# Quality by Design for mRNA Products

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# Outline

The challenges faced by developers & reviewers

Science and Quality by Design to the rescue

Translating to practice

# Challenge #1:

New modalities are **new**.

# Challenge #2: Acceleration

1966 – 2016

ASU Foundation Professor Connie Borror

ASQ Shewhart Medal 2016

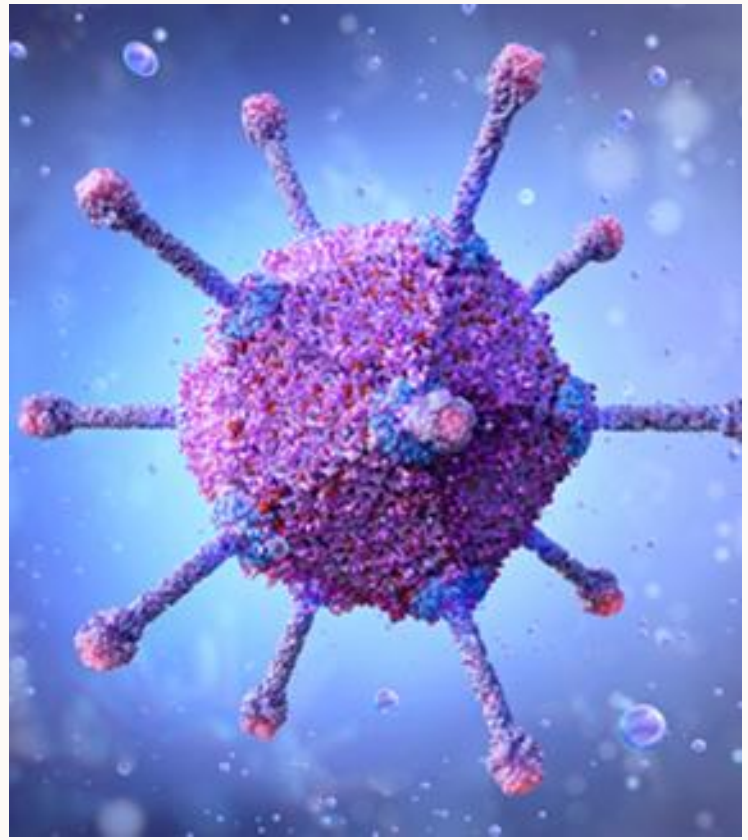
# Challenge #3: Traditional Reliance on Quality by Inspection

Complex “large molecule” biological products were considered too difficult to fully characterize.

“A fixed process equals a fixed product.”

Don’t change anything!

# Challenge #4:
# Analytical Characterization Can Be Complex



# Summary of Challenges Faced By Developers & Reviewers

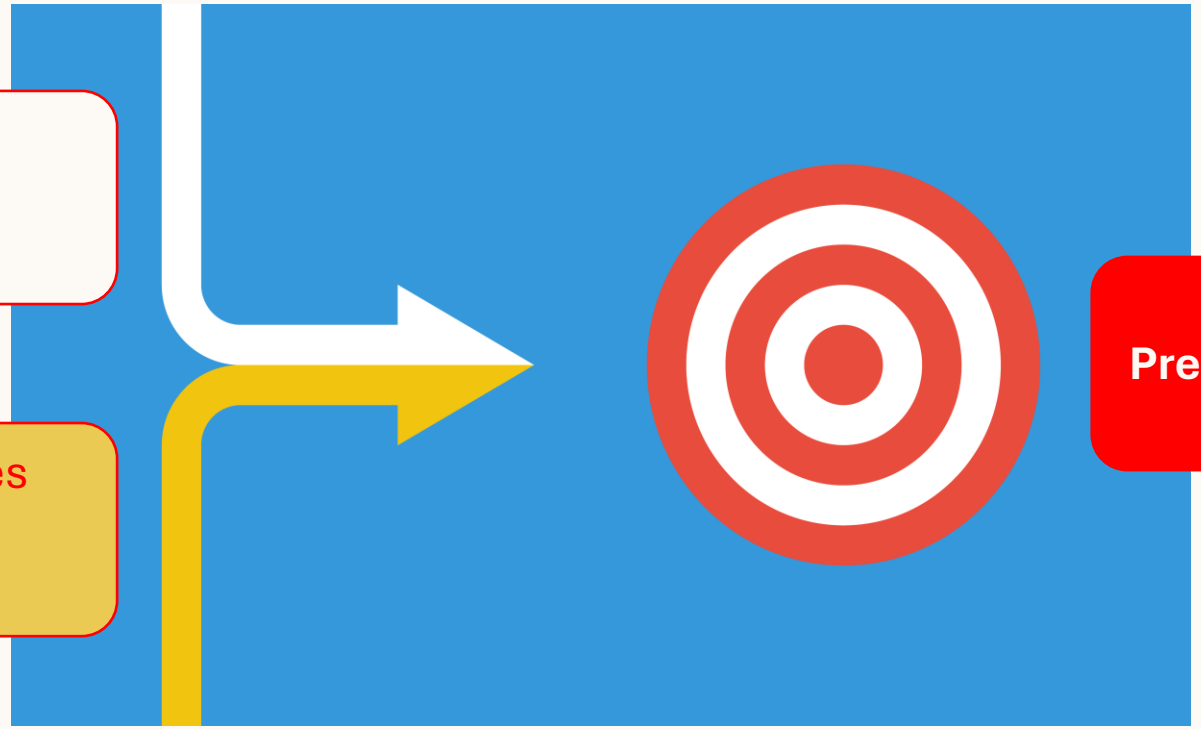
- New modalities are NEW
- Urgency
- Traditional reliance on Quality by Inspection
- Complexity of assays

# Science (and Precision QbD) to the Rescue

# Precision QbD Helps Us Overcome These Challenges.

Advances in Immunology

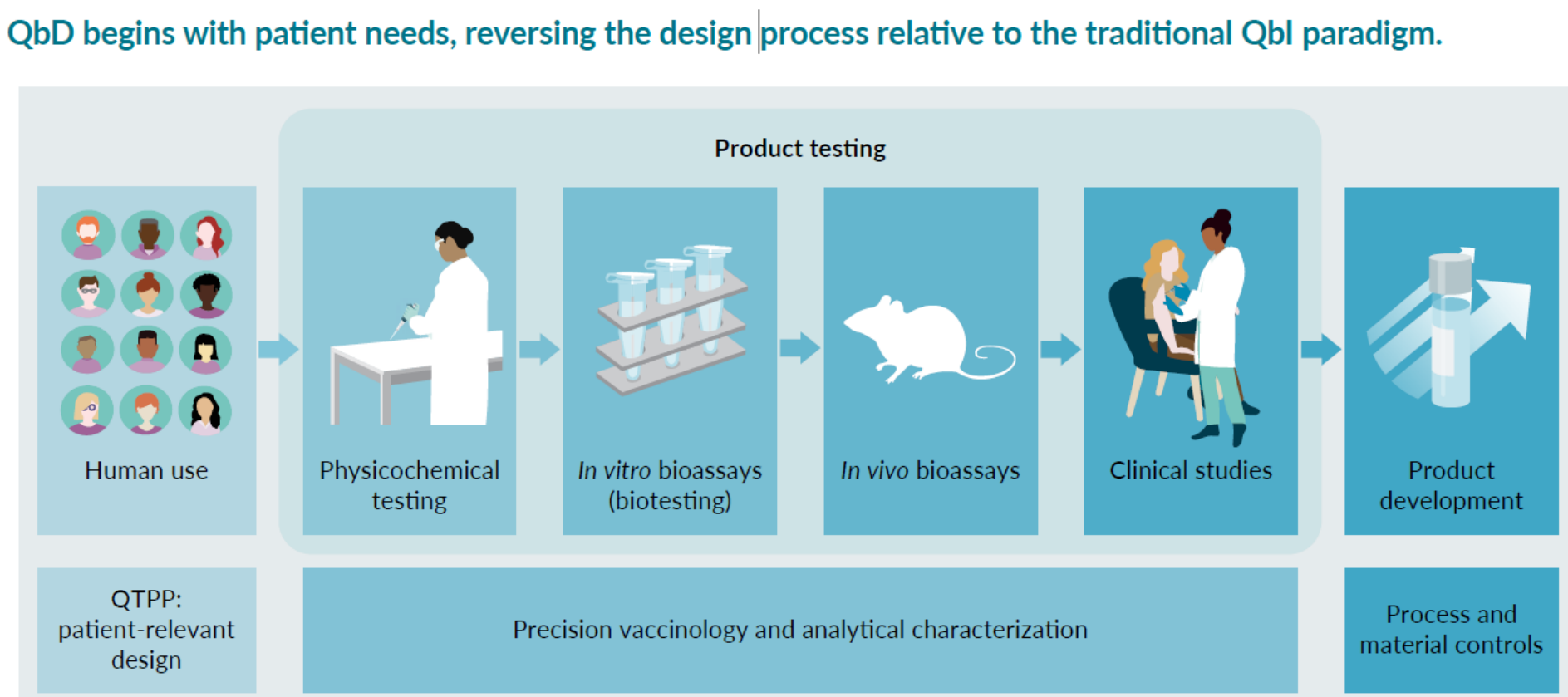
Biotechnologies accessible to developers



**Precision QbD**

# Quality by Design Begins with the Patient.

Vaccine Insights; DOI: 10.18609/vac.2024.023



# Vaccine Critical Quality Attributes

SPECIFICATION OF DRUG SUBSTANCES AND PRODUCTS DEVELOPMENT AND VALIDATION OF ANALYTICAL METHODS THIRD EDITION

| 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 | | |

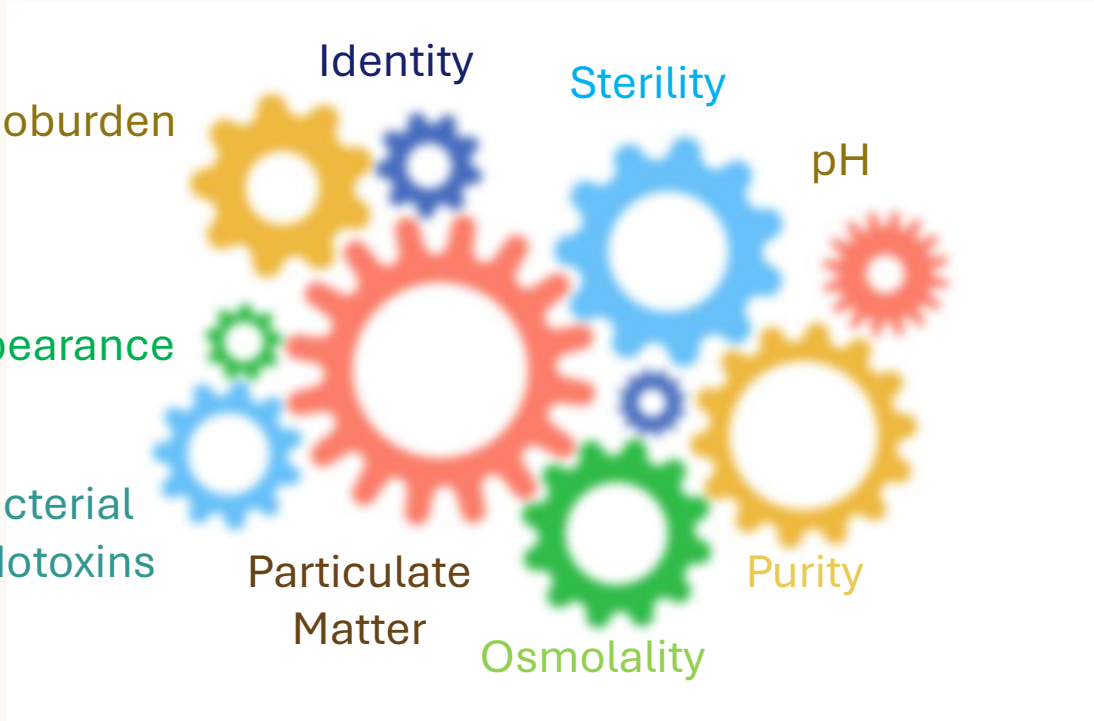
# Claim: Analytical Characterization Can Predict Both Safety & Effectiveness.

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

Safety

Effectiveness

# 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

# Learnings from Safety Risk Monitoring for Vaccines Administered To Very Large Groups

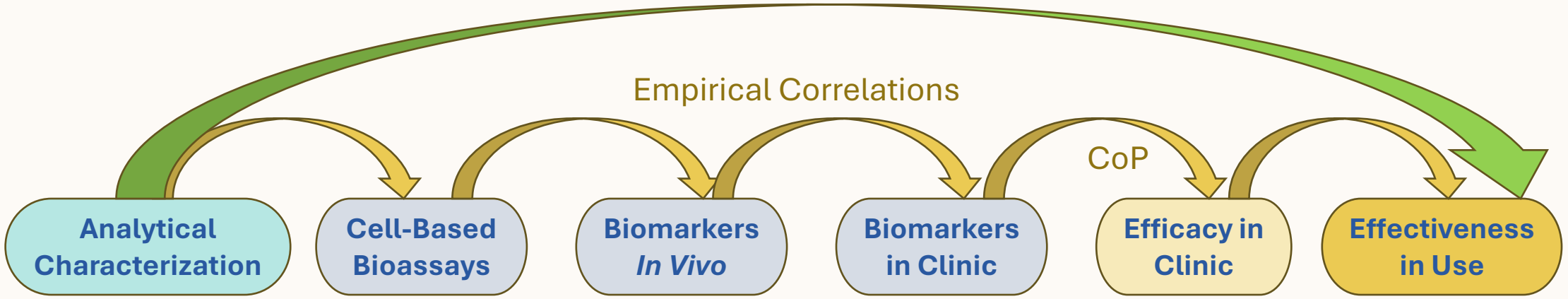
| Stage | Example Group Size | Expected Myocarditis Events | | |
|---|---|---|---|---|
| | | Unvaccinated | Vaccinated | Infected |
| ***Rate of Mycarditis per Million*** | | ***6*** | ***22*** | ***103*** |
| Phase 1 | 100 | 0.00 | 0.00 | 0.01 |
| Phase 2 | 500 | 0.00 | 0.01 | 0.05 |
| Phase 3 | 3,000 | 0.02 | 0.07 | 0.31 |
| Phase 2/3 (COVID) | 21,720 | 0.14 | 0.49 | 2.25 |
| In Use (one billion) | 1,000,000,000 | 6,391 | 22,369 | 103,424 |

DIREXA

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

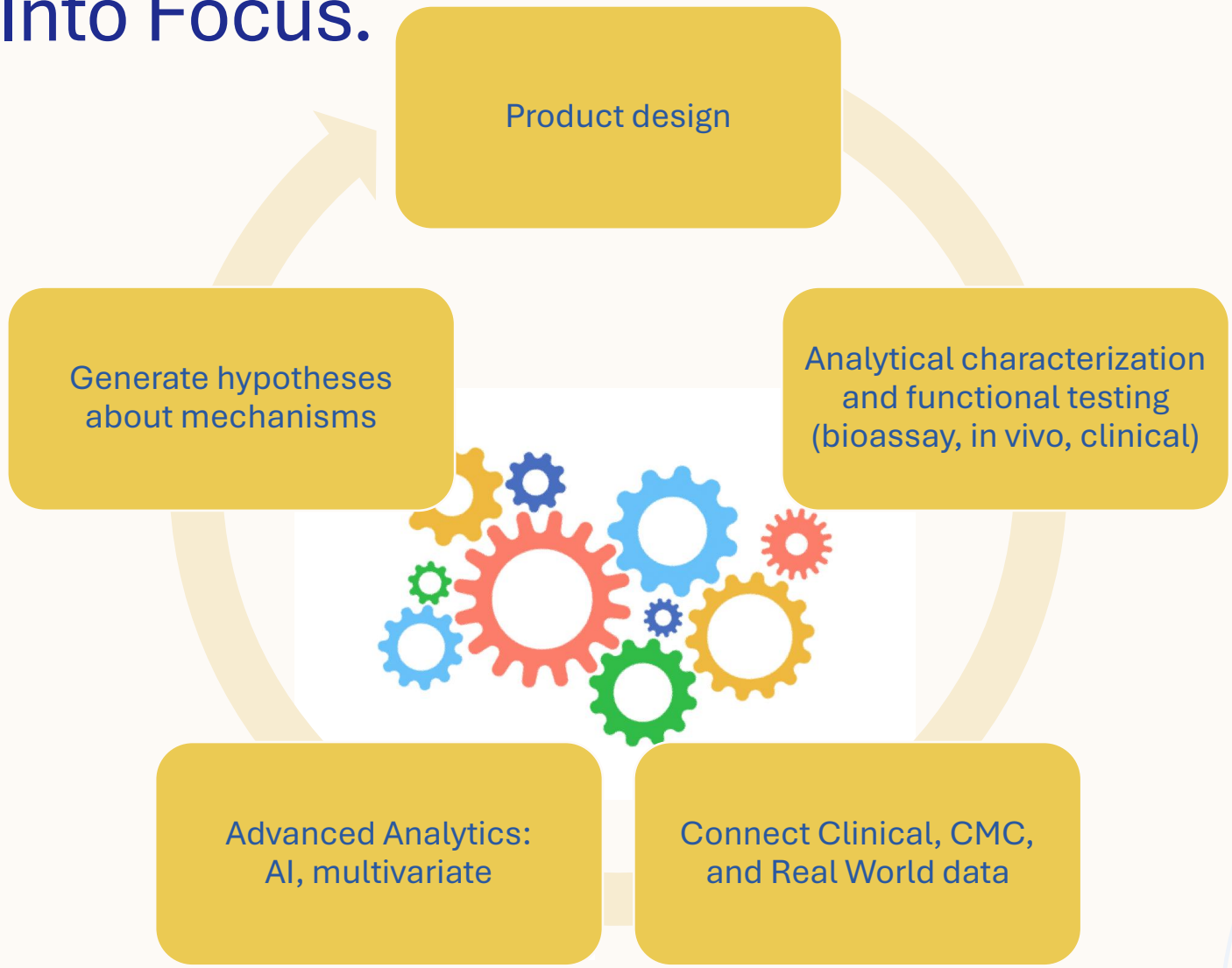
# Predicting Effectiveness Has Other Challenges.

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

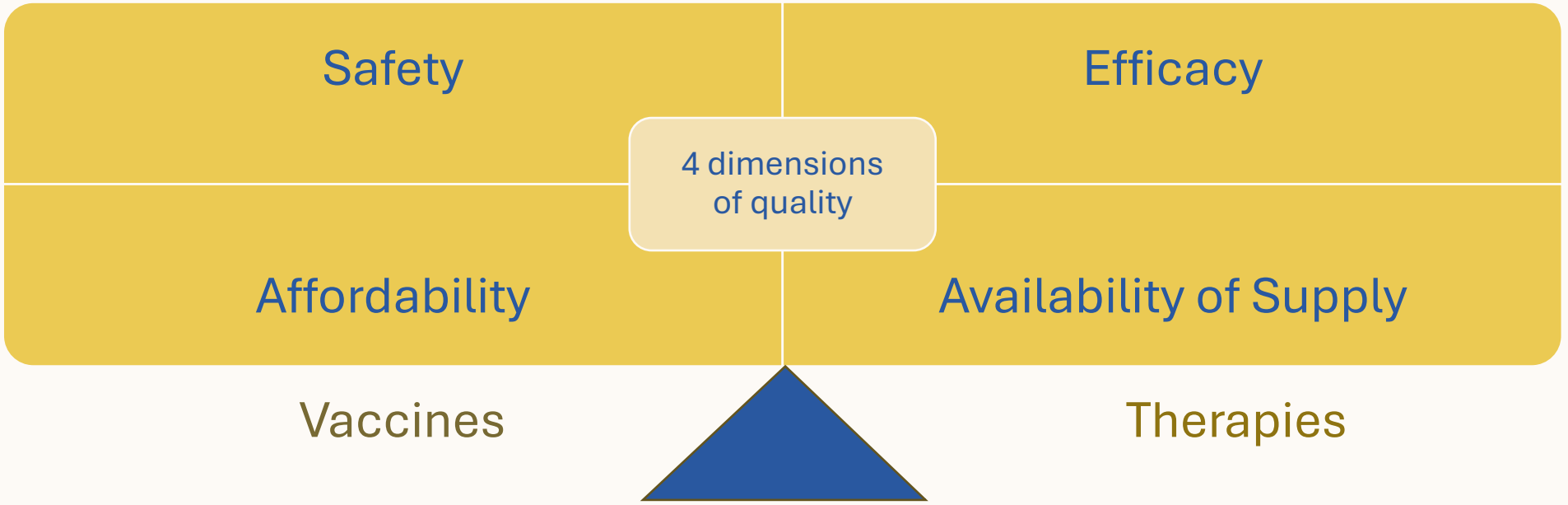



| | | | | | |
|---|---|---|---|---|---|
| **Correlates to effectiveness?** | Via mechanism of action | “Functional tests”, empirical correlation | | | Ultimate measure. Gold standard. |
| **Represents diversity in recipients?** | Independent of recipients | Designed for homogeneity but inherently variable | 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 |

# Precision QbD and Advanced Analytics Bring Mechanisms Into Focus.



# What really matters to patients and health care practitioners?



# How Science and QbD Enable mRNA Therapies

- Advances in immunology, biotechnologies, and advanced analytics prepare us to predict safety and effectiveness from product characterization
- The dimensions of quality important to patients and health care providers are very similar for vaccines and therapies – the weighting is different

# Translating to Practice

# Specifications for Individualised mRNA cancer immunotherapies

MHRA Draft Guideline published 3 February 2025

741 **4.2.7. Release testing and potency**

742 The specifications define the active substance regardless of variation in the starting
743 material. Wherever possible, the active substance, and final product should be
744 subject to release testing. It may be acceptable to omit release testing for the drug
745 substance if justified and authorised, but exhaustive control is expected at the drug
746 product level. Some release testing might not be possible on the formulated drug
747 product for technical reasons, so testing at the drug substance level will be required.
748
749 A typical set of mRNA drug substance tests could include appearance, particulates,
750 pH, endotoxin, bioburden, entire nucleotide sequence, RNA concentration, capping
751 efficiency, poly(A) tail, mRNA integrity, mRNA purity, residuals (which may be
752 template, enzymes, solvents, and nucleotides), and the functionality of the desirable
753 mRNA drug substance (e.g. protein expression). Where applicable, pharmacopoeial
754 limits should be adopted. This is not an exhaustive or prescriptive list, but it will

# ~~*Vaccine*~~ Therapeutic Critical Quality Attributes

| Typical Vaccine Critical Quality Attributes and Expected Relevance | | |
|---|---|---|
| **Safety** | **Efficacy** | **Compendial** |
| Identity | Identity | |
| Appearance | Activity | pH |
| Particulate matter | Immunogenicity | Osmolality |
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| Process-related Impurities | | |
| Product-related Impurities | | |

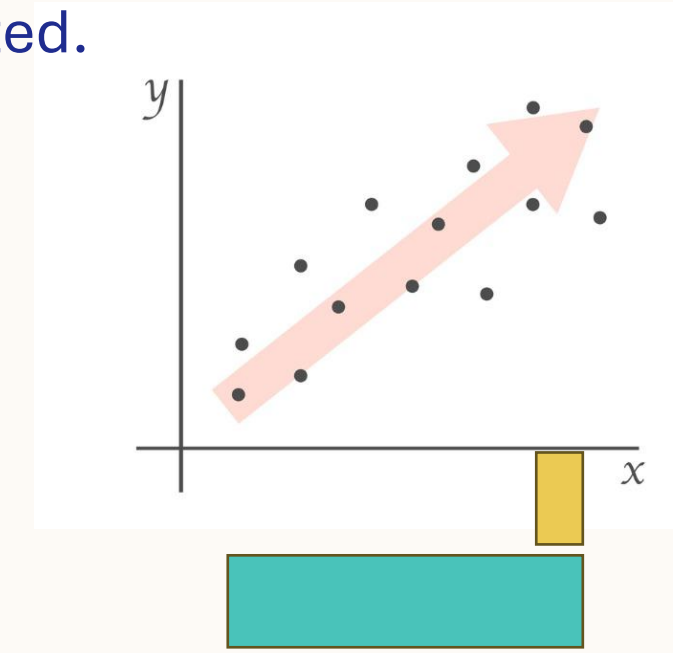
# Potency for Individualised mRNA cancer immunotherapies MHRA Draft Guideline published 3 February 2025

- Potency is the quantitative measure of biological activity based on the attribute of the product linked to the relevant biological properties.
- The potency assay should be based on the intended biological effect and ideally related to the clinical response. This is expected to be a challenge for individualised mRNA neoantigen immunotherapies.
- It is possible to justify the use of a potency assay that measures a product attribute that has been demonstrated to correlate with the intended biological effect. An analytical method that measures a correlate – such as protein expression - is considered a functionality assay rather than a true potency assay. The use of physicochemical measures, as a functionality test, in place of a cell-based expression assay need to be substantiated with adequate data to support biological correlation.

# 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

# Summary

Precision QbD overcomes traditional challenges in 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.

Precision Quality by Design delivers safety, efficacy, AND access.

# Call To Action

Accelerate development and expand access by adopting patient-relevant design, enabled by precision QbD.

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!

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