Analytical Characterization for Precision Biologics

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Outline

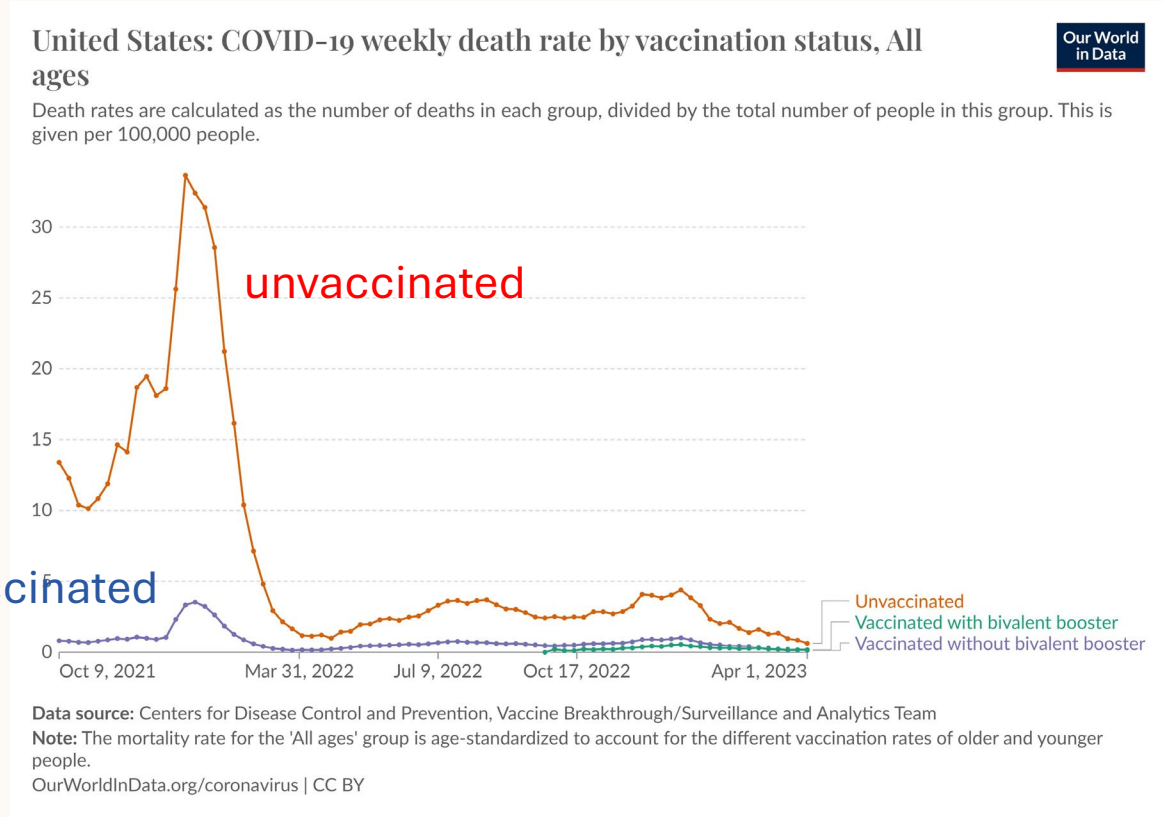
The challenges faced by developers

Precision medicine to the rescue

Translating to practice: vaccine case study

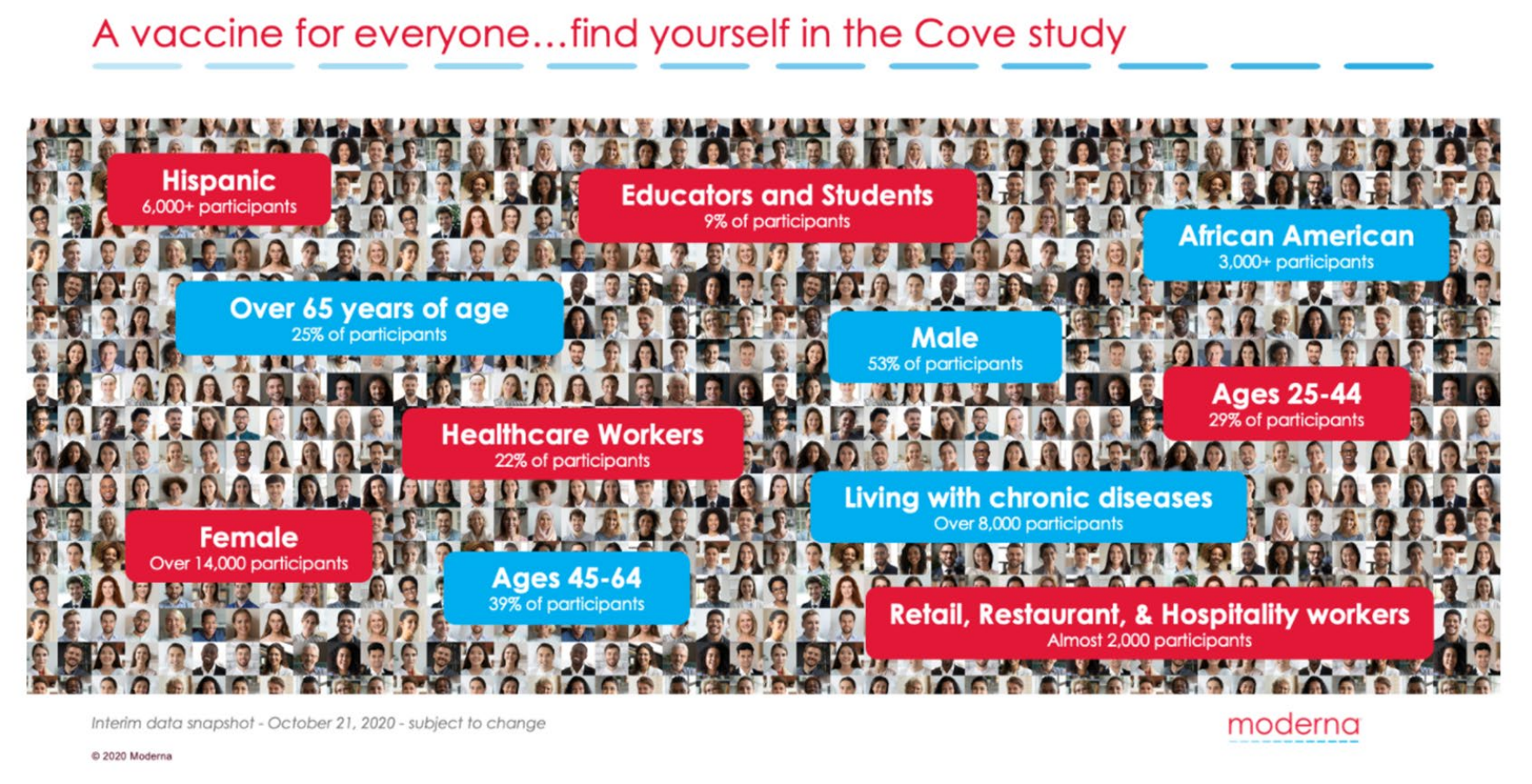
Effectiveness Is Our Ultimate Goal.

Vaccination reduces the death rate from COVID-19. This was more pronounced in the early weeks when there was no population immunity from prior infection.



https://ourworldindata.org/covid-deaths-by-vaccination

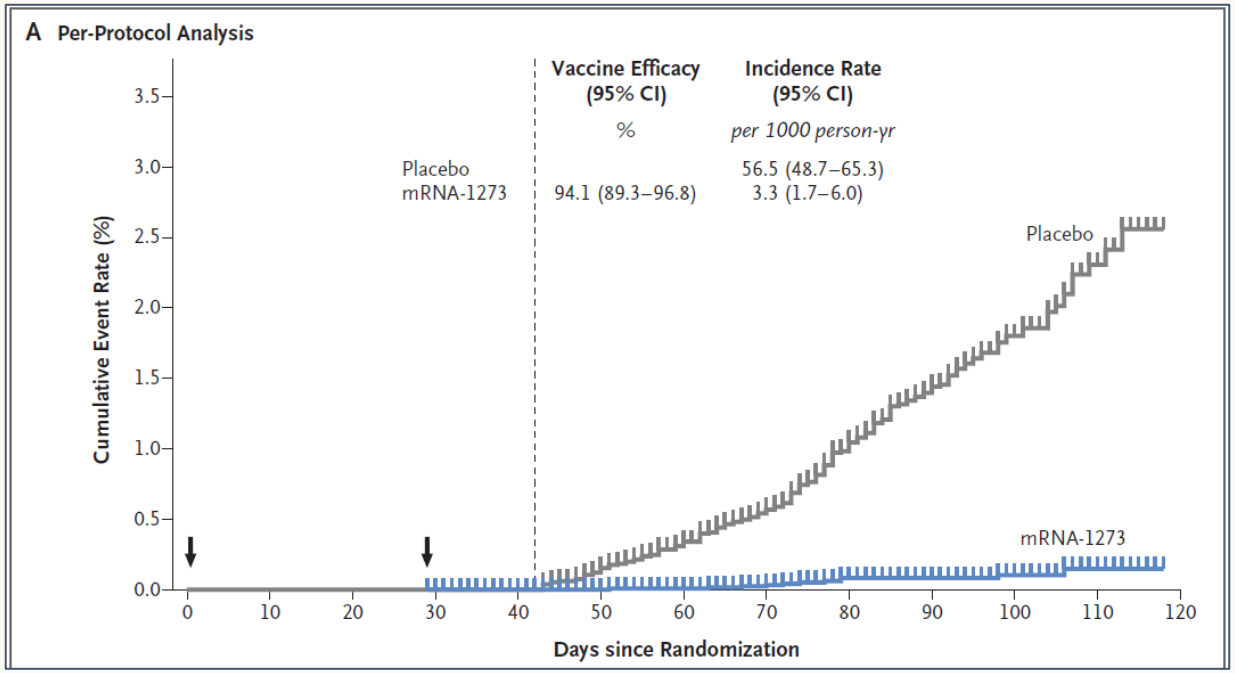
Vaccines Need to Work for Heterogeneous Populations.



Efficacy Is An Important But Imperfect Metric.

Phase 3 Efficacy = 94.1%
for Moderna mRNA-1273

symptomatic SARS-CoV-2 infection



NEJM.org Jan 2021

Rare Safety Risks Emerge Only When Vaccines Are Administered To Very Large Groups.

Stage	Example Group Size	Expected Events		
		Unvaccinated	Vaccinated	Infected
Rate per Million		6	22	103

Example for illustration: Myocarditis rates in Israel, BNT162b2 vaccine. NEJM 2021

Faster Clinical Trials Put Development On The Critical Path.

-Janet Woodcock, MD,
Former US Acting Commissioner of Food and Drugs,
advocates for modernizing development.

J. Wechsler, "FDA Continues to Promote Quality Drug Production,"
Pharmaceutical Technology 41 (7) 2017.

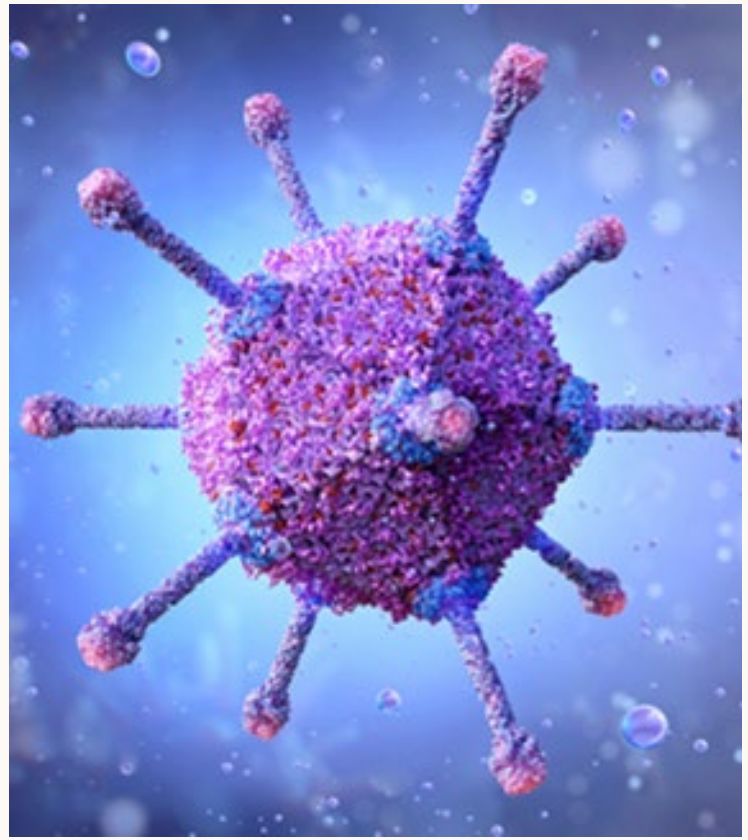
"In the past,

efficient manufacturing scale-up

was not that important because

clinical development took so long"

Analytical Characterization of Vaccines Can Be Complex



Quality by Inspection focuses on safety & efficacy, but neglects affordability & availability.

Product Development

Physico-Chemical Testing

In Vitro Bioassays

- Potency (typically)

In Vivo Bioassays

- Non-clinical model

Clinical Studies

- Biomarkers, immunology
- Efficacy

Human Use

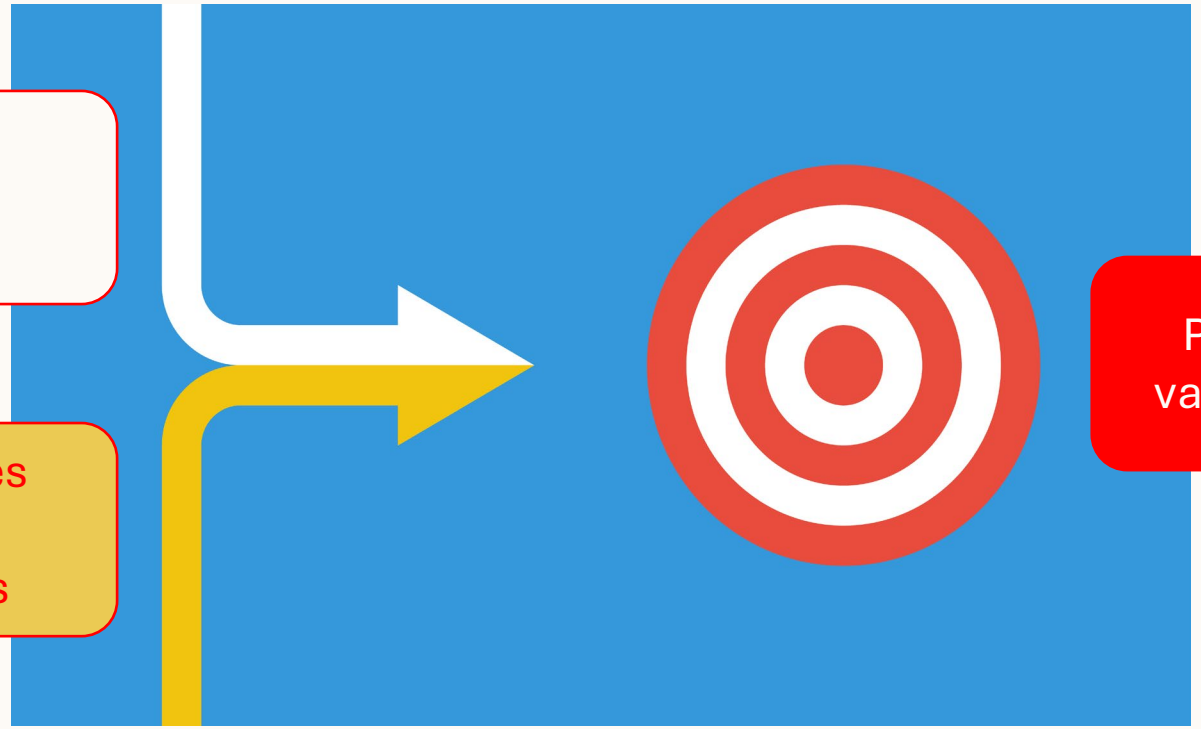
Ensure CONSISTENCY with original materials tested in clinic

Precision Medicine to the Rescue

Precision Medicine Helps Us Overcome These Challenges.

Advances in Immunology

Biotechnologies accessible to vaccinologists

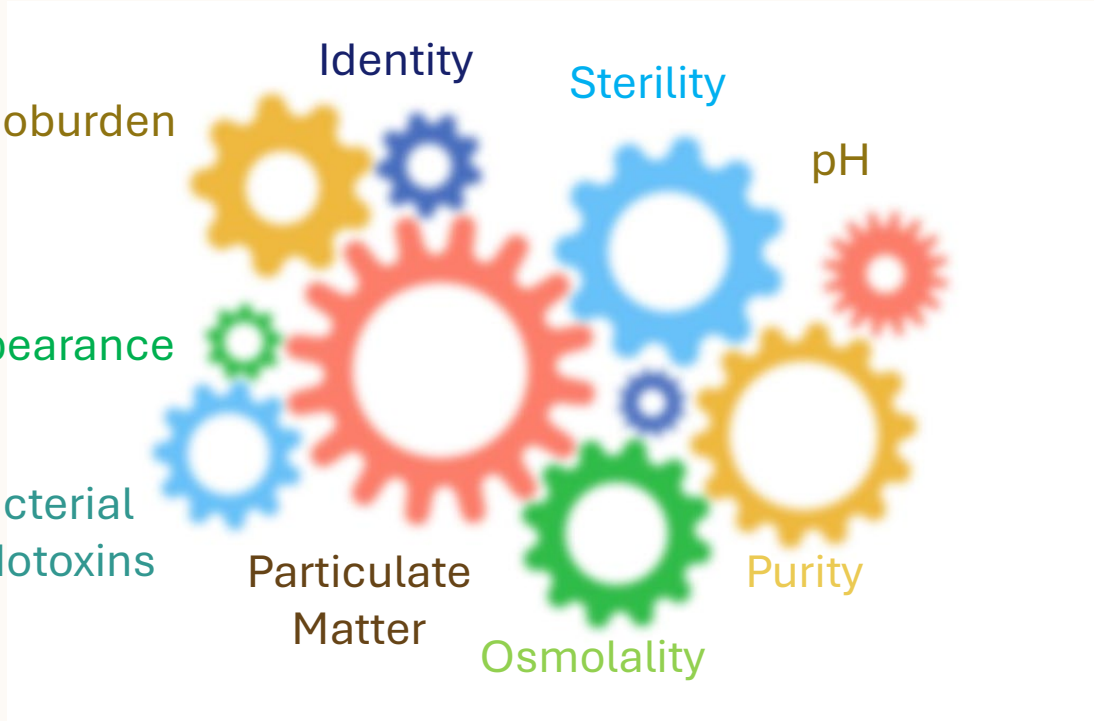


Precision vaccinology

Vaccine Critical Quality Attributes Are Expected to Relate to Safety, Efficacy, or Both.

Typical Vaccine Critical Quality Attributes and Expected Relevance		
Safety	Efficacy	Compendial
Identity	Identity	
Appearance	Activity	pH
Particulate matter	Immunogenicity	Osmolality
Bacterial Endotoxins	Container Content, Deliverable Volume	
Sterility	Content	
Purity	*** Potency ***	
Process-related Impurities		
Product-related Impurities		

Traditional Test Panel “Predicts” Safety, But Our View Was Blurred.



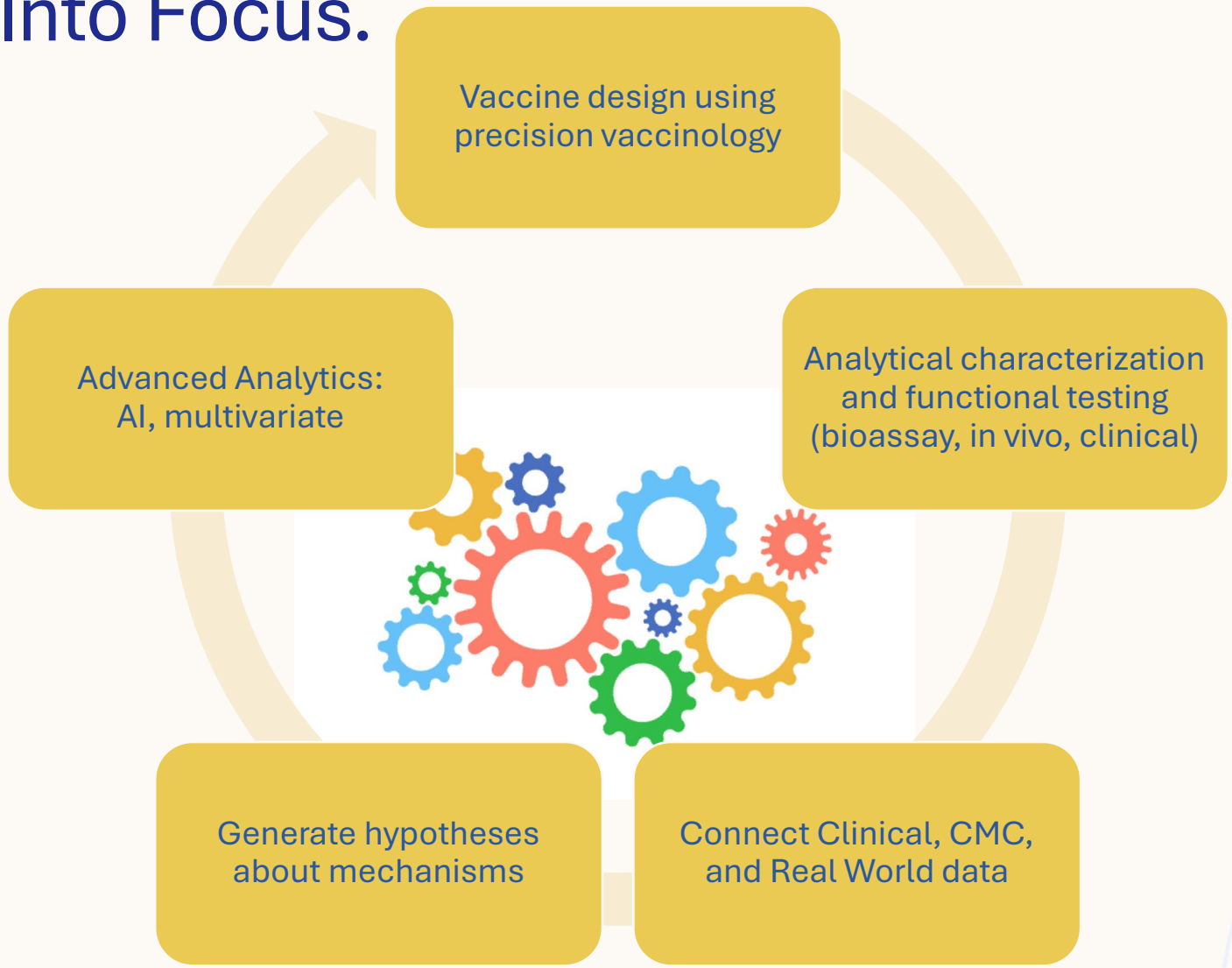
injection site reactions: tenderness, swelling of the lymph nodes, swelling (hardness), and redness

general side effects: fatigue, headache, muscle pain, joint pain, chills, nausea and vomiting, fever, and rash

myocarditis, pericarditis

severe allergic reaction

Precision Vaccinology and Advanced Analytics Bring Mechanisms Into Focus.



Claim: Analytical Characterization Can Predict Both Safety & Effectiveness.

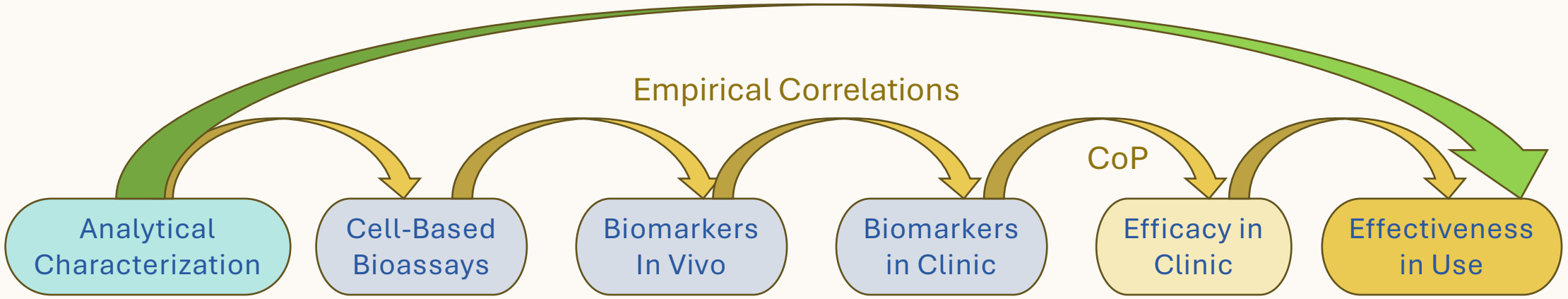
Product Analytical Characteristics:
strength
infectivity
expression
identity
purity
bioburden
endotoxins
product-related impurities
process-related impurities
et al.

Vaccine Safety

Vaccine Effectiveness

Predicting Effectiveness Has Other Challenges.

Precision Vaccinology: predict effectiveness based on biological knowledge of mechanism of action



Correlates to effectiveness?	Via mechanism of action	"Functional tests", empirical correlation			Ultimate measure. Gold standard.
Represents diversity in recipients?	Independent of recipients	Designed for homogeneity but inherently variable	Constrained diversity (by design)	Limited diversity of subjects, regions, timeframe	Tremendous diversity in subjects, regional, seasonal, long-term
Information quality	High: precise, accurate, informative	Limited: relative measures, different scale	Medium: continuous measures, different scale	Low: discrete metrics, yes/no or time-to-event	Very low: metrics dependent on monitoring systems, clouded by confounding factors

Cell & Gene Therapy Provides A Useful Template

Potency Assurance for Cellular and Gene Therapy Products: Draft Guidance for Industry

A. Licensed CGT Products

To obtain a biologics license, a biologics license application (BLA) must contain data demonstrating that the product is safe, pure, and potent, and the continued safety, purity, and potency of the product must be assured.[10] Additional potency-related requirements for licensed products are as follows:

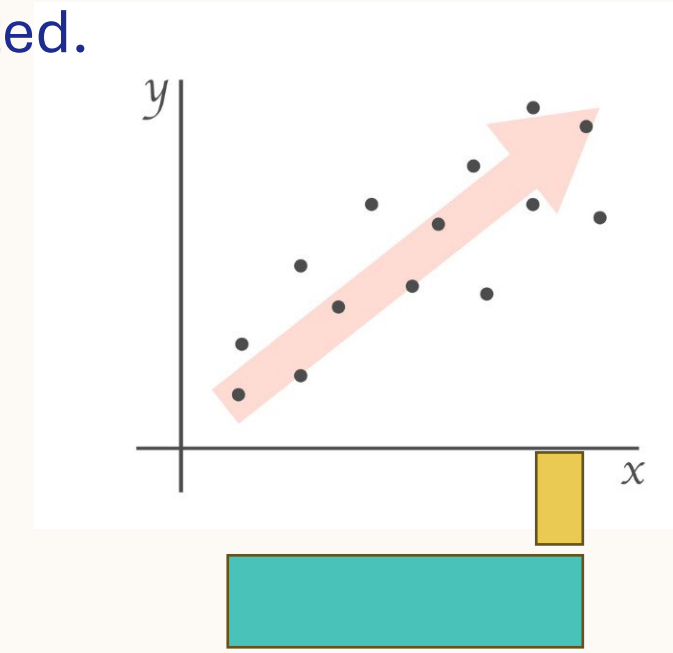
- Each lot of product must be tested for potency, and potency assays must be performed on a sample that is taken after completing all manufacturing steps that may affect potency.[11] The Center for Biologics Evaluation and Research (CBER) may permit an alternative approach to the requirements for lot release testing for potency in Title 21 Code of Federal Regulations (CFR) 610.1 and 21 CFR 610.10, but only if you demonstrate that the alternative approach will provide assurance of potency that is equal to or greater than the assurance of potency that would be provided by following the requirements in 21 CFR 610.1 and 21 CFR 610.10.[12]

- Clinical data may be used to establish a correlation(s) between biological activity and a more practical potency measurement(s) that can be used for lot release, stability, and/or comparability studies.
- As used in this document, “correlation” means a statistical and biological relationship between two or more variables such that systematic changes in the value of one variable are accompanied by systematic changes in the other.

Empirical Correlation Has Limitations.

It may be necessary to correlate a more-precise result (analytical characterization panel) to a less-precise result (bioassay, in vivo, or clinical).

Statistical correlation depends strongly on the range tested.



Potency can be confirmed by a suite of precise analytical characterization assays, confirmed by a cell-based potency assay.

Specification

The active substance specifications contain tests for: Appearance (visual), Identity RT- Sanger Sequencing), Total RNA content (UV), Purity (RP-HPLC), Product-related impurities (RP-HPLC), % 5' Capped (RP-UPLC), % PolyA tailed RNA (RP-HPLC), Residual DNA template (qPCR), pH (pharmacopoeial), Bacterial endotoxin (pharmacopoeial), Bioburden (pharmacopoeial).

EUROPEAN MEDICINES
SCIENCE MEDICINES

11 March 2021
EMA/15689/2021 Corr.1*[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

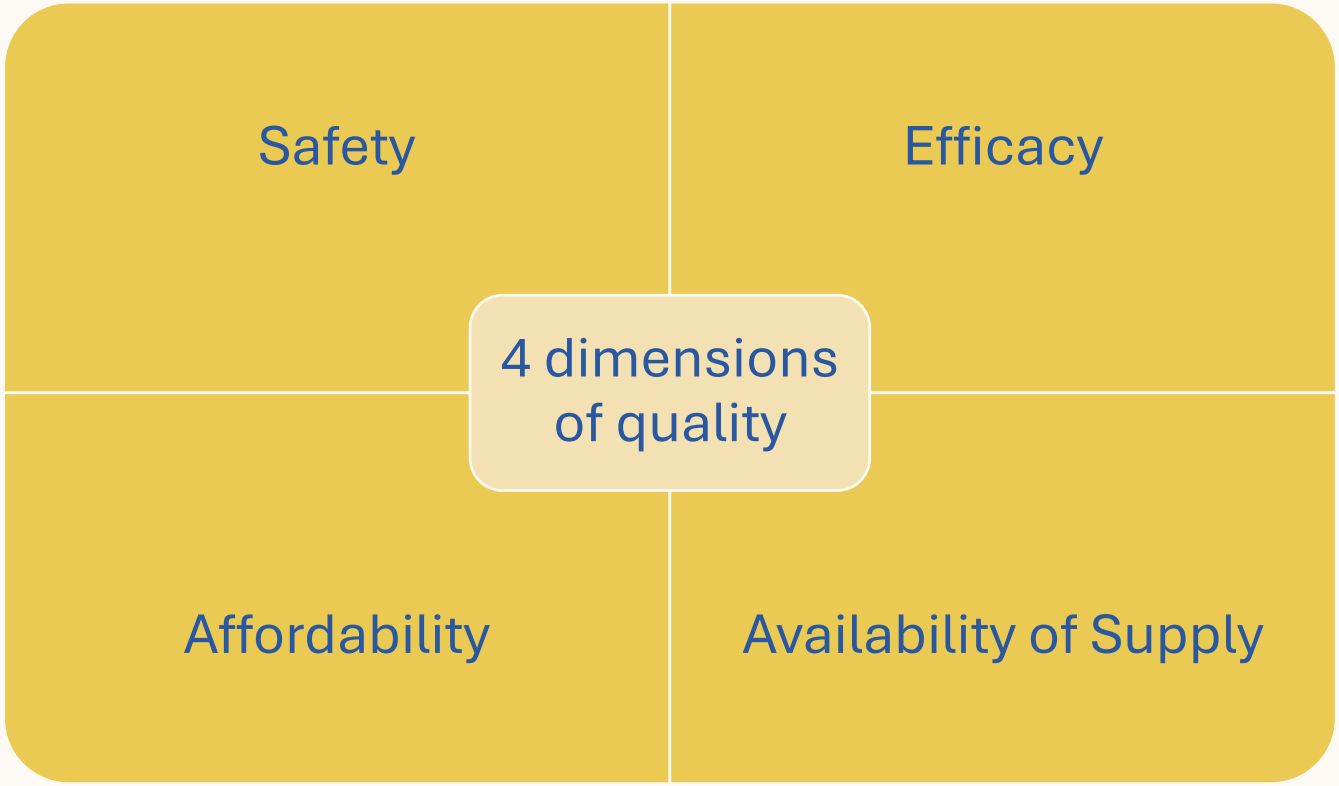
COVID-19 Vaccine Moderna

Common name: COVID-19 mRNA Vaccine (nuc

Procedure No. EMEA/H/C/005791/0000

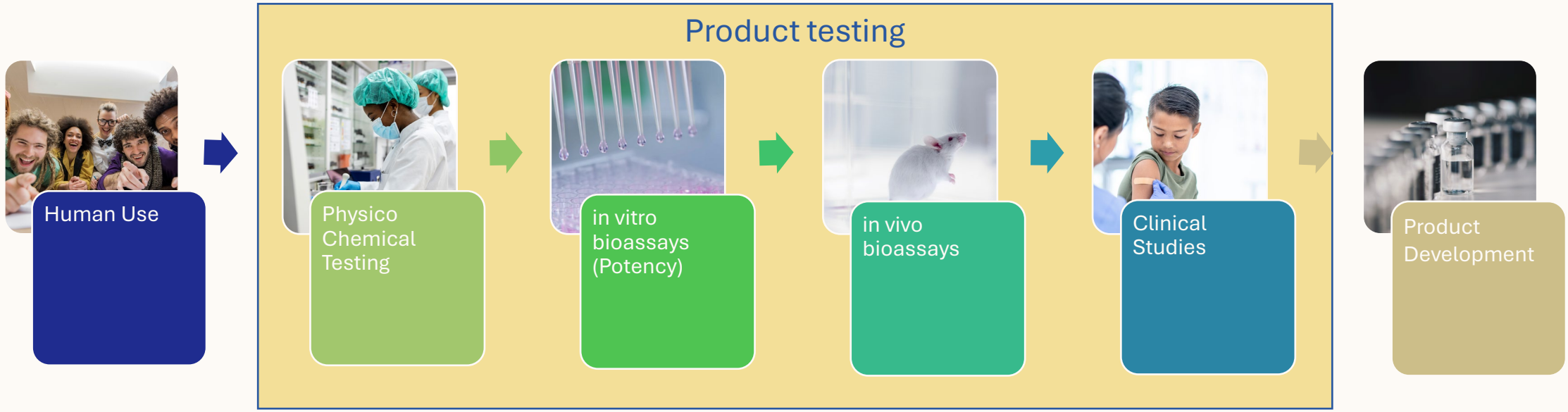
DIREA

What really matters to patients?



Quality by Design Begins with the Patient.

Begin with the end in mind.



QTTP:
Patient relevant design

Precision vaccinology & analytical characterization

Process & material controls

Quality by Design delivers all 4 dimensions important to patients.

Dimension	Quality by Inspection	Quality by Design
Safety	✓ yes	✓ yes
Efficacy	✓ yes	✓ yes
Affordability	○ no	✓ yes
Reliability of Supply	○ no	✓ yes

Summary

Precision vaccinology overcomes traditional challenges in vaccine development and enables patient-relevant design and acceleration.

Predicting effectiveness based on analytical characterization has the potential to deliver greater insight than cell-based Potency assays.

Quality by Design employing precision vaccinology delivers safety, efficacy, AND access.

Our Call to Action:
Lead the Transformation to Quality by Design

We can have greater impact here

We often work here

	Quality by Inspection	Quality by Design
Statistics Incorrectly Applied	Wrong Things Wrong	Right Things Wrong
Statistics Correctly Applied	Wrong Things Right	Right Things Right

Key Application: Specifications

	Specifications Based on Process History	Patient-Centered Quality Standards
Statistics Incorrectly Applied	Wrong Things Wrong	Right Things Wrong
Statistics Correctly Applied	Wrong Things Right	Right Things Right

Key Application: Stability

	Empirical Models	Predictive Models
Statistics Incorrectly Applied	Wrong Things Wrong	Right Things Wrong
Statistics Correctly Applied	Wrong Things Right	Right Things Right

Call to Action:
Statisticians Can Lead The Transformation

Accelerate development and expand access by adopting patient-relevant design and predictive stability, enabled by precision analytical characterization.

Mine the depths of connected Clinical-CMC-real world data using AI, machine learning, and advanced multivariate data analysis.

Put the Potency assay in its (proper) place.

Thank you!

Campa, C. and O'Neill, J., Specifications for Vaccines In: Riley and Nguyen, eds. Specification of Drug Substances and Products: Development and Validation of Analytical Methods, Third Edition. Elsevier, 2024.

O'Neill, J. Analytical Characterization in an Era of Precision Vaccinology. Vaccine Insights 2024; 3(4), 125–135. DOI: 10.18609/vac.2024.023