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Enhanced Approaches Support Robust Harmonized Vaccine Potency Specifications

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YOUR HEALTH AND SAFETY... OUR PRIORITY.

Declarations

I have no financial conflicts of interest to disclose.

The views and opinions expressed herein do not represent the official policy or perspective of Health Canada*

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Key points

1. Specifications should be set using available clinically-meaningful data
   - Supports goal of harmonization
   - But alone will not achieve 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 must move the science forward together
   - Forward-looking pre-clinical and clinical work
   - Scientific, risk-based regulation that keeps the clinical profile in focus using all relevant data

Dose Ranging Studies to Establish Enhanced 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 at Health Canada.

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

Enhanced Specifications cont'd

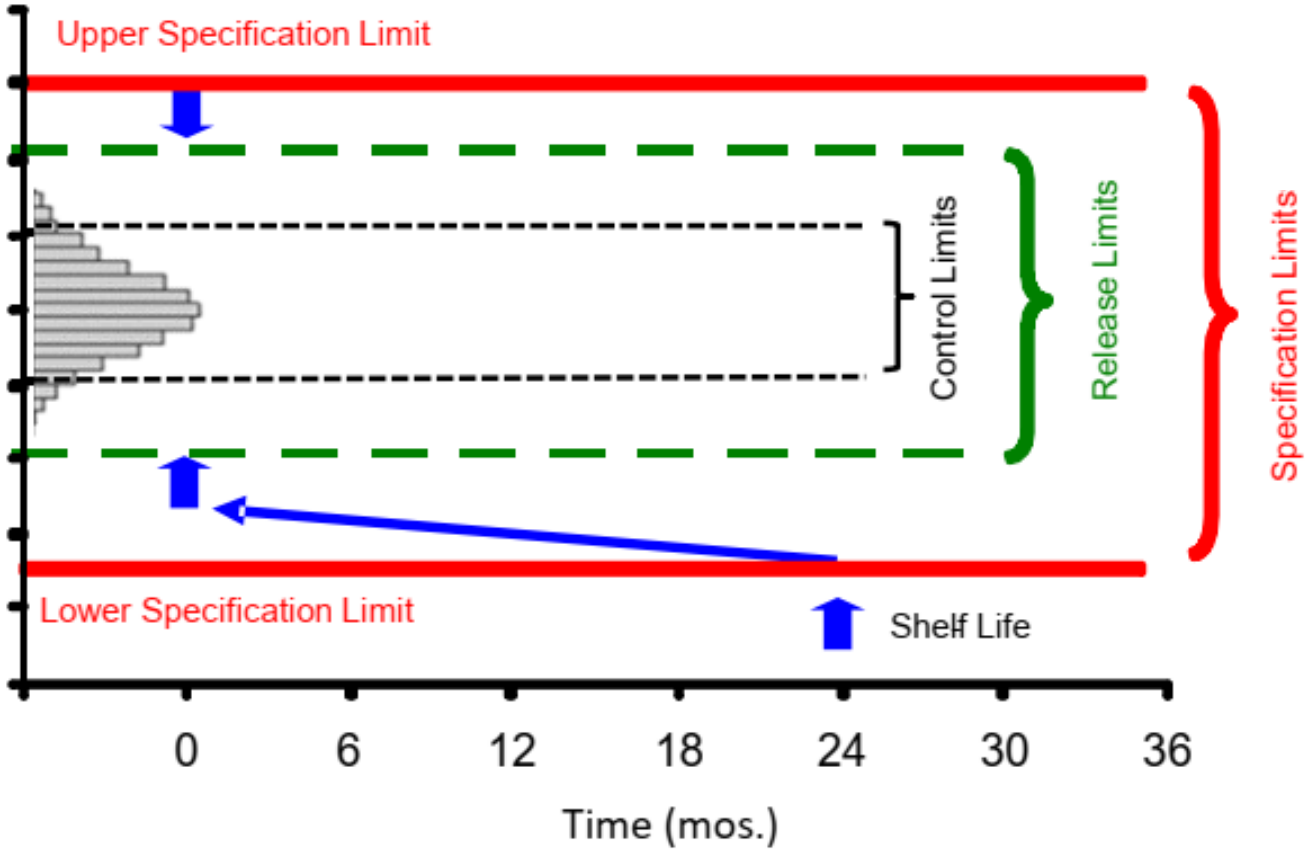
- There is a regulatory tendency to tighten specifications that are **perceived** to lack a robust clinical basis (e.g., limited to phase 3 lot data and manufacturing capability). Whereas, broadly characterized clinically-linked specifications should support manufacturing improvements though a product's life-cycle.

- Recognition of the value of robust enhanced specifications, incentivises assay and process improvement, if agencies resist tightening specifications following assay improvements and or process capability, and the specification is uncoupled from CMC control strategy.

<u>Key message</u>: Robust immunogenicity characterization in early phase dose ranging studies for vaccines enable more defendable harmonized specifications and other advantages.

Patient-centric specifications

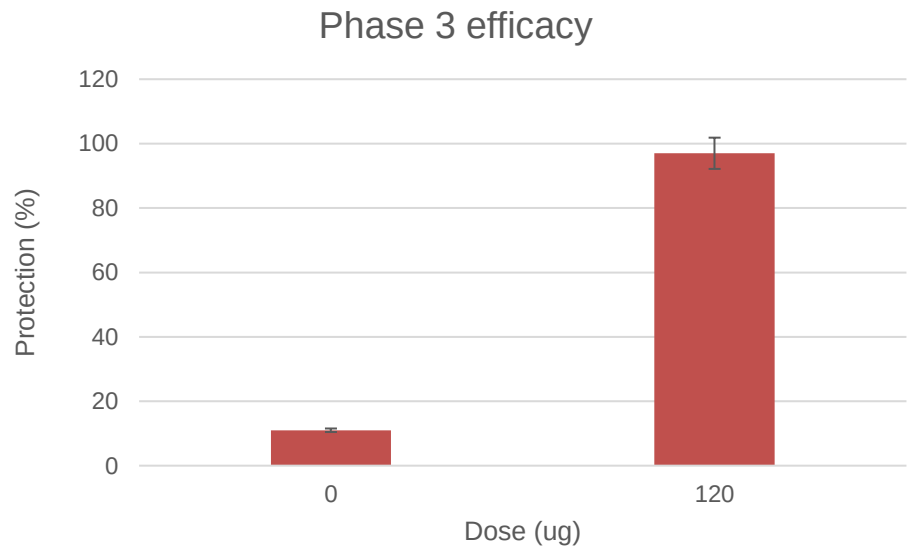
Manufacturing-based specifications tie the hands of both regulators and manufacturers!



Adapted from Tim Schofield CASSS NA CMC Strategy Forum 2023

Case Studies

Thought experiment: 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
  - 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

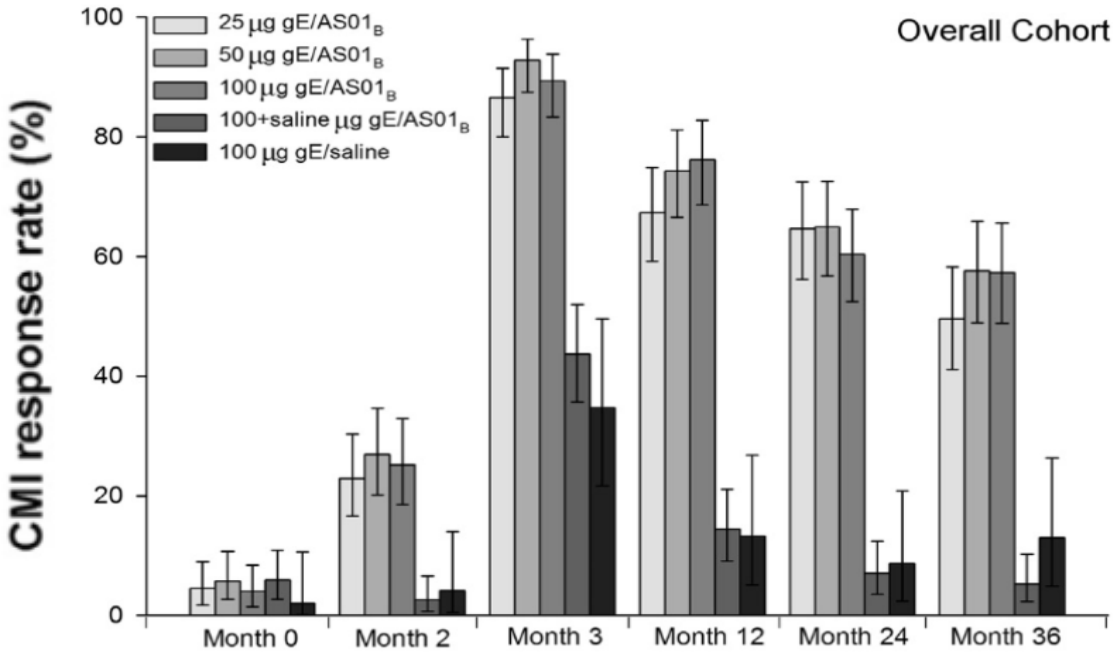
Case Study: Shingrix

- 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

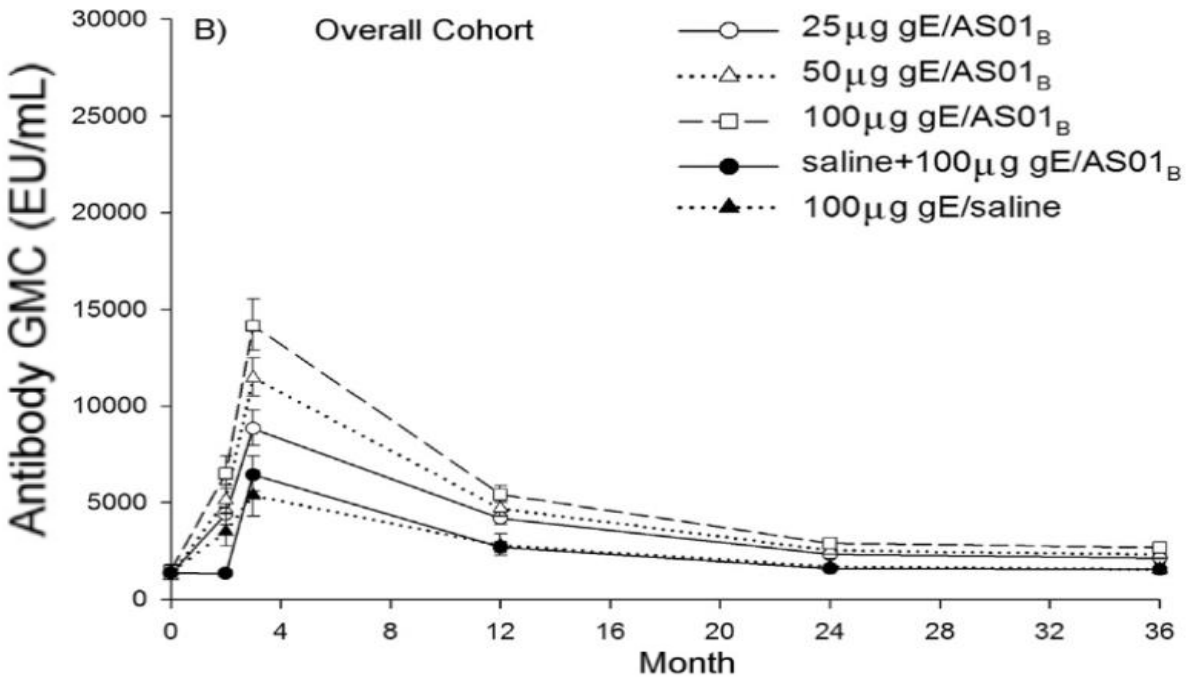


CMI

- 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



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

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

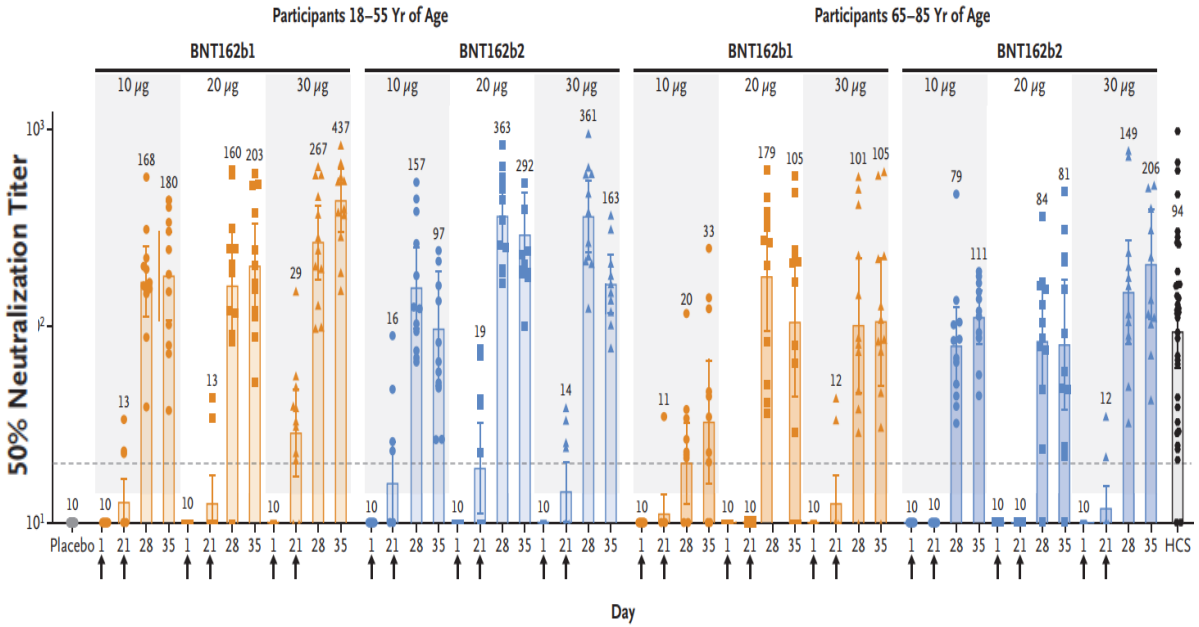
However, this was not an easy regulatory process for any of the parties, because the enhanced approach to product developed was not articulated to all agencies to the same extent.

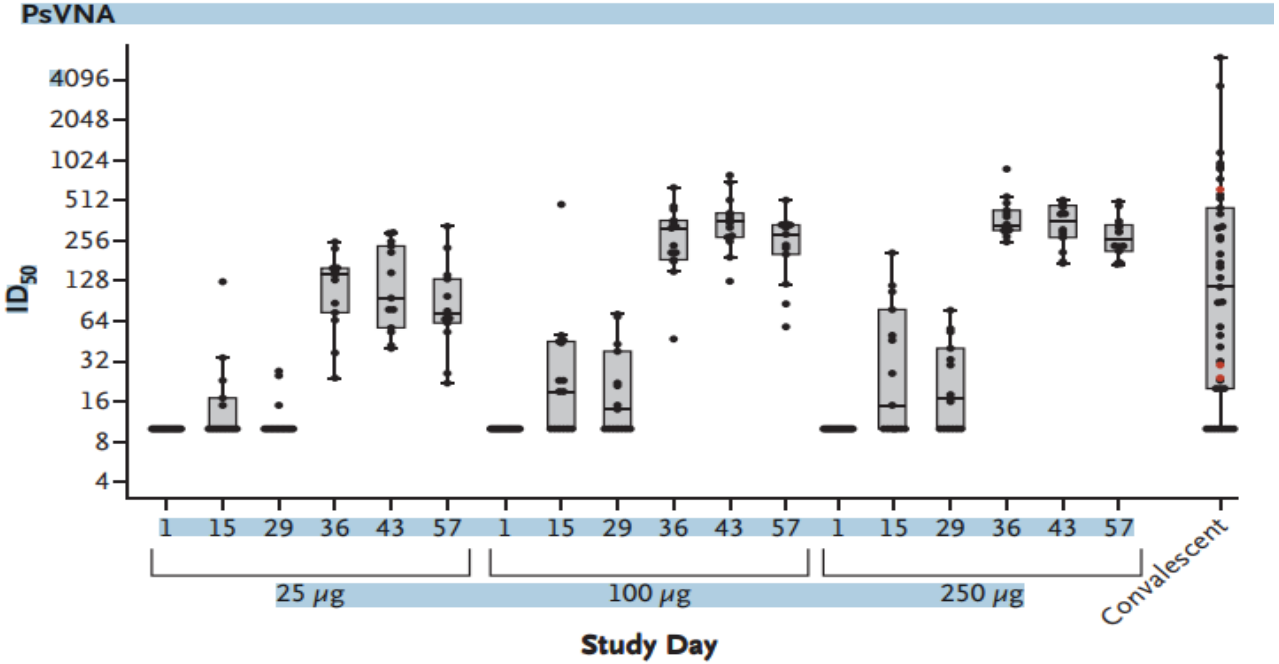
Case Study: COVID-19 mRNA vaccines

- 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 Study: 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 specification, stability data from development/clinical materials, without necessarily knowing process window at scale!

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

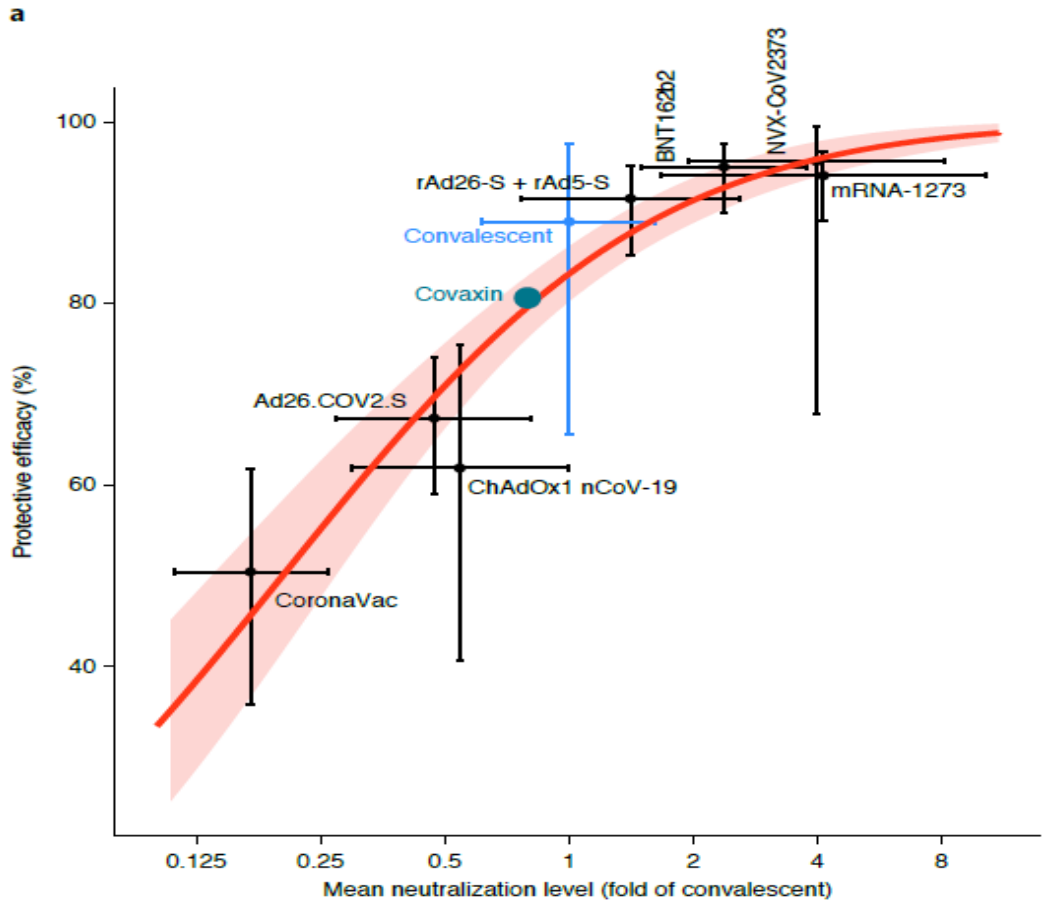
Case: COVID-19 mRNA vaccines

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

- Supported by preclinical studies

- Graph from Davenport group (Khoury et al., 2021 Nature Med.)
  - Relevant across multiple platforms

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



Immunogenicity Dose Ranging Study Conclusions

- Early phase, well characterized immunogenicity dose ranging studies support:
  - Robust and defendable harmonized product specifications that are less prone to agency pressures to tighten over product lifecycle,
  - Rapid scale up in emergency situations where additional manufacturing optimization is challenging, and
  - CoP analyses that expedited future clinical and product development.

- A key harmonization lesson from Merck's experience with 2014 Ebola outbreak and the general experience from the COVID-19 pandemic is:
  - If manufacturers propose and encourage submission data sharing between key regulators, as well as regulatory coordination of questions and responses, this and further efforts to support reliance would drive harmonized regulatory decisions.

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!

Thank You!

Questions?