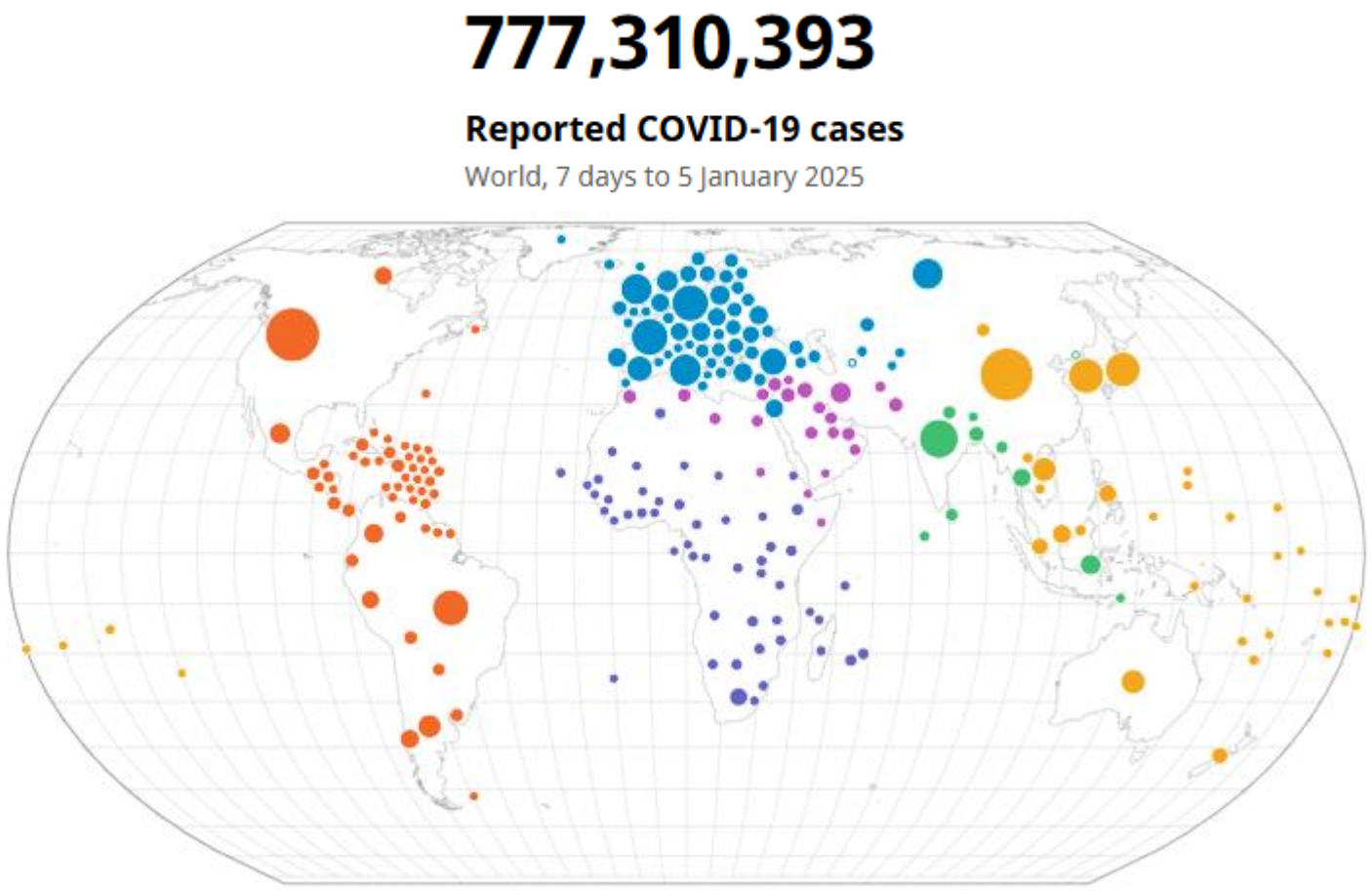
- COVID variants continue to emerge as the virus evolves
- Pfizer/BioNTech continue to prepare for any and all future needs to adapt the COVID vaccine

www.coronavirusremoval.org/covid-vaccinations.html

As of January 23, 2025

Looking to the Future





World Health Organization