The Need for Science and Risk-Based Approaches to Setting Specifications: A Regulatory Perspective

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Disclaimer

The views and opinions expressed in this presentation are those of the presenter and do not necessarily reflect the official policy or position of Health Canada or the Government of Canada.

How industry feels about regulations…

"Regulatory audit today?"

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*Temporarily not engaged with ECBS, due to current US Administrant’s position regarding WHO

Key Points

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

2. Contemporary experience (pre- and peri-pandemic) shows the value of enhanced approaches and stable clinically relevant specifications*
   - But it also highlights barriers facing both industry and regulators

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

Specifications

Setting specifications

- Specifications have typically 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
- However, the assumption that tighter specifications are superior must now be challenged, since this approach does not serve regulatory or patient needs*.

Specifications vs Process control

Specifications should be within the clinically relevant lower and/or upper specification limits for CQA (e.g., potency, impurities, etc.) that assure the *efficacy and safety* profile established in clinical trials, and as supported by platform and prior knowledge as scientifically justified.

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.

Current paradigms affecting specifications

- Push for global harmonization
  - One product in all jurisdictions
  - Equitable allocation, access and supports pharmacovigilance*
- Revisit 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
- Enhanced approaches to setting specifications
  - ICH Q8A(R2): QTPP links quality to safety/efficacy
  - Q6(R1) science driven, risk-based approaches as justified for intended use, not restricted to batch data*, and will now include vaccines, ATMPs, oligonucleotides and complex drug-device combinations

Traditional vs Enhanced Approaches

- “Traditional approach” (TA): CQAs with Phase 3 lots in pivotal trials,

  least data input = **most** conservative specification

- “Enhanced approaches”(EA) based on clinically relevant data, and hopefully the Q6(R1) process will emphasize the need for TA or EA generated data to establish clinically relevant (CR) stable specifications*

- **What data can be used to support EA clinically relevant specifications?**
  - Early phase trials can help define appropriate lower and upper limits for EA specifications

    Currently not common, nor always feasible
  - Clinically relevant prior knowledge and platform data
  - Need consensus on the extent and type of data needed

    Industry can drive, but regulators need to adjust approach given the value of clear science-based clinically relevant justifications, anchored in prior-knowledge, and platform experience

Stable clinically relevant (CR) specifications

- 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
- Traditional and enhanced approaches for stable specifications provide an incentive for assay and process improvements over a lifecycle (i.e., continuous improvement)
  - Tightening of specifications based solely on batch data is a disincentive for assay and process improvement,
- CR limits can be adapted as required but not reduced due to improved manufacturing
  - New clinical data, RWE, post-market surveillance should inform all specifications

Why is there capability-based spec. tightening ?

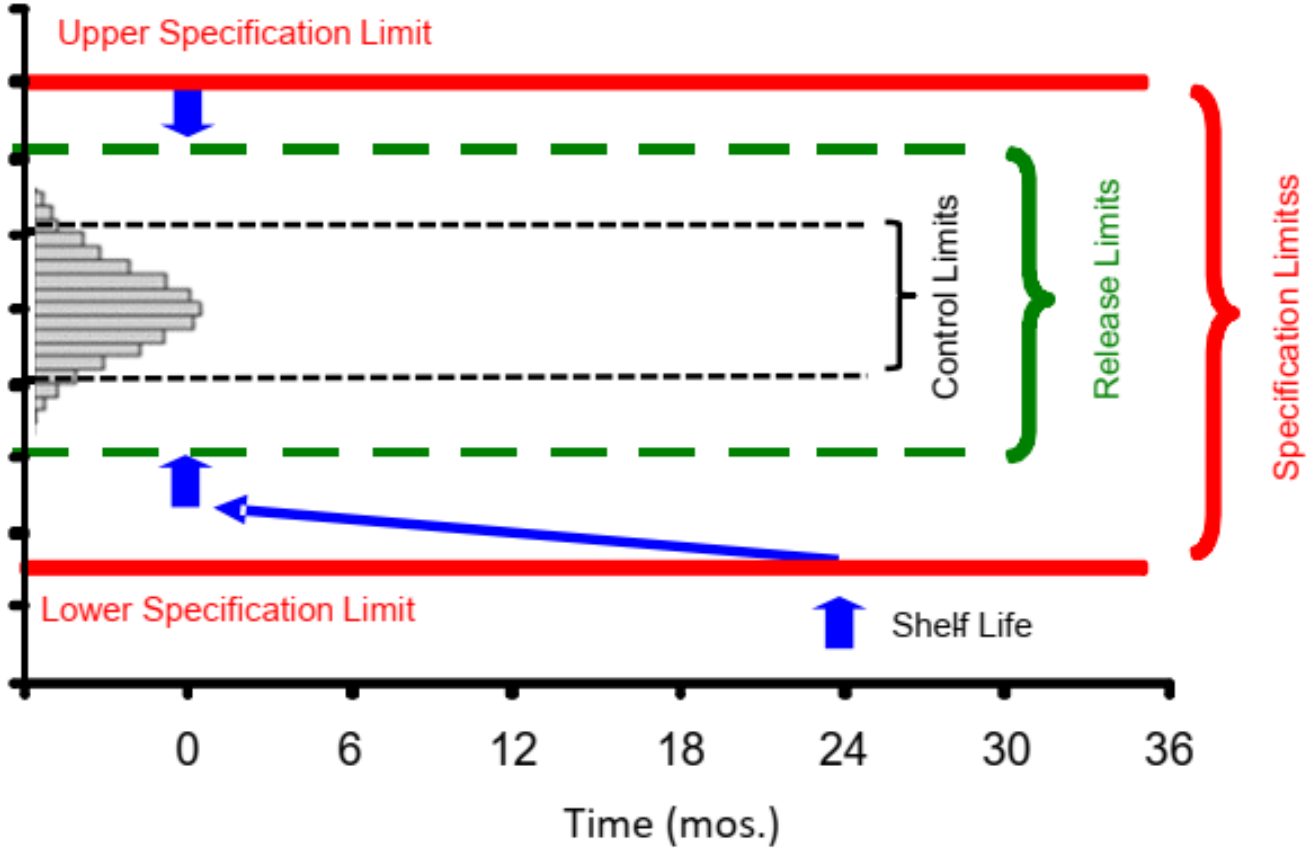
- Process controls, robust quality systems keep manufacturing processes under control, *not specifications,* although many regulators still believe otherwise.

- 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 must get away from the belief that release specifications assure quality – they **confirm**
    - e.g., Sterility. **Material/process controls/design** results in a sterile product

Enhanced-approach specifications

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



Adapted from Tim Schofield CASSS NA CMC Strategy Forum 2023

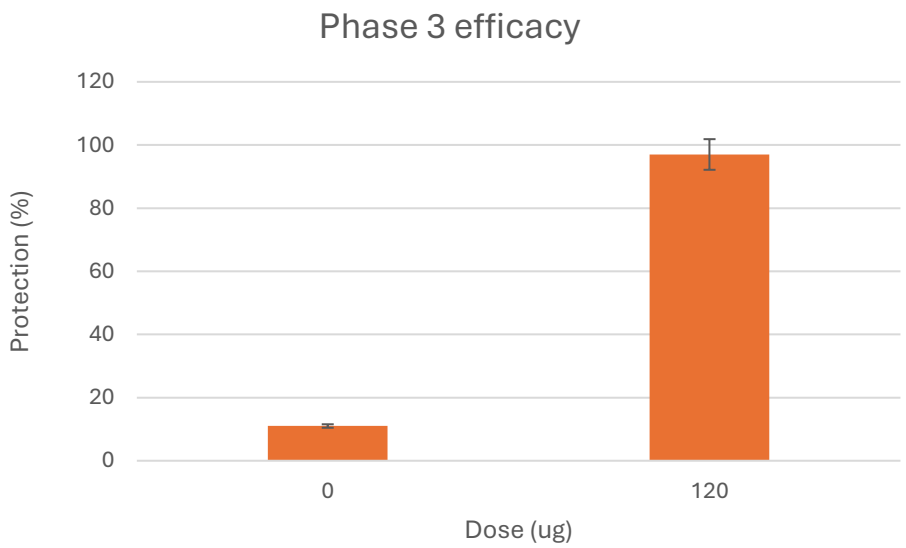
Dose ranging Studies with Enhanced Approach Vaccine Potency Specifications

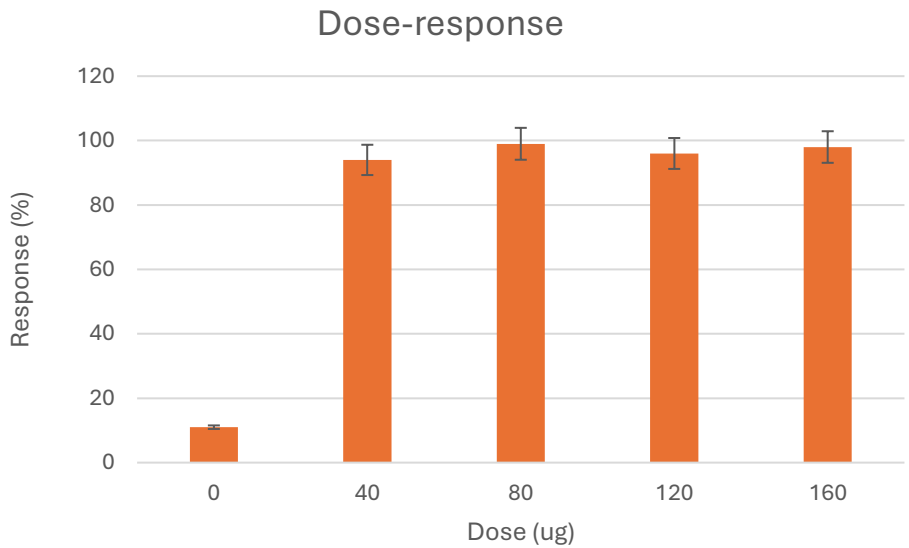
- Broadly characterized immunogenicity (e.g., binding & neutralizing antibodies (Ab), antigen (Ag) specific cell mediated immunity (CMI)) in early dose ranging trials, linked to stability indicating critical quality attributes (CQA) required for clinical performance such as potency supports:
  - clinical / product development and manufacturing scale up,
  - expedited COVID-19 authorizations.

- Well characterized immunogenicity in dose ranging studies also supports correlates of protection (CoP) analyses and expedites future development.

Case Studies

Dose-Ranging Can Support Potency Specification



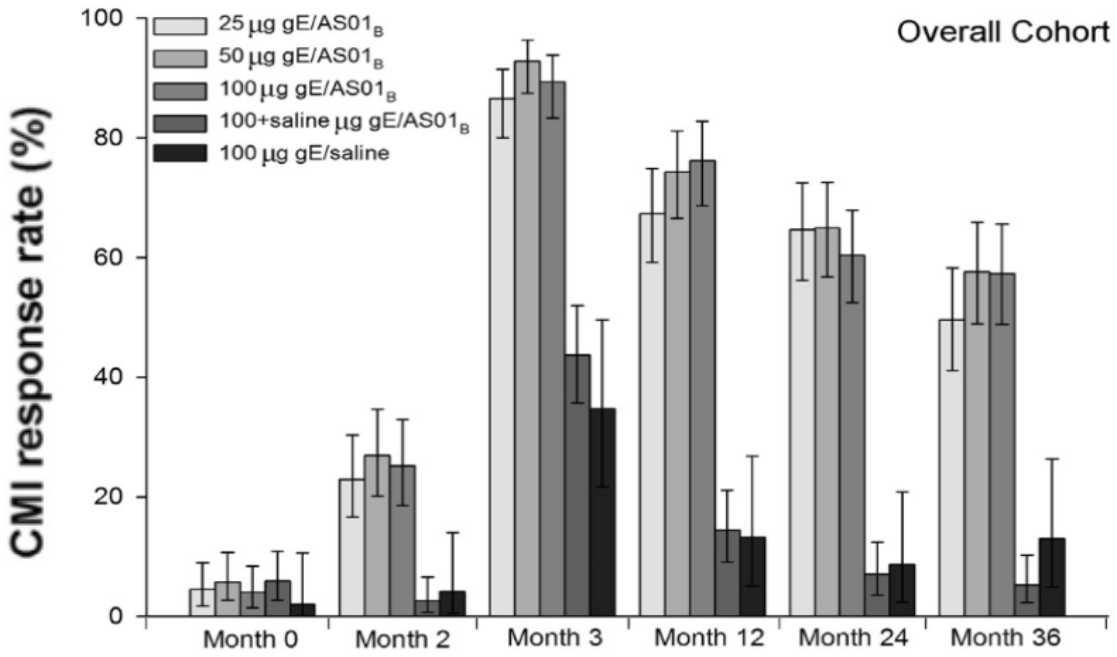


- Phase 3 Simulated data: safe, efficacious dose is 120 µg
- Phase 2 Simulated data: underlying response saturated at doses NLT 40 µg
- Wider release specification supports scale-up/out, process improvement over lifecycle
    - End of shelf-life (EOSL) specification to maximize shelf-life
    - Pre-clinical immunogenicity and pathogen challenge studies, as well as other sources of data may support these determinations

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

Case Study: Shingrix

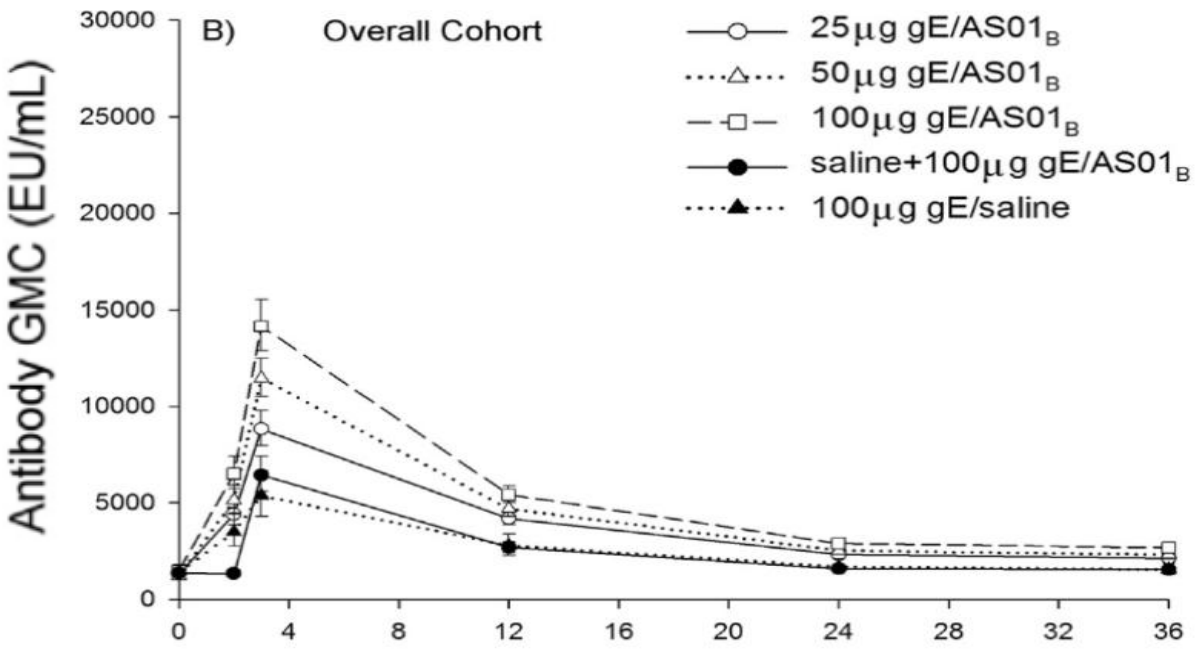


CMI

- 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

Case Study: Shingrix



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

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

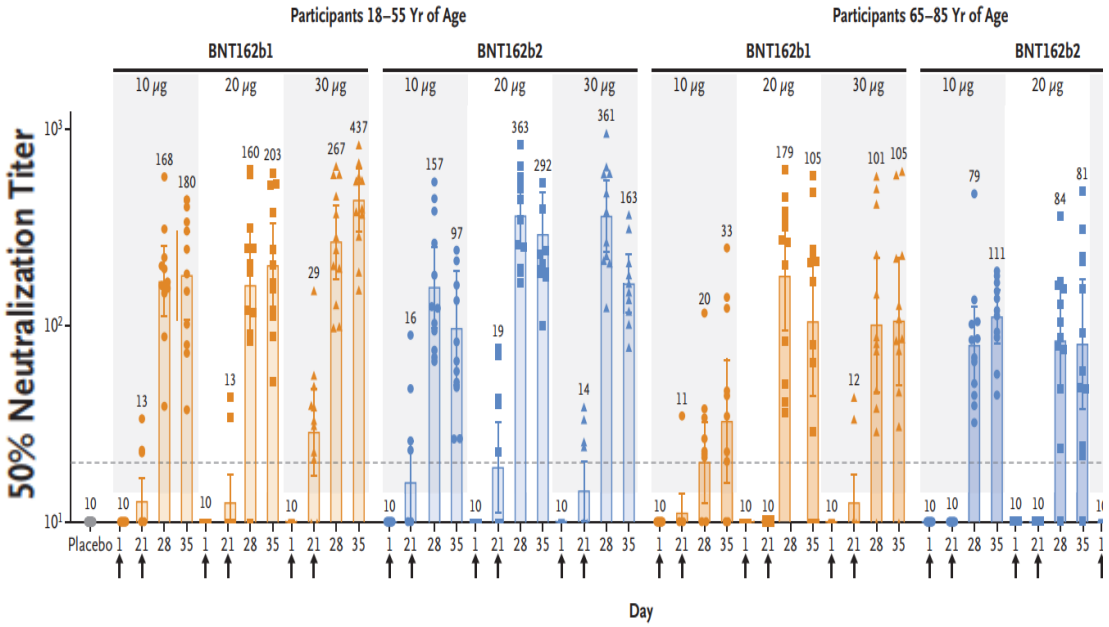
Case Study: Shingrix

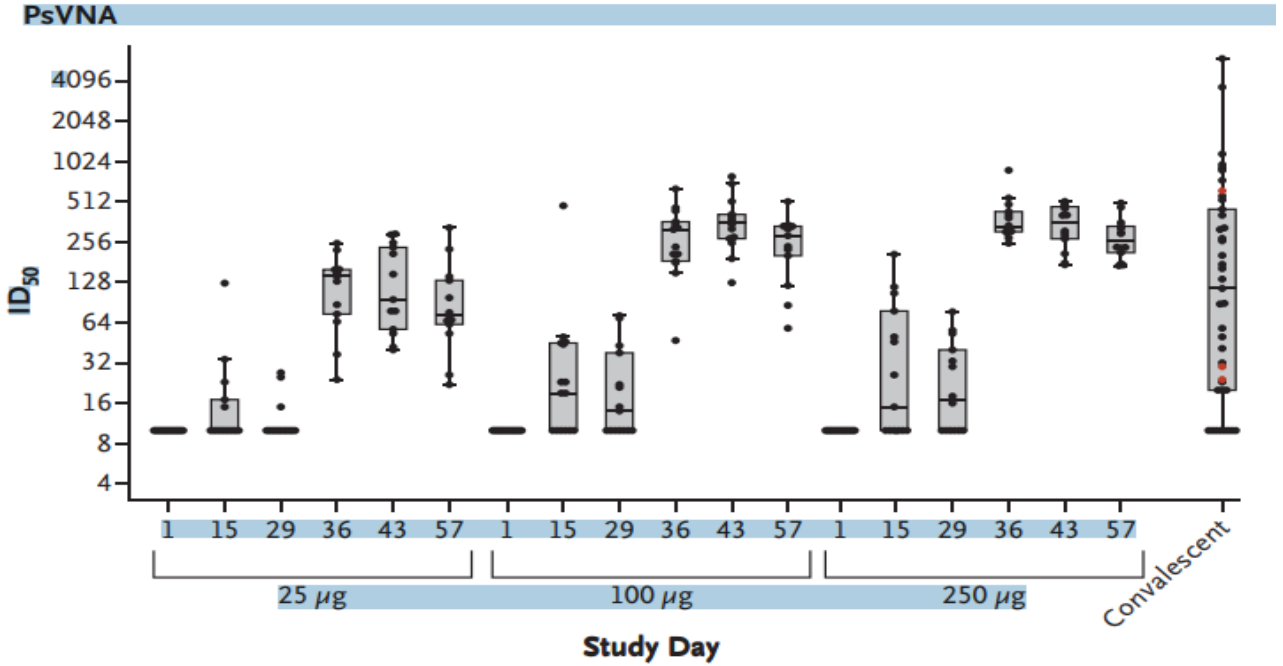
- Broad potency specification approved based on Phase 3 efficacy data, **supported by phase 2 immunogenicity data**
- Specification broader than phase 3 clinical trial and PPQ batch potencies
  - Specification is derived from *clinical performance*
- Specification was harmonized across HC/FDA/EMA
  - Example of regulatory co-operation
  - Simplified lot allocation, release
- However, this was not an easy regulatory process for any of the parties, because the enhanced approach to product developed was not articulated clearly to all agencies.

Case Study: 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 Study: COVID-19 mRNA vaccines





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

Moderna
https://10.1056/NEJMoa2022483

Case: COVID-19 mRNA vaccines

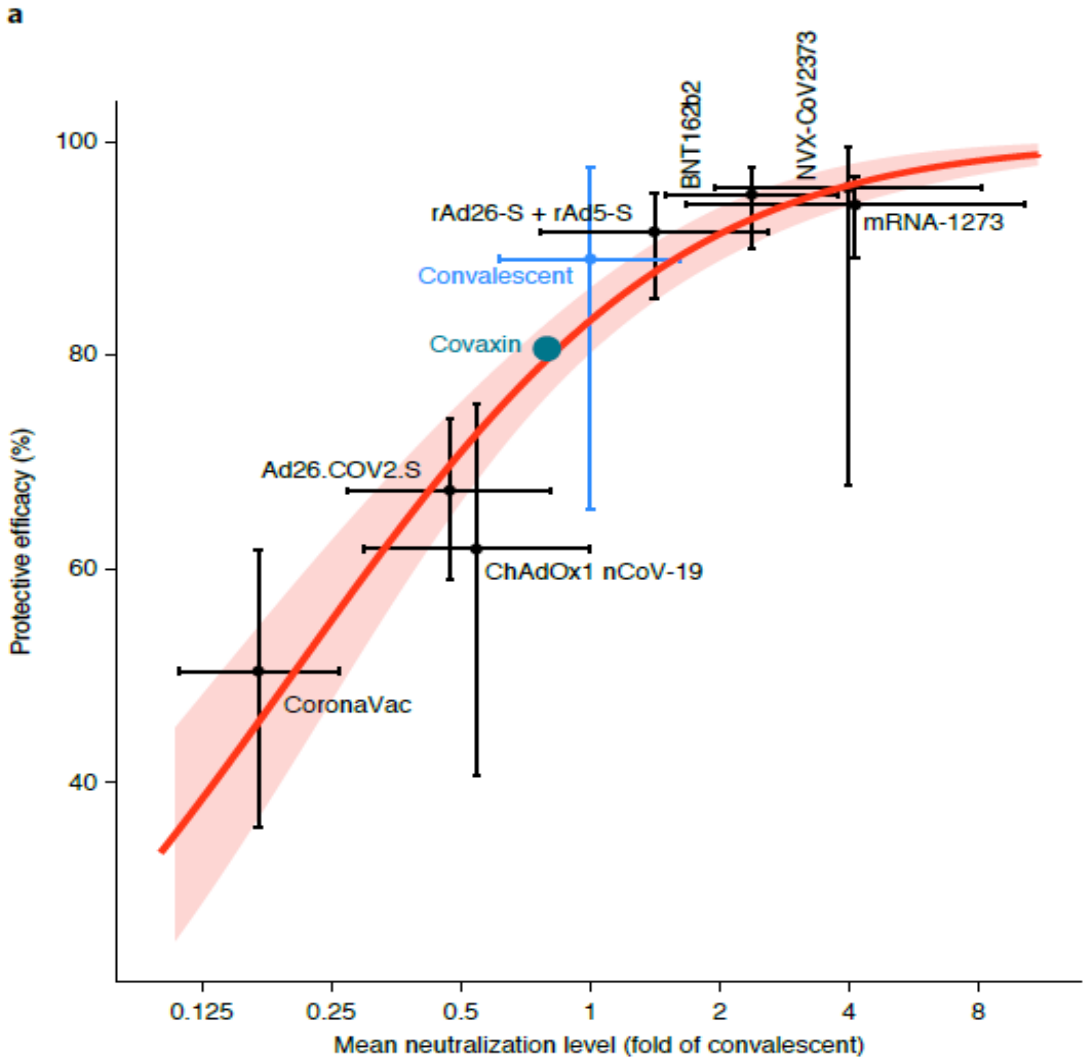
- Broad immunogenicity characterization from phase 2 studies:
  - Permitted harmonized (FDA, HC and EMA) specifications wider than phase 3 clinical lot potencies*
  - Supported rapid scale-up and scale-out, QbD approach to process validation
  - Expedited approvals
- Using QbD expedited approvals
  - Could approve shelf-life using enhanced approach EOSL spec, with stability data from development/clinical materials that demonstrated first order kinetics under thermal degradation. Hence data suitable for predicative stability assessment 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 clinically relevant EA specs

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 EA specifications, manufacturers benefit from process improvements vs penalization under a manufacturing-based specification
- CoP analyses can expedite future clinical and product development

Potential benefits of clinically relevant EA specs

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 clinically relevant EA specs

- Lack of consensus regarding the value for both regulators and manufactures of stable clinically relevant TA or EA 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!