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What Was Gained / Lost with the Harmonization of Specifications with COVID-19 Vaccines

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Declarations

I have no financial conflicts of interest to disclose.

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How industry feels about regulations…

"Regulatory audit today?"

Key points

1. Specifications should be set using available clinically-meaningful data
   - Supports goal of harmonization

2. Contemporary experience (pre- and peri-pandemic) shows the value of a patient-centric approach
   - But it also highlights barriers facing both industry and regulators

3. We have to move the science forward together
   - Forward-looking pre-clinical and clinical work
   - Scientific, risk-based regulation that keeps the clinical profile in focus

Specifications

Setting specifications

- Specifications have traditionally been based on release results from lots manufactured using the final commercial process.
  - Expectation is that specification will be revised as manufacturing experience increases
  - When X < 30, we accepted a wider specification based on 2 or 3 standard deviations from the target value based on the variability of the assay.

- Based on an assumption that tighter specifications reflect/assure better control of product quality.
  - Process is under control
  - Assay is fit for purpose

Specifications vs Process control

Specifications should be within the clinically relevant lower and/or upper limits (“clinical window”) for CQA (e.g., potency, impurities, etc.) that assure the *efficacy and safety* profile established in clinical trials.

Process controls ensure that manufacturing is executed and operates consistently, within approved ranges/boundaries.

- The more robust the control strategy, the more confidence one should have with sample test results near the limits.

New paradigms affecting specifications

- Push for global harmonization
  - One product in all jurisdictions
  - Equitable allocation/access/surveillance
- Quality by Design – better understanding of overall process
  - “The process is the product”
  - “You can’t test quality in”
- Need to define and capture product shelf-life
  - End of shelf-life vs release specifications
- Patient-centricity
  - ICH Q8A(R2): QTPP links quality to safety/efficacy
  - Q6B (though vax excluded) criteria acceptable for intended use

Patient-centric Specifications

- PCS already in use (based on pivotal trial materials), but the concept is not officially defined in guidance
  - Least data input = **most** conservative specification

What data can be used to support setting PCS?

- Early phase trials can help define appropriate lower and upper limits for PCS
  Not common, nor always feasible

- Need consensus on the extent and type of data needed
  Industry can drive, but regulators need to adjust approach

“The PCS is too wide...”

- Manufacturing capability-based specifications can lead to challenging regulatory exchanges
  - “Arbitrary” regulatory decisions from an industry perspective, which can repeat over the product lifecycle
  - Globally, there remains a regulatory tendency to require tightening of specifications that are based on manufacturing capability
  - Process controls and quality systems assure of quality

- PCS provide more leeway for assay and process improvements over a lifecycle
  - Resistance can be a disincentive for assay and process improvement, since that may also result in agency requests for specification tightening.

- PCS limits don’t need to be fixed, but shouldn’t be subject to manufacturing!
  - New clinical data, RWE, post-market surveillance

Are PCS too wide?

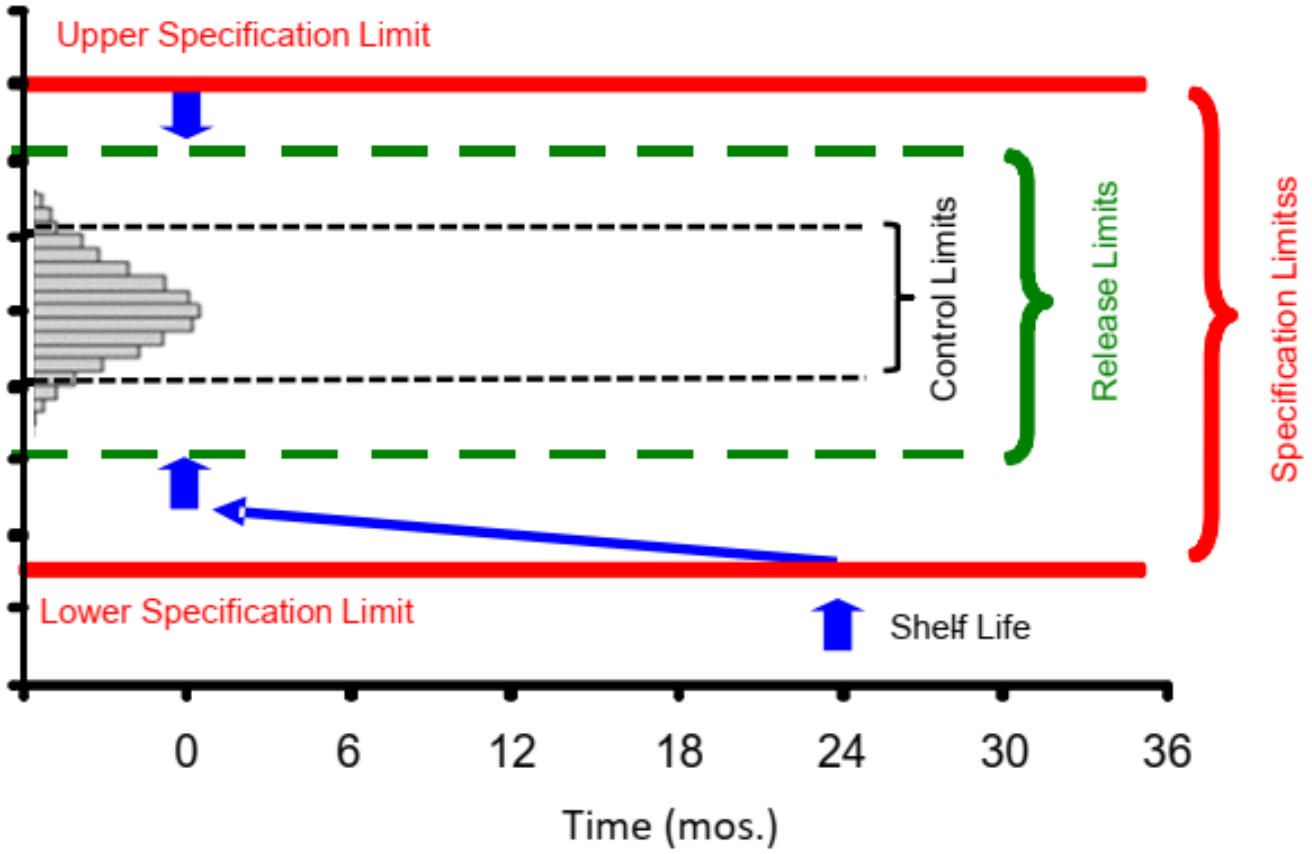
- Process controls, robust quality systems keep manufacturing processes under control, *not specifications*

- Manufacturing still subject to trend analysis, process improvements
  - This supports ongoing process development and lifecycle management !

- More robust process control means greater confidence in the release test result.
  - We need to get away from the belief that release specifications assure quality – they **confirm**
    - e.g., Sterility. **Material/process controls/design** result in a sterile product

Patient-centric specifications

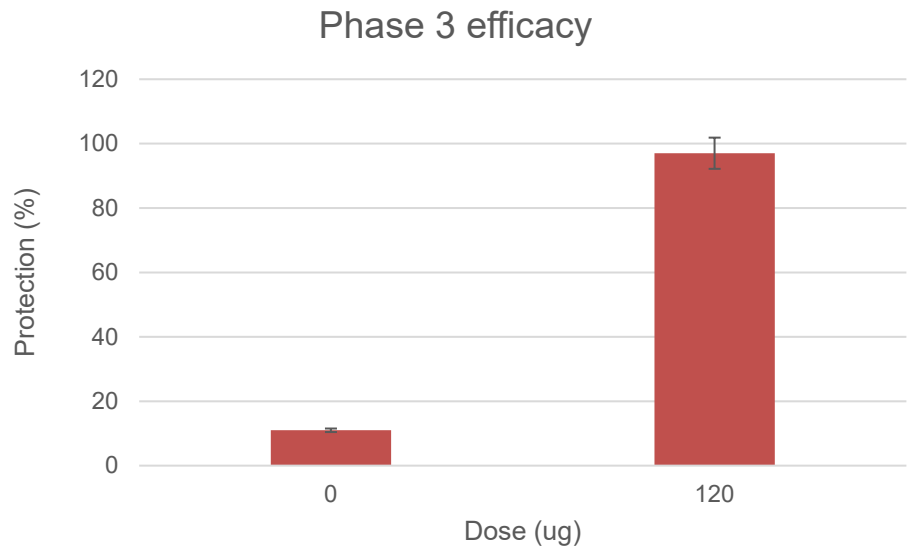
Manufacturing-based specifications tie the hands of both regulators and manufacturers!



Adapted from Tim Schofield CASSS NA CMC Strategy Forum 2023

Case studies

Thought experiment: PCS and dose-ranging



- Phase 3: safe, efficacious dose is 120 µg
- Phase 2: underlying response saturated at doses NLT 40 µg

- Wider release specification supports scale-up/out, process improvement over lifecycle
  - EOSL specification to maximize shelf life
  - Pre-clinical, other sources of data may support these determinations

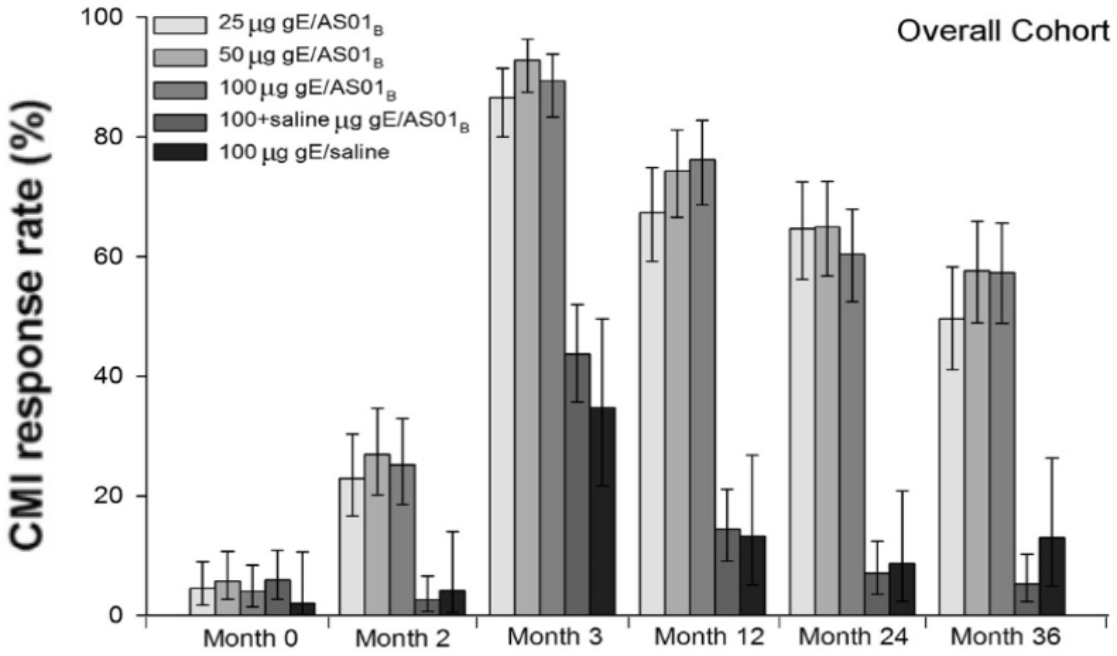
PCS case study: Shingrix

- Varicella-zoster virus subunit (VZV gE) vaccine, $AS01_B$ adjuvant.
  - **Phase 3 efficacy**:
    - Placebo-controlled (1:1)
    - 2 doses (50 ug gE + $AS01_B$)
    - Primary endpoint: reducing risk of herpes zoster & postherpetic neuralgia
    - https://doi.org/10.1056/NEJMoa1603800

  - **Phase 2 dose ranging:**
    - 2 doses 25, **50** or 100 μg gE in $AS01_B$
    - 1 dose 100 μg gE in $AS01_B$
    - 2 doses of 100 μg gE in saline.
    - https://doi.org/10.1016/j.vaccine.2014.01.019

- No established shingles correlate of protection (CoP)
  - CMI correlated with reduced HZ severity/postherpetic neuralgia
  - Humoral response not correlated with protection

PCS case study: Shingrix



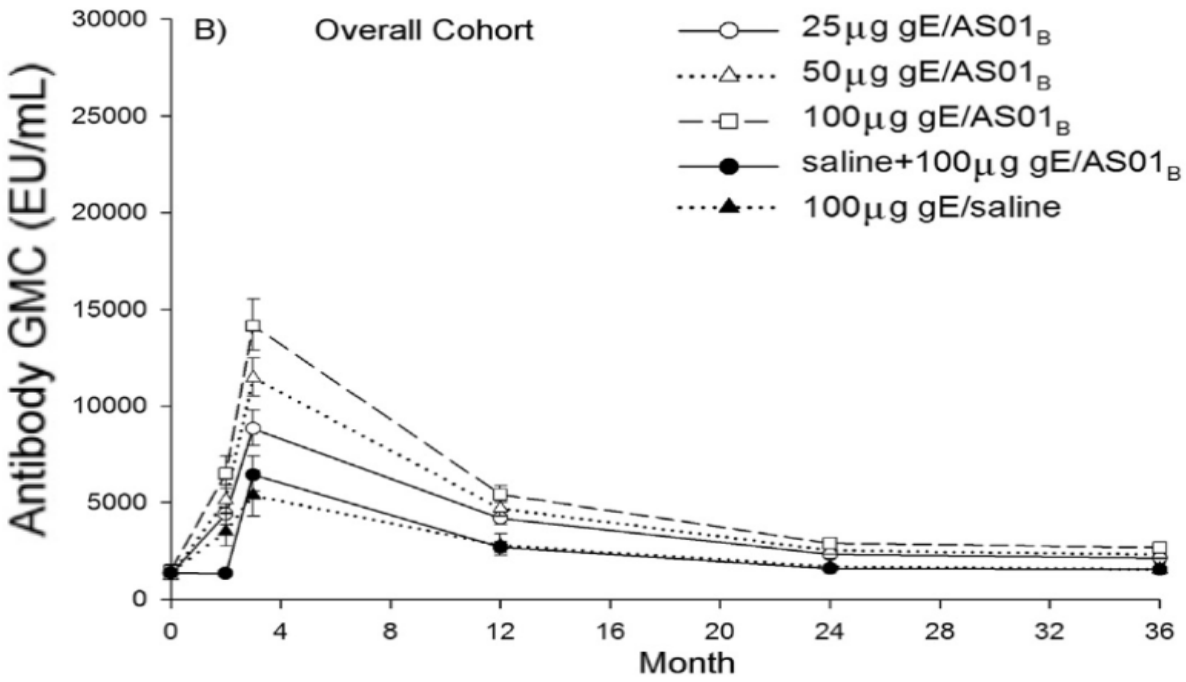
CMI

- Proportion of subjects with gE-specific $CD4^+$ cells
  - ≥ two activation markers (e.g., IFN-γ, IL-2, TNF-α, and CD40L) per 10^6 cells
  - Proportions overlapped over all 2x dose ranges

- $CD8^+$ gE-specific T cells undetectable following immunization, as well as with a LAIV comparator

https://doi.org/10.1016/j.vaccine.2014.01.019

PCS case study: Shingrix



Humoral response

- Serum anti-VZV/ IgG by ELISA.
- Concentrations comparable in 50/100 µg (2x) dose groups, lower in 25 µg (2x) group
- N.B., humoral responses not correlated with protection

https://doi.org/10.1016/j.vaccine.2014.01.019

PCS case study: Shingrix

- Broad potency specification approved based on Phase 3 efficacy data, **supported by phase 2 immunogenicity data**

- Specification broader than phase 3 clinical trial and PPQ batch potencies
  - Spec is derived from *clinical performance*

- Specification was harmonized across HC/FDA/EMA
  - Example of regulatory co-operation
  - Simplified lot allocation, release

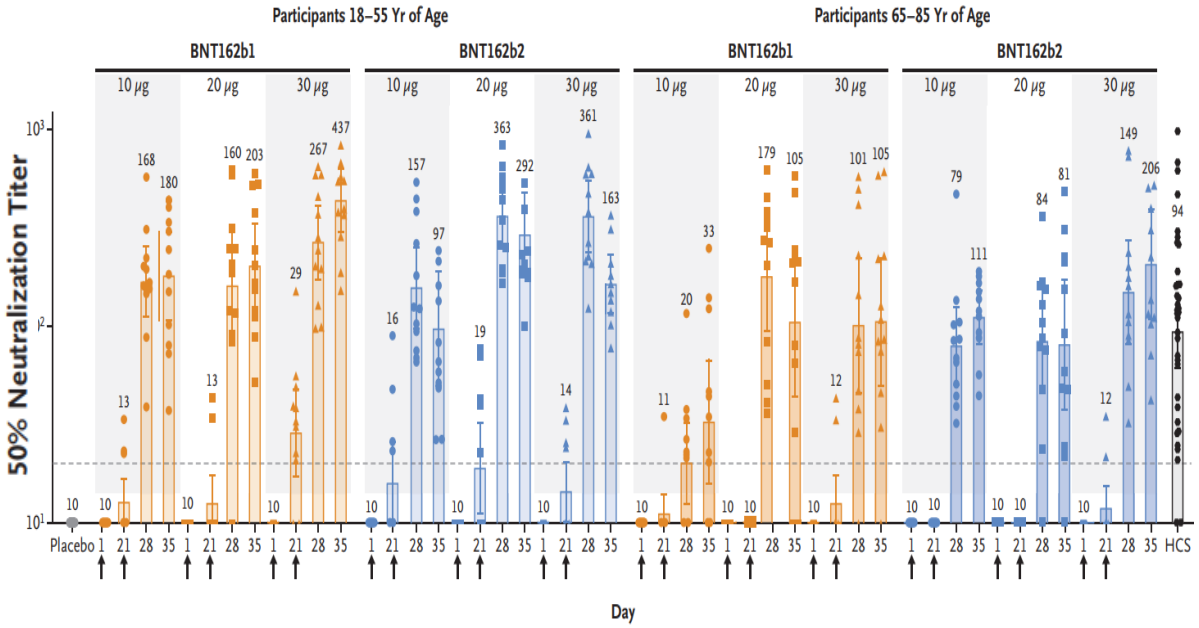
However, this was not an easy regulatory process for any of the parties.

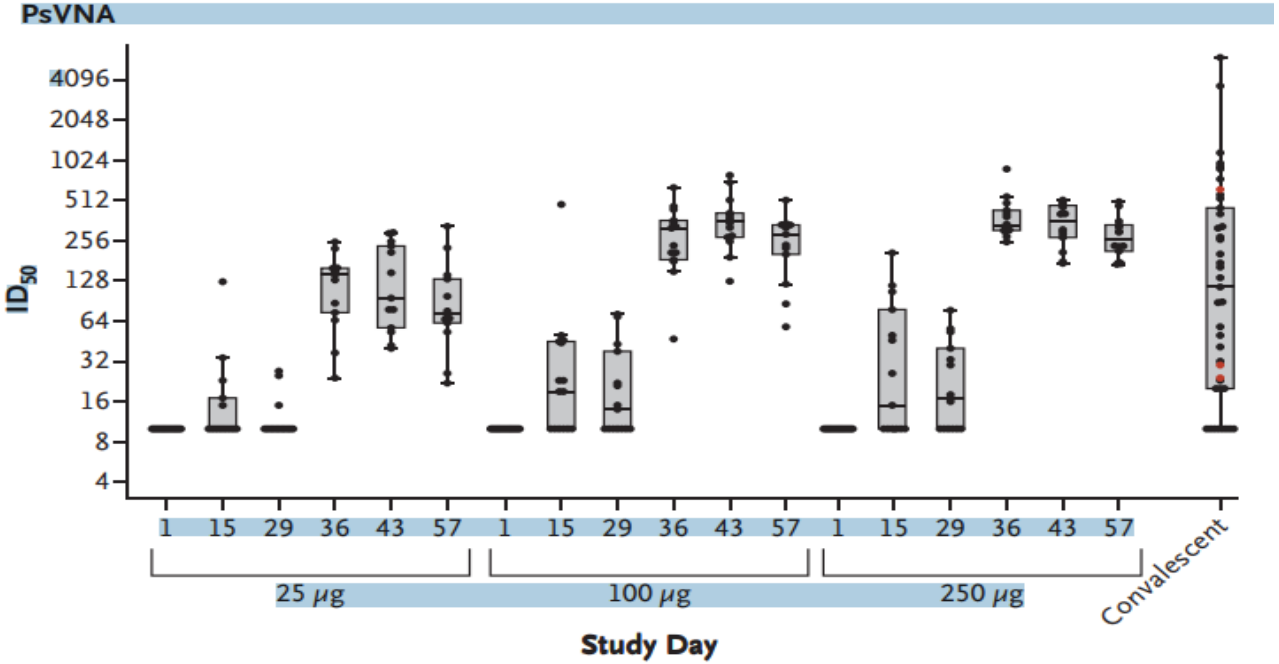
Case: COVID-19 mRNA vaccines

- Phase 2 studies for both Pfizer-BioNtech and Moderna included:
  - Dose-ranging elements
  - Immunogenicity characterization (bAb/nAb, CMI, Th_1/Th_2, etc.)
  - Aggregate potency assessment:
    - 5’ cap/3’ poly A tail
    - % encapsulation in lipid nanoparticle
    - % full-length sequence

- No CoP
  - Pre-clinical studies supported nAb as an important mediator of protection

Case: COVID-19 mRNA vaccines





Pfizer-BioNtech
https://doi.org/10.1056/NEJMoa2027906

Moderna
https://10.1056/NEJMoa2022483

Case: COVID-19 mRNA vaccines

- Broad immunogenicity characterization from phase 2 studies:
  - Permitted harmonized (FDA, HC and EMA) specifications wider than phase 3 clinical lot potencies
  - Supported rapid scale-up and scale-out, QbD approach to process validation
  - Expedited approvals

- Using QbD expedited approvals
  - Could approve shelf life using patient-centric EOSL spec, stability data from development/clinical materials, without necessarily knowing process window at scale!

- Post-authorization effectiveness studies using compliant marketed lots supported this approach

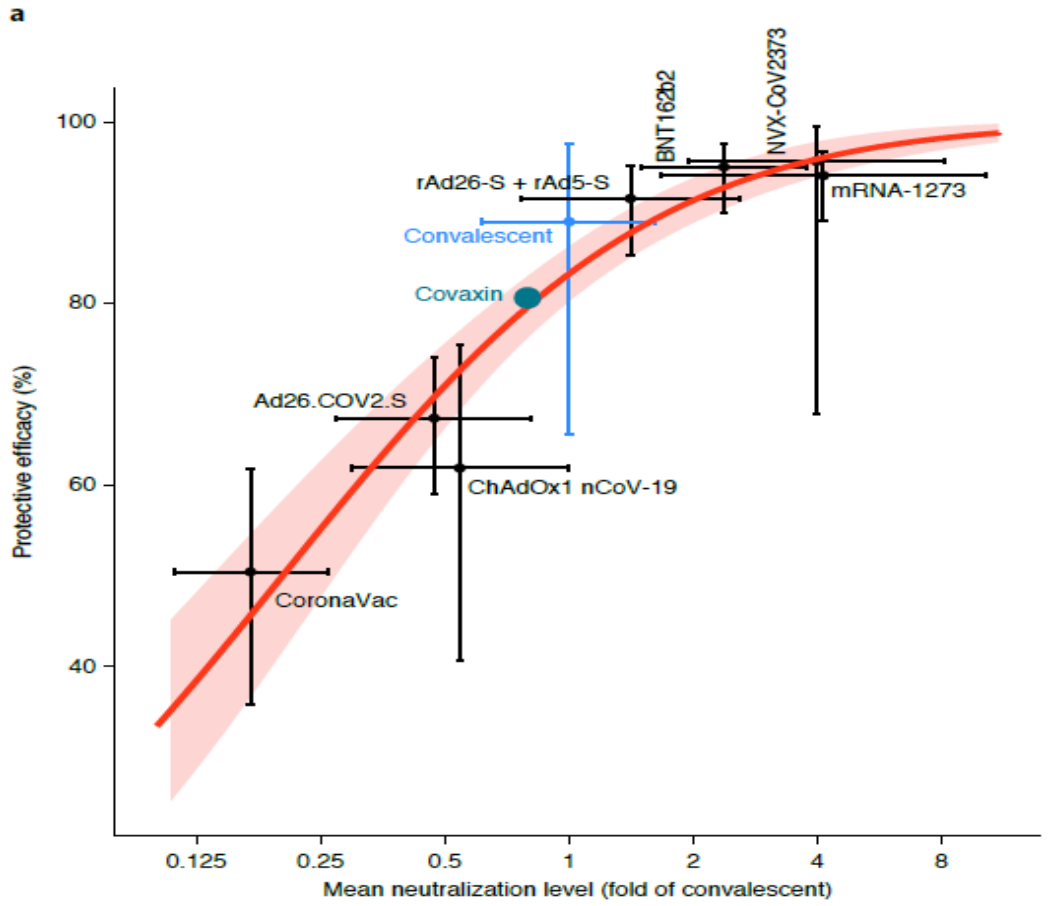
Case: COVID-19 mRNA vaccines

Wide number of studies support nAb as an important effector of protection

- Supported by preclinical studies

- Validated by work of Davenport group (Khoury et al., 2021)
  - Relevant across multiple platforms

Pre-clinical and phase 2/3 data-informed specifications helped expedite and maximize supply without jeopardizing effectiveness



Final thoughts

Potential benefits of PCS

For manufacturers:

- Fewer OOS, longer shelf life, easier process/analytical improvement, lower-risk regulatory interactions, targets for QbD

- Forward-thinking pre-clinical and clinical studies can support:
  - Robust and defensible harmonized product specifications that should not be prone to tightening over lifecycle
  - Rapid scale up in emergency situations where additional manufacturing optimization is challenging due to public health needs/time constraints

- By investing in strategies to set PCS, manufacturers benefit from process improvements vs penalization under a manufacturing-based specification

- CoP analyses can expedite future clinical and product development

Potential benefits of PCS

For regulators:

- More extensive data sets facilitate decision-making
- Globally harmonized specifications
- Increased confidence that specifications assure desired quality
- Reduced likelihood of shortages affecting supply
- Ensure equitable lot access (impacts post-market surveillance)

Barriers to using PCS

- Lack of a of consensus regarding the value for both regulators and manufactures of PC vs. manufacturing-based specifications.
- Lack of transparency/coherence of specification justifications
- Restrictions on inter-agency communications that might otherwise aid collaboration in harmonizing specifications
- National and/or regional regulations or requirements, including pharmacopeia

Final words

Basing specifications on all elements of clinical and manufacturing experience including prior clinical/scientific knowledge and platform experience, rather than only process capability, has many advantages for regulators, manufacturers, and patients!

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