Ensuring Quality and Safety of mRNA Vaccines Today & Tomorrow

Sarita K. Acharya, Principal Scientist, Global Biologics, USP

CASSS Discussion Groups, mRNA Vaccines: A Platform in the Making, December 14th, 2022

Agenda

- Introduction to USP
- Supporting vaccine quality
- Introduction to mRNA vaccines
  - What is mRNA and how does it work?
  - mRNA vaccines landscape
- Quality assessment of mRNA vaccines
  - mRNA draft guideline
  - Summary of feedback received to date
  - Next steps
- USP vaccine resources

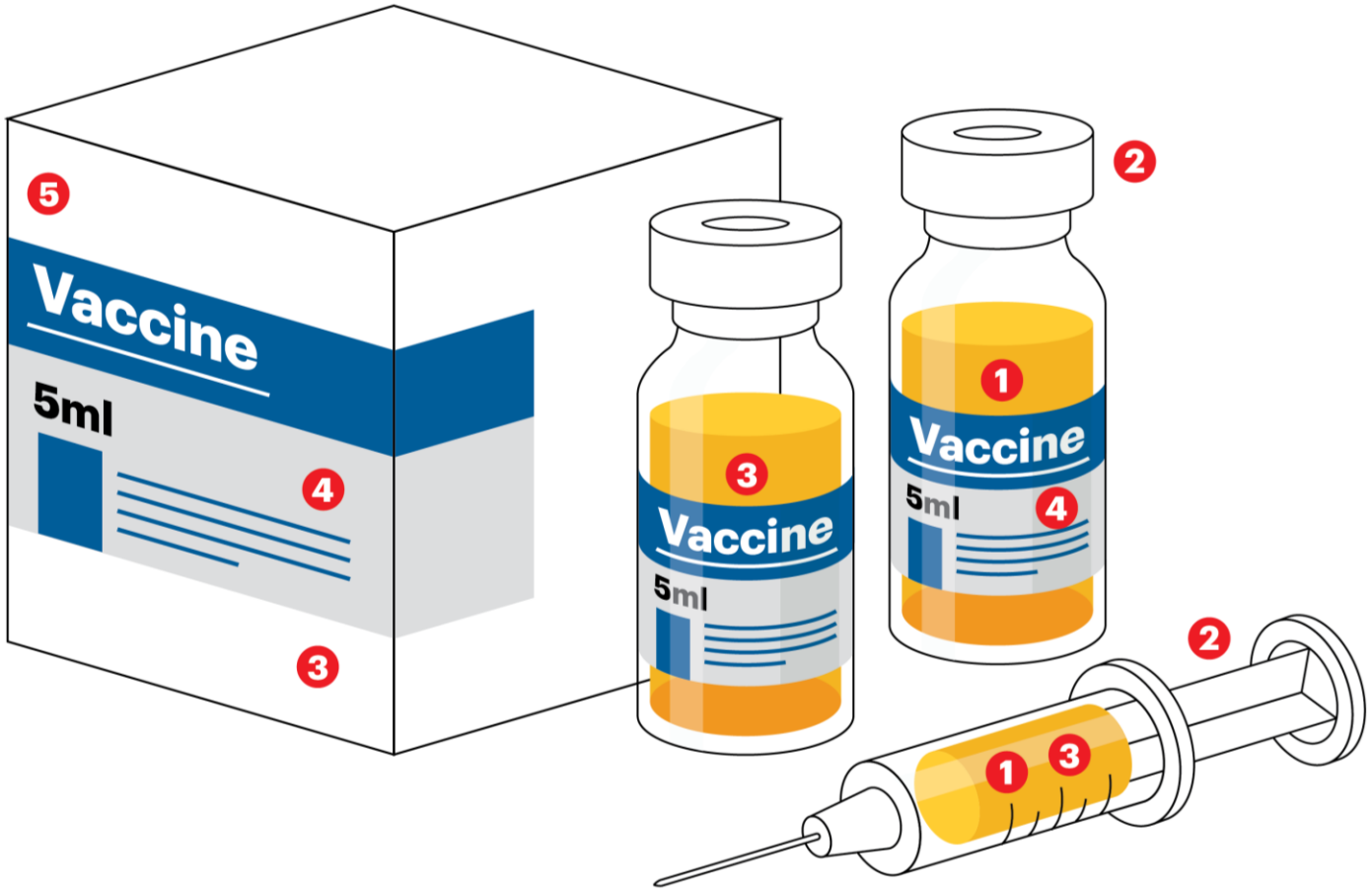
1 Introduction to USP

USP Mission

Supporting the distribution of high-quality vaccines is embedded in the USP Mission

- For over 200 years the United States Pharmacopeia (USP) has provided public standards in medicine, dietary supplements, and food to protect patient safety and improve public health.
- USP is an independent, scientific nonprofit organization focused on building trust in the supply of safe, quality medicines.
- As the USP continues to adapt, grow and evolve with science and medicine, we strive for a world where everyone trusts the medicines we rely on to save lives.
- The USP works globally with our Partners to help ensure vaccines are stored, transported, and administered properly.
- The USP works globally with our Partners to help ensure testing and public standards are available to verify the quality of vaccines for patient safety.

USP Standards and Quality Vaccines



USP standards are publicly available tools that vaccine manufacturers can use to help answer questions such as:

1 Ingredients

How can I be sure my ingredients are appropriate for my vaccine process? Are they pure? Is there a consistent supply from a reliable supplier?

2 Containers

Will the items used, such as syringes, make it easy for the patient to get the vaccine? Do they leak? Does the container react with the vaccine and change its quality?

3 Sterility

Is the vaccine sterile? For multi-dose vials, is the antimicrobial agent effective?

4 Labeling

Does the label clearly and accurately indicate the name, dose and how it should be administered?

5 Packaging and distribution

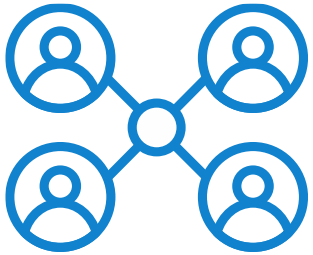
Is the vaccine packaged correctly to avoid damage and temperature fluctuations during storage and shipping?

** List not exhaustive*

Building Solutions through Collaboration

Access to quality vaccines and therapeutics

Partnering with our expert volunteers and Vaccine Advisory Group



Partnering with stakeholders, including industry practitioners, and academia

Partnering with global regulators, including U.S. and international food and drug authorities

USP staff and volunteers have expertise across the supply chain

Biologics

Biologics Monographs 1–Peptides & Oligonucleotides
Michael De Felippis

Biologics Monographs 2–Proteins
Wendy Saffell-Clemmer

Biologics Monographs 3–Complex Biologics & Vaccines
Earl Zablackis

Biologics Monographs 4–Antibiotics
Matthew Borer

Biologics Monographs 5–Advanced Therapies
Mehrshid Alai

Small Molecules

Small Molecules 1
Mary Seibel

Small Molecules 2
Justin Pennington

Small Molecules 3
Eric Kesslen

Small Molecules 4
Kim Huynh-Ba

Small Molecules 5
Amy Karren

Over-the-Counter (OTC) Methods & Approaches
Raphael Ornaf

Excipients

Simple Excipients
Eric Munson

Complex Excipients
Otilia Koo

Excipients Test Methods
Chris Moreton

General Chapters

General Chapters–Dosage Forms
Martin Coffey

General Chapters–Chemical Analysis
Nancy Lewen

General Chapters–Microbiology
Donald Singer

General Chapters–Packaging & Distribution
Renaud Janssen

General Chapters–Measurement & Data Quality
Jane Weitzel

General Chapters–Statistics
Charles Tan

General Chapters–Physical Analysis
Xiaorong He

Healthcare Quality & Safety

Nomenclature & Labeling
Stephanie Crawford

Healthcare Safety & Quality
Melody Ryan

Compounding
Brenda Jensen

Healthcare Information & Technology
Jeanne Tuttle

Dietary Supplements & Herbal Medicines, Food Ingredients

Botanical Dietary Supplements & Herbal Medicines
Robin Marles

Non-botanical Dietary Supplements
Guido F Pauli

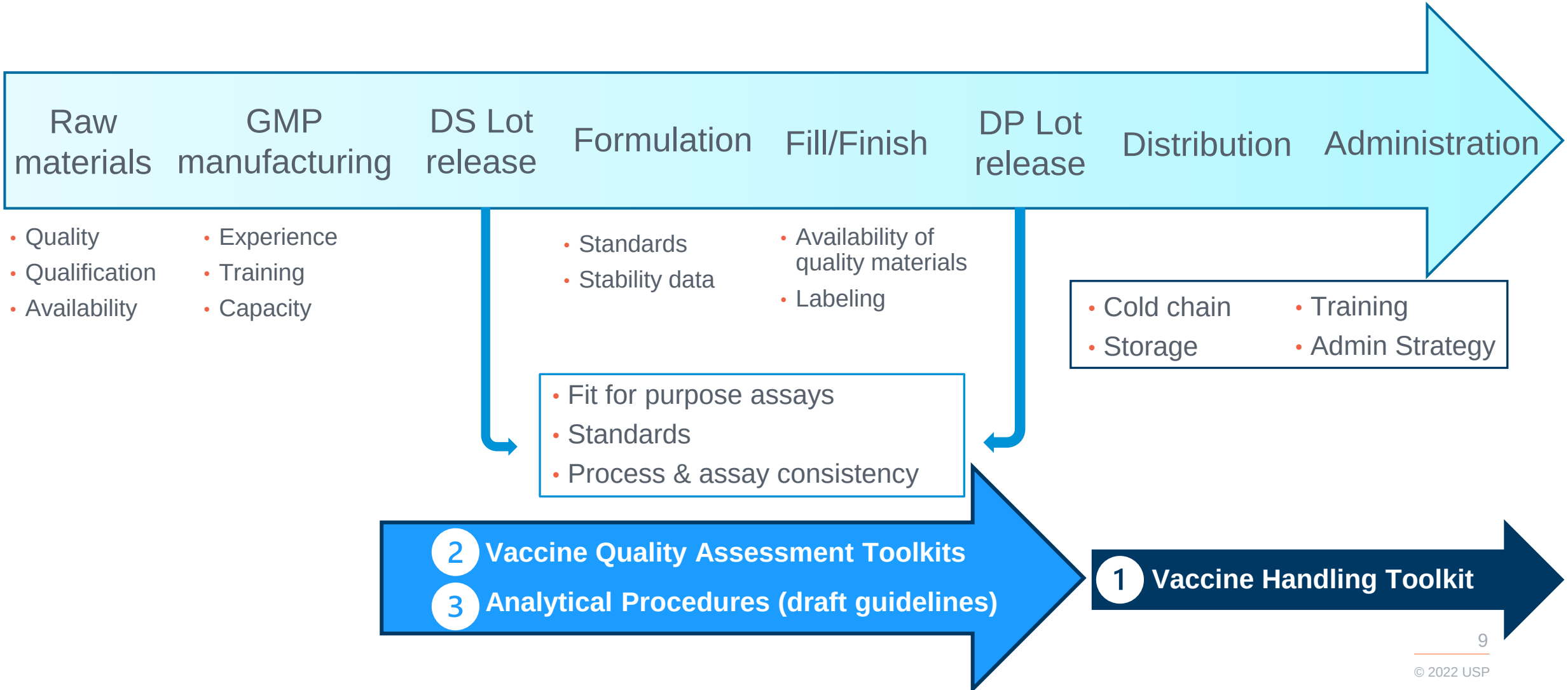
Dietary Supplements Admission Evaluation & Labeling
Tieraona Low Dog

Food Ingredients
Jon DeVries

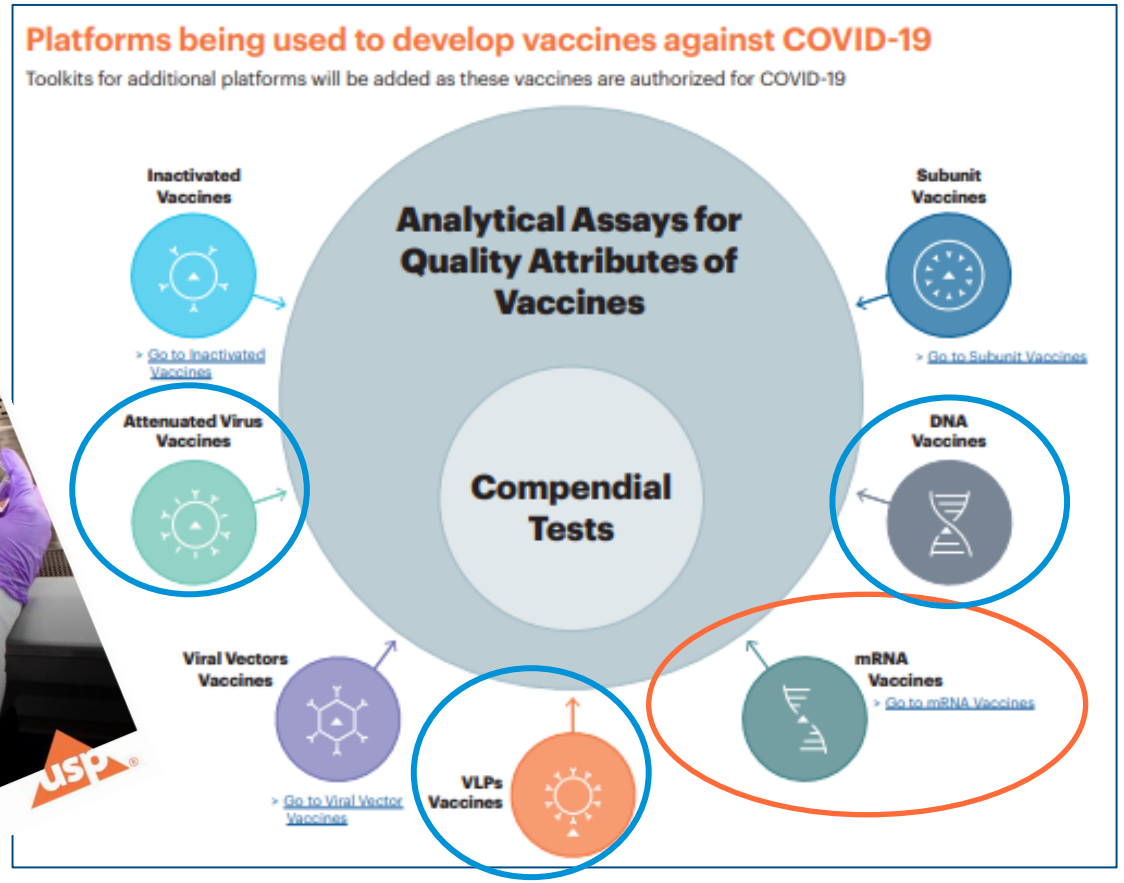
Supporting Vaccine Quality

Supporting Vaccine Quality

Potential risks to vaccine manufacturing and distribution



USP COVID-19 Vaccine Quality Assessment Toolkits



- Released in June 2021
  - Updated in Jan 2022 to include subunit vaccines
- Provide information regarding the tests used to release vaccines
- Link to existing USP chapters relevant to vaccines
- Can be helpful for interpreting data in lot release certificates
- DNA, VLP and attenuated toolkits – COMING SOON

https://www.usp.org/covid-19/quality-attributes-toolkits

USP Toolkit for mRNA Vaccines

mRNA

Approved COVID-19 mRNA Vaccines

Pfizer/BioNTech

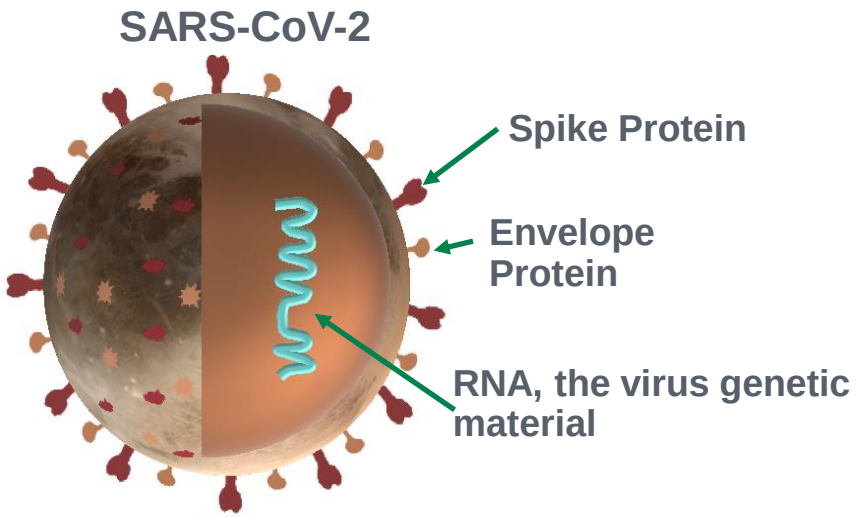
Moderna

Toolkit for Assessing Quality Attributes: **mRNA Vaccines**

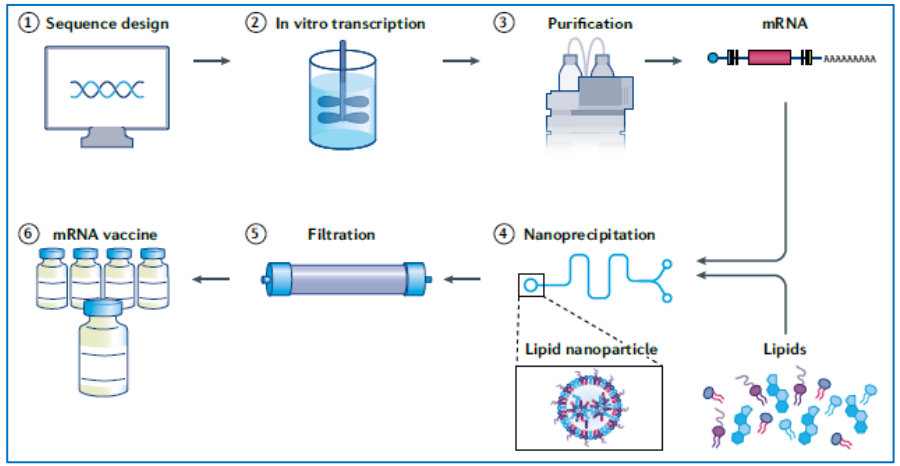
Category	Attribute	Possible Methods	Resource
Identity	Sequence confirmation	Sequencing	<1125>, <1126>
		RT-qPCR	<1126>, <1127>
Purity	RNA Integrity	CGE	<1053>
		Agarose Gel Electrophoresis for nucleic acids	<1126>
	Product-related impurities	IP-RP-HPLC	<621>
Potency	Antigen expression	Western blot	<1104>
		Flow cytometry	<1027>
		Other cell-based assays	<1032>, <1033>, <1034>
Concentration	RNA Content	RT-qPCR	<1127>
		Fluorescence spectroscopy	<853>
		UV Absorbance	<857>
		Anion exchange chromatography	<1065>
Particle Size	Nanoparticles	Light Scattering	<1430.2>, <1430.3>, <1430.5>, <1430.6>

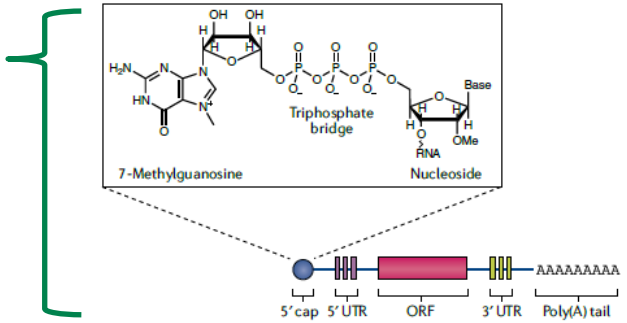
Introduction to mRNA Vaccines

What are mRNA vaccines and how do they work?



- The viral genetic code contains instructions for making proteins of the virus
- Spike protein on the surface of the virus helps the virus penetrate cells and initiate an infection
- mRNA that encoded the spike protein is packaged in lipid nanoparticles
  - Limits degradation
  - Facilitates cellular mRNA update
- Once the RNA is inside of human cells, the cells produce the viral spike protein
- The spike protein, encoded by the mRNA, triggers an immune response



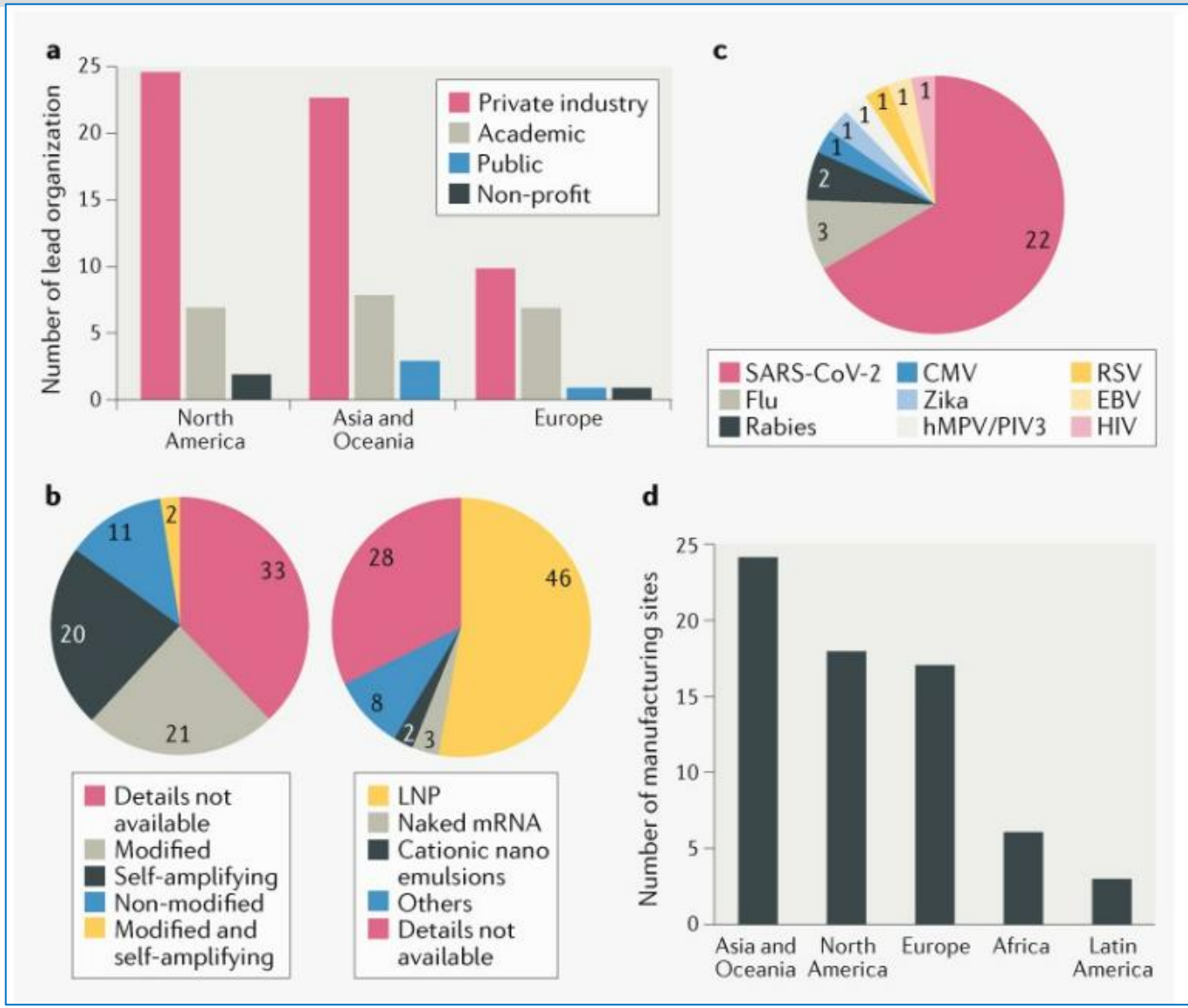


Ionizable lipid, cholesterol variants, helper lipid and PEGylated lipid

Chaudhary, N., Weissman, D. & Whitehead, K.A. Author Correction: mRNA vaccines for infectious diseases: principles, delivery and clinical translation. Nat Rev Drug Discov 20, 880 (2021). https://doi.org/10.1038/s41573-021-00321-2

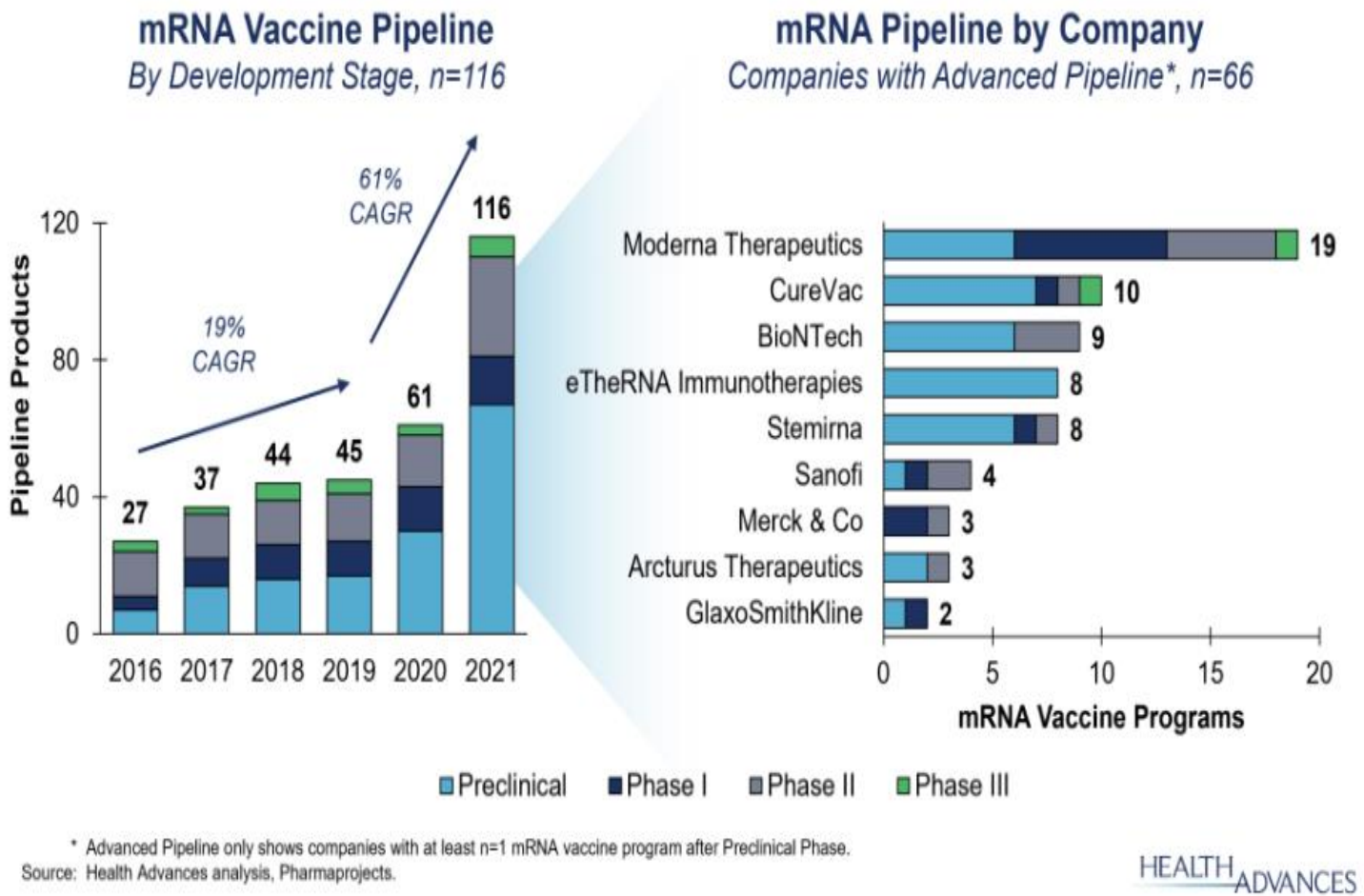
mRNA vaccines global landscape – Infectious diseases

- At least 90 lead developers – as of 2/2022
- 137 mRNA vaccine candidates – mostly SARS-CoV-2 as main target
  - 76% in preclinical/exploratory
  - 24% in clinical development
- Led by biopharma based in North America & Asia
- For most, mRNA technology format is not available
- Lead developers using LNP as a delivery vehicle

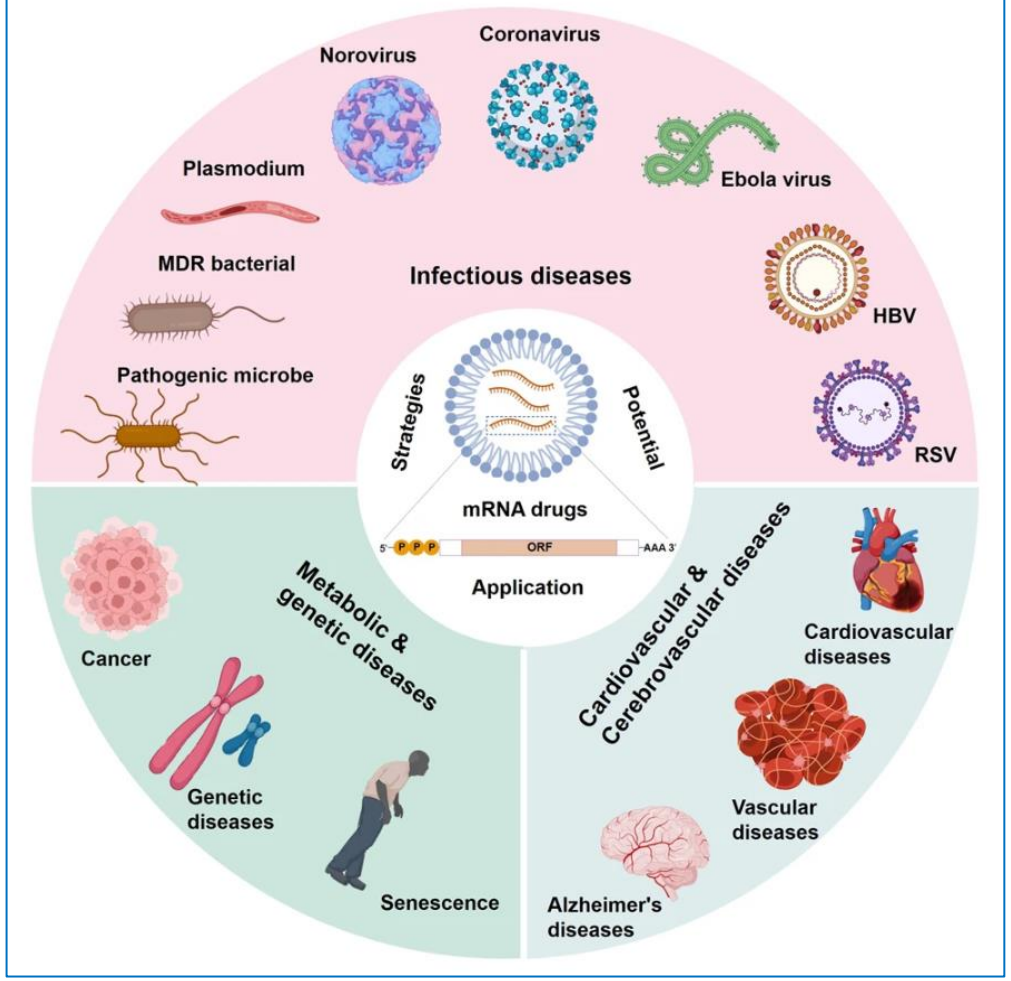


https://www.nature.com/articles/d41573-022-00035-z#:~:text=The%20COVID%2D19%20pandemic%20has,of%20future%20epidemics%20and%20pandemics.

Broader Landscape of mRNA-based Therapeutics - Growth & Opportunities



https://healthadvancesblog.com/2022/06/24/from-treating-cancer-to-curing-cancer-the-promise-of-mrna-vaccines-in-oncology/

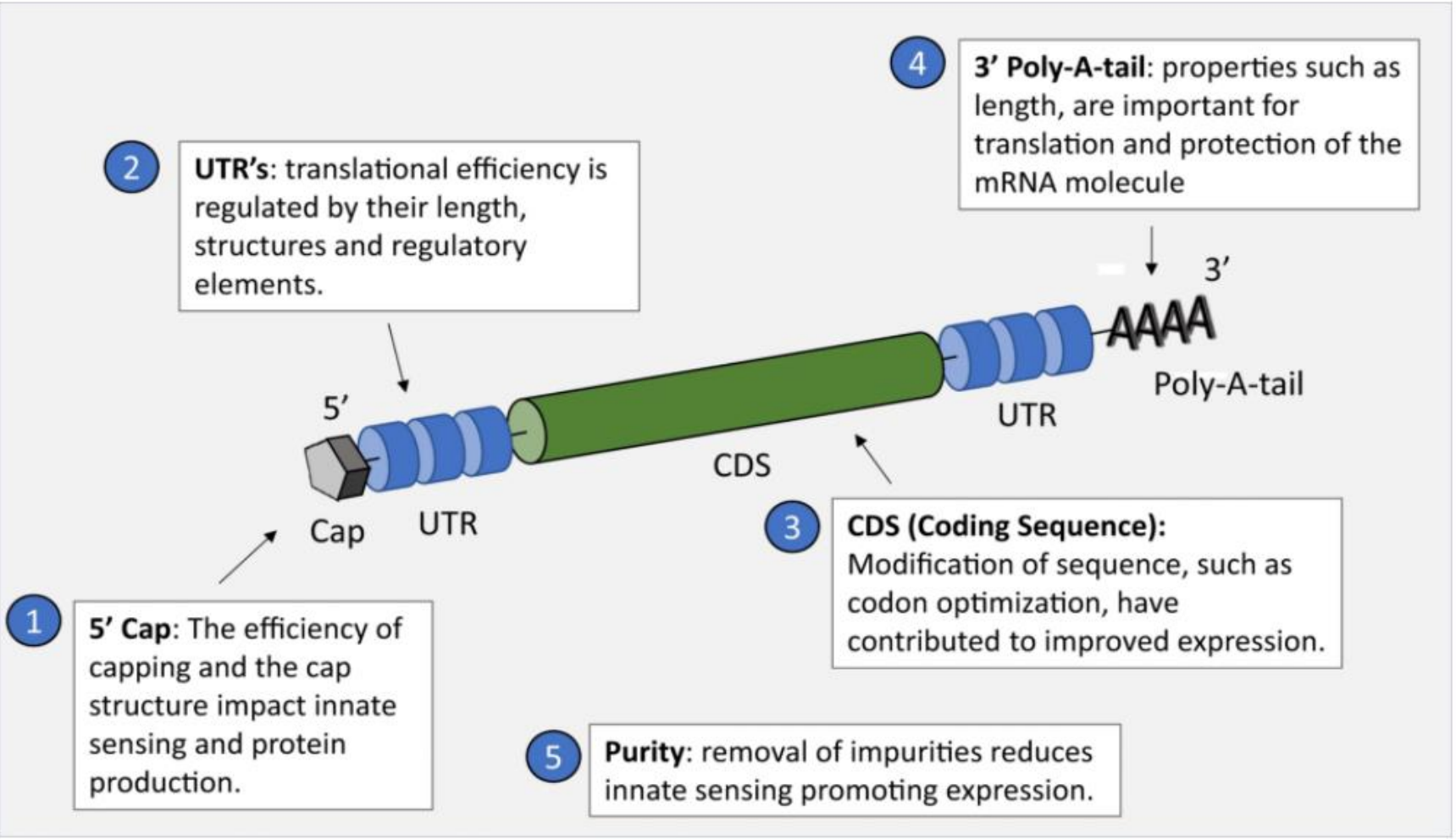


https://www.nature.com/articles/s41392-022-01007-w

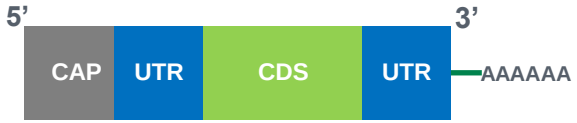
Quality Assessment of mRNA Vaccines

Quality Attributes for mRNA Vaccines

Identity, Purity, Stability, Immunogenicity and Homogeneity



Non-replicating mRNA (NRM)



Self-amplifying mRNA (SAM)

Source: npj Vaccines 5, 11 (2020). https://doi.org/10.1038/s41541-020-0159-8

Analytical Procedures – Draft Guidelines

- Toolkits are supporting documents
  - Chapters referenced in toolkits provide high level information on methods and best practices
  - More detail is needed on specific quality attributes and specific test methods
- Guidelines will support testing of quality attributes with step-by-step procedures
  - Applicable across a product class
  - Prioritized mRNA and viral vectored vaccines based on stakeholder input
  - Provide options for the same attribute
- Toolkits and platform-based guidelines are not meant to be specific to any one vaccine – not pursuing monographs for individual vaccines

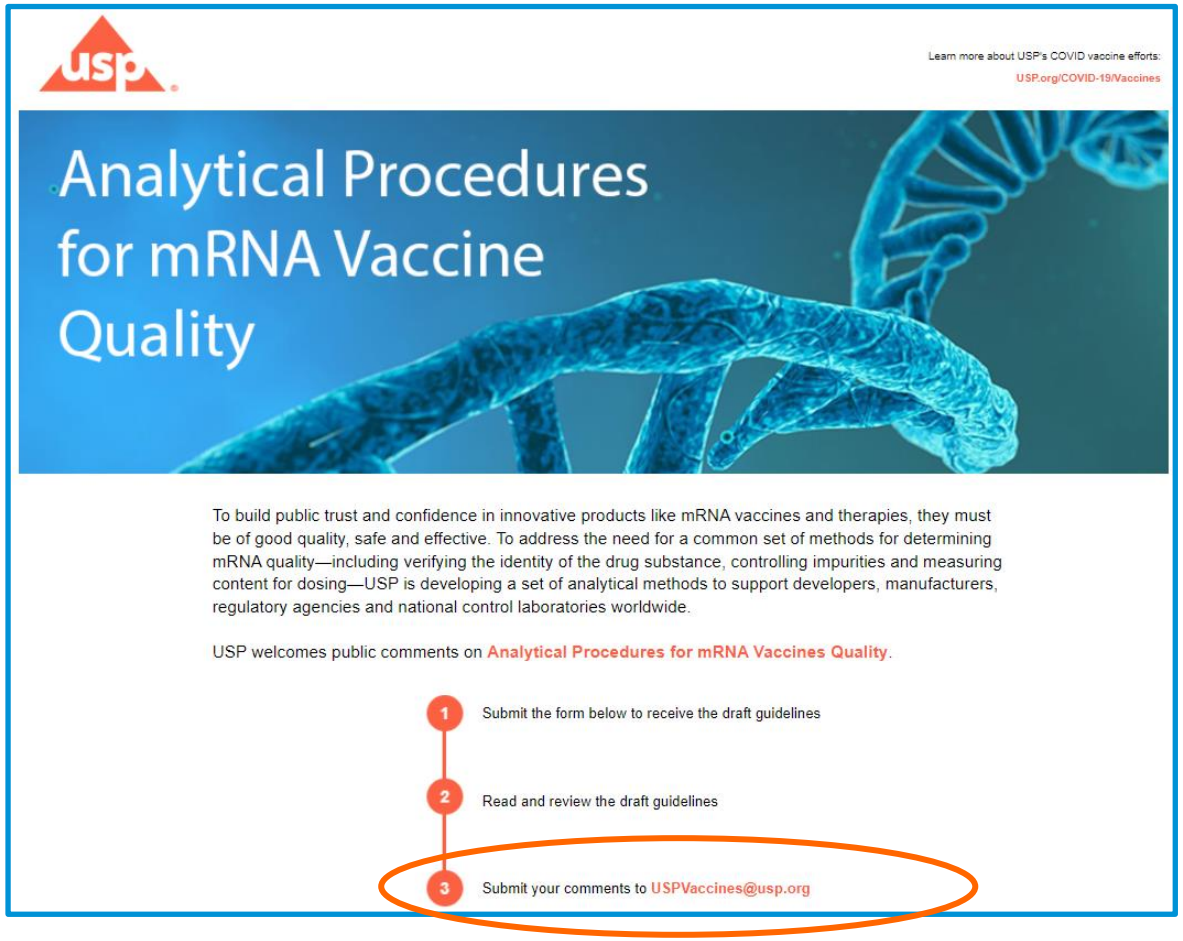
Goals

- Support quality of vaccines by providing detailed analytical procedures for testing common quality attributes
  - Chapters with step-by-step procedures
- Provide a starting point for manufacturers and global testing labs
  - Guidelines provide basic “recipe” for analytical testing from which labs can develop their own methods
  - Validated methods would provide additional support and facilitate development of official USP chapter
- Provide multiple options for the same attribute
  - Some technology platforms may not be available in all testing labs

Our Approach to mRNA Vaccine Guidelines

- Specific methods identified and adapted from public sources
  - New rapid response process – not direct pathway to the compendia
- Draft reviewed and refined by vaccine experts
  - USP Expert Committee
  - USP vaccine advisory group
- Taking similar approach for other vaccine types
  - Viral vectored vaccines – https://go.usp.org/viral-vectors

USP Identified Analytical Quality Attributes for mRNA Vaccine Drug Substance - Draft guidelines



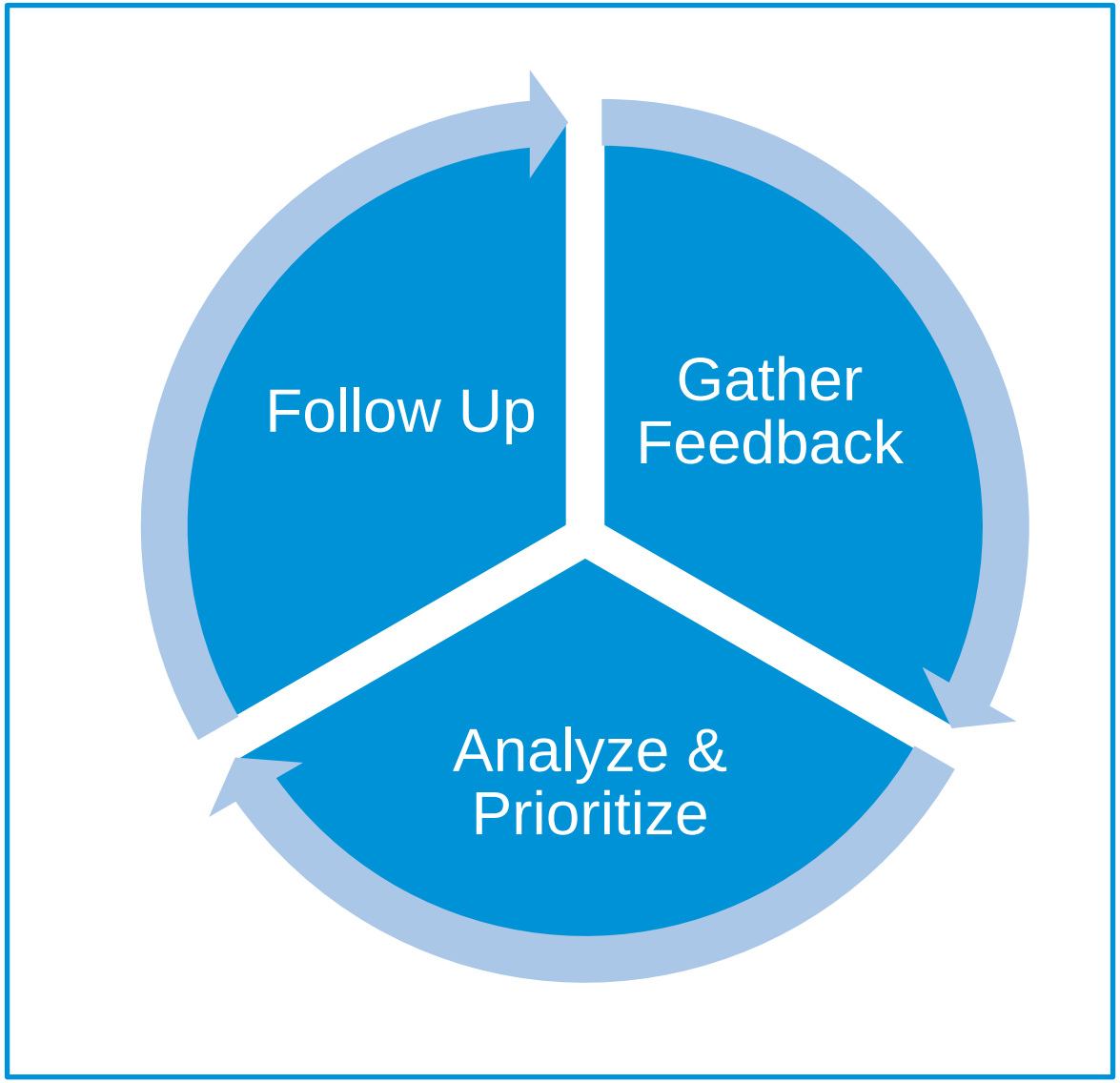
Quality	Attribute	Method
Identity	Sequence confirmation	Next generation sequencing (NGS)
		Sanger sequencing
		Reverse Transcriptase – PCR
Content	RNA content	RT-qPCR and RT–dPCR, Ultraviolet Spectroscopy
Integrity	Percentage of intact mRNA and fragment mRNA	Capillary gel electrophoresis
	5′ cap	IP–RP–HPLC
	3′ poly(A)	RP–HPLC
	mRNA Integrity	Gel electrophoresis
Purity	Product related impurities - dsRNA	Immunoblot
	Residual DNA template	qPCR
Safety	Endotoxin	USP <85>
	Bioburden	USP <61>, <62>, <1115>
	Sterility	USP <71>
Other	Appearance	USP <1>, <790>
	pH	USP <791>

Available Online at: www.usp.org/mrna-quality

Summary of Feedback Received to Date

Total of 287 comments to date

- Comments have been submitted by manufacturers, regulators, vendors, testing labs and academia
- Following comments/feedback received to date
  - Include methods pertaining to drug product (e.g., LNP)
  - Multiple comments included ways to improve suggested methods (columns, buffers, etc.) in terms of resolution and better output of signal
  - Other suggested methods – e.g., residual cap, nucleosides, etc.
  - Methods received to assess identity of encoded RNA sequence, mRNA integrity and quantitation



Summary

- New draft guidelines can support vaccine quality by:
  - Establishing a common understanding of quality attributes
  - Providing testing methods that can be used as a starting point to assess quality attributes (e.g. identity, quantity, purity and safety)
  - Providing multiple options for testing of the same attribute

Next Steps

- Collect feedback on concept and proposed methods
  - Comments received to date from manufacturers, regulators, vendors, testing labs
  - Submit comments to USPvaccines@usp.org
- Encourage submission of alternative methods and validation packages
- Publication of additional draft guidelines for other vaccine types in process

Future Directions and Requests from Vaccine Community

To support expansion of Global Capabilities related to quality of mRNA Vaccines, USP is seeking:

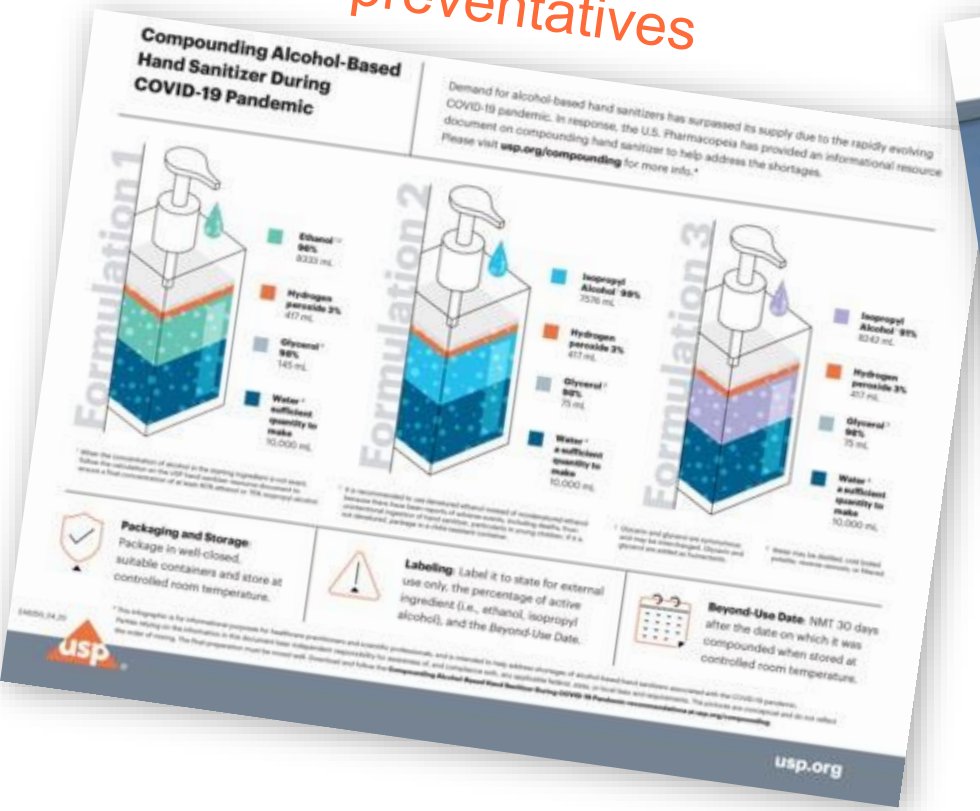
- Vaccine sample donations for testing to ensure method suitability
- API bulk donations to develop control materials to support analytical methods
- Partners to support training and proficiency of receiving laboratories and regulatory stakeholders

5 USP Vaccine Resources

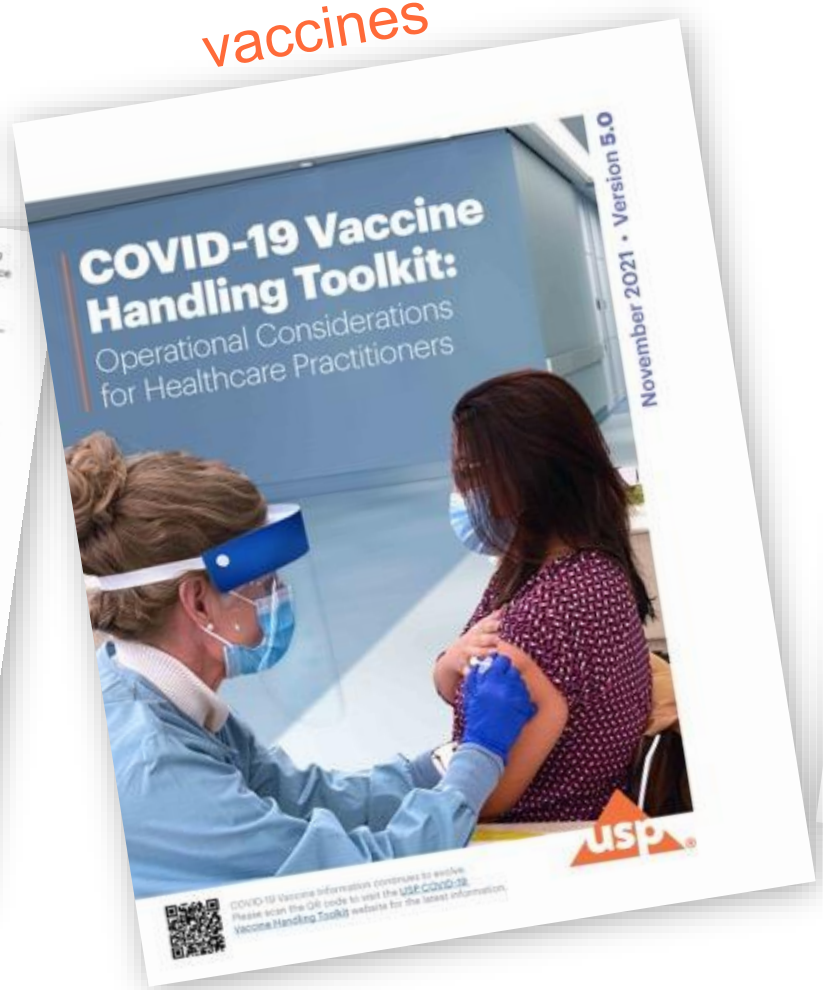
COVID-19 Response

Helping to ensure the supply of quality vaccines, treatments and health information

preventatives



vaccines



treatments

General chapters for vaccines based on product class or platforms

USP chapters provide best practices for ensuring quality

Products of similar structure, manufacturing route ("platform"), impurities and use, which…

- ✓ Have common critical quality attributes (CQAs)
- ✓ Require common or similar testing methods and standards

USP-NF general chapters for vaccine product classes:

- ✓ <1235> *Vaccines for Human Use – General Considerations*
- ✓ <1238> *Vaccines for Human Use – Bacterial Vaccines*
- ✓ <1239> *Vaccines for Human Use – Viral Vaccines*
- ✓ <1234> *Vaccines for Human use – Polysaccharides & Glycoconjugate Vaccines*
- ✓ <1047> *Gene Therapy Products* – may also be useful for certain vaccine platforms
- ✓ <198> *Nuclear Magnetic Resonance Spectroscopy Identity Testing of Bacterial Polysaccharides Used In Vaccine Manufacture*

https://www.usp.org/sites/default/files/usp/document/our-impact/covid-19/standards-for-quality-vaccines.pdf

USP-NF Vaccine Related General Chapters

USP-NF Vaccines (uspnf.com)

- ▶ Identification
- ▶ Characterization
- ▶ Equipment
- ▶ Misc. Tests
- ▶ Description
- ▶ Safety
- ▶ Assay
- ▶ Physicochemical
- ▶ Impurities

▼ **Identification**

- (198) *Nuclear Magnetic Resonance Spectroscopy Identity Testing of Bacterial Polysaccharides Used in Vaccine Manufacture*
- (621) *Chromatography*
- (736) *Mass Spectrometry*
- (761) *Nuclear Magnetic Resonance Spectroscopy*
- (1030) *Biological Assay Chapters—Overview and Glossary*
- (1032) *Design and Development of Biological Assays*
- (1033) *Biological Assay Validation*
- (1034) *Analysis of Biological Assays*
- (1052) *Biotechnology Derived Articles—Amino Acid Analysis*
- (1053) *Capillary Electrophoresis*
- (1054) *Biotechnology Derived Articles—Isoelectric Focusing*
- (1055) *Biotechnology Derived Articles—Peptide Mapping*
- (1056) *Biotechnology Derived Articles—Polyacrylamide Gel Electrophoresis*
- (1057) *Biotechnology Derived Articles—Total Protein Assay*
- (1102) *Immunological Test Methods—General Considerations*
- (1103) *Immunological Test Methods—Enzyme-Linked Immunosorbent Assay (ELISA)*
- (1104) *Immunological Test Methods—Immunoblot Analysis*
- (1126) *Nucleic Acid-Based Techniques—Extraction, Detection, and Sequencing*
- (1127) *Nucleic Acid-Based Techniques—Amplification*
- (1128) *Nucleic Acid-Based Techniques—Microarray*
- (1129) *Nucleic Acid-Based Techniques—Genotyping*
- (1234) *Vaccines for Human Use—Polysaccharide and Glycoconjugate Vaccines*
- (1235) *Vaccines for Human Use—General Considerations*
- (1238) *Vaccines for Human Use—Bacterial Vaccines*
- (1736) *Applications of Mass Spectrometry*
- (1761) *Applications of Nuclear Magnetic Resonance Spectroscopy*
- (1776) *Image Analysis of Pharmaceutical Systems*

Other Resources

- COVID-19 vaccine resources: https://www.usp.org/covid-19/vaccines
- Quality Assessment Toolkits: https://www.usp.org/covid-19/quality-attributes-toolkits
- Analytical Procedures for mRNA vaccines: https://www.usp.org/mrna
- Analytical Procedures for viral vectored vaccines: https://go.usp.org/viral-vectors

COVID-19 vaccine platforms: Delivering on a promise?

Mark Verdecia [1], John F Kokai-Kun [1], Maura Kibbey [1], Sarita Acharya [1], Jaap Venema [1], Fouad Atouf [1]

Affiliations + expand

PMID: 34033528 PMCID: PMC8381795 DOI: 10.1080/21645515.2021.1911204

Assessing Quality Of mRNA Vaccines: Key Considerations

By Diane McCarthy, USP

Assessing Quality Of Viral Vectored Vaccines

By Diane McCarthy, USP

Thank You!

Questions? Please email:

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