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Gains and Losses Regarding the Harmonization of Specifications during the COVID-19 Pandemic: Science Versus the Fear Factor

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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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Several regulatory and industry colleagues who (regrettably) must remain anonymous

How industry feels about regulations…

"Regulatory audit today?"

Opening Thoughts

Overcoming our “training” and transitioning to new a paradigm

- The power of challenges to our thinking
  - It was a submission in 2017
  - Going public with a challenging idea, IABS Global Harmonization of Speciation’s 2019

- CASSS WCBP 2020
  - A pandemic without a name … yet
  - A Merck Ebola case study
  - FDA Directors and Clinically Justified Specifications, but …
  - Platform Technologies and expedited submissions

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Opening Thoughts cont'd

A barrier to the globally harmonized product specification is an **interpretation** of ICH Q6 B that favors specifications linked to process capability, over a specifications "justified based on data obtained from lots used in preclinical and/or clinical studies"… "and relevant development data".

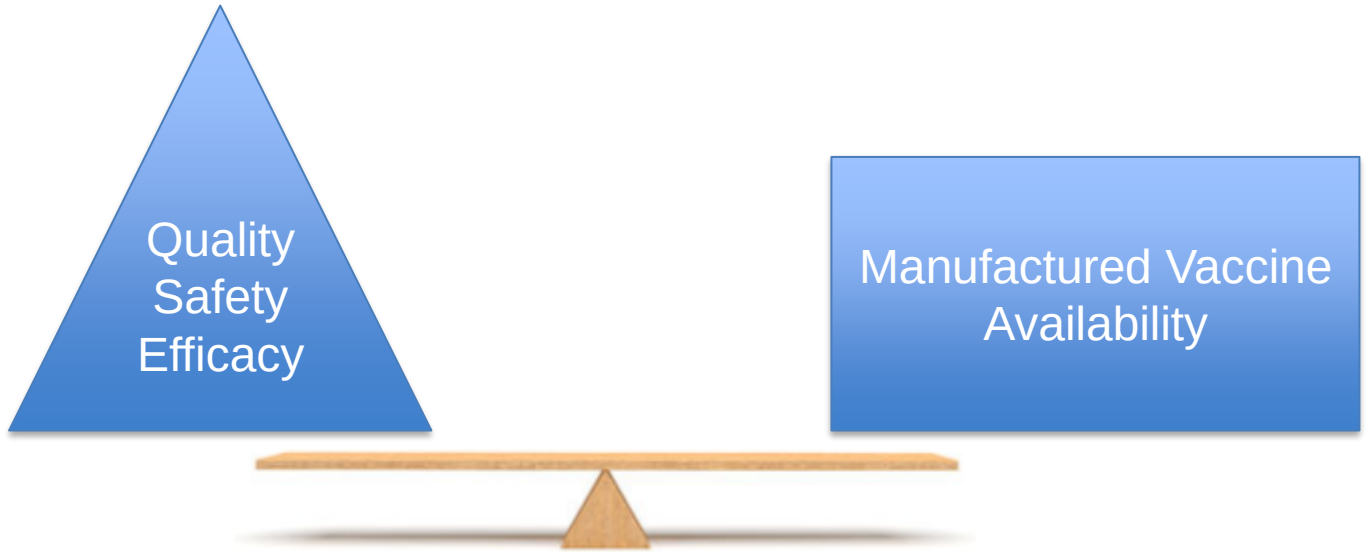
ICH Q6 B

- Specifications…should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

- Acceptance criteria should be established and **justified based on data obtained from lots used in preclinical and/or clinical studies**, data from lots used for demonstration of manufacturing consistency, and data from stability studies, **and relevant development data**.

If regulators **believe** that patients are best served by a tighter specification based on process capability, versus the totality of data available relevant to safety and efficacy of the product, the scientific basis for a specification can be lost.

What is the goal … what are the hurdles?



Requires:

- Innovative thinking by regulatory authorities and industry
- Science-based decision making (ICH Q8 – Q 12) to support manufacturing and QC test strategies that can lead to global regulatory harmonization / convergence and effective patient-centric specifications (PCS)

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

Specifications

Setting specifications

- Specifications have traditionally been based on release results from lots manufactured using the final commercial process in a phase 3 trial.
  - Expectation is that specification will be revised (typically tightened) 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 for CQAs (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 statistical 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 (pharmacovigilance)

- 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 (**not** a new concept, just new terminology)
  - 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 (seems like improvements in assays and process are penalised)
  - Process controls and quality systems assure quality

- PCS supports assay and process improvements over a lifecycle
  - When a PCS specification is “uncoupled”* from improvements in assays and manufacturing, the reduced variability and enhanced robustness is a reward to both the manufacture and the patient

- PCS don’t need to be fixed** but shouldn’t be tightened due to improvements in manufacturing capability!
  - **New clinical data, RWE, post-market surveillance may support a broader PCS

Are PCS too wide?

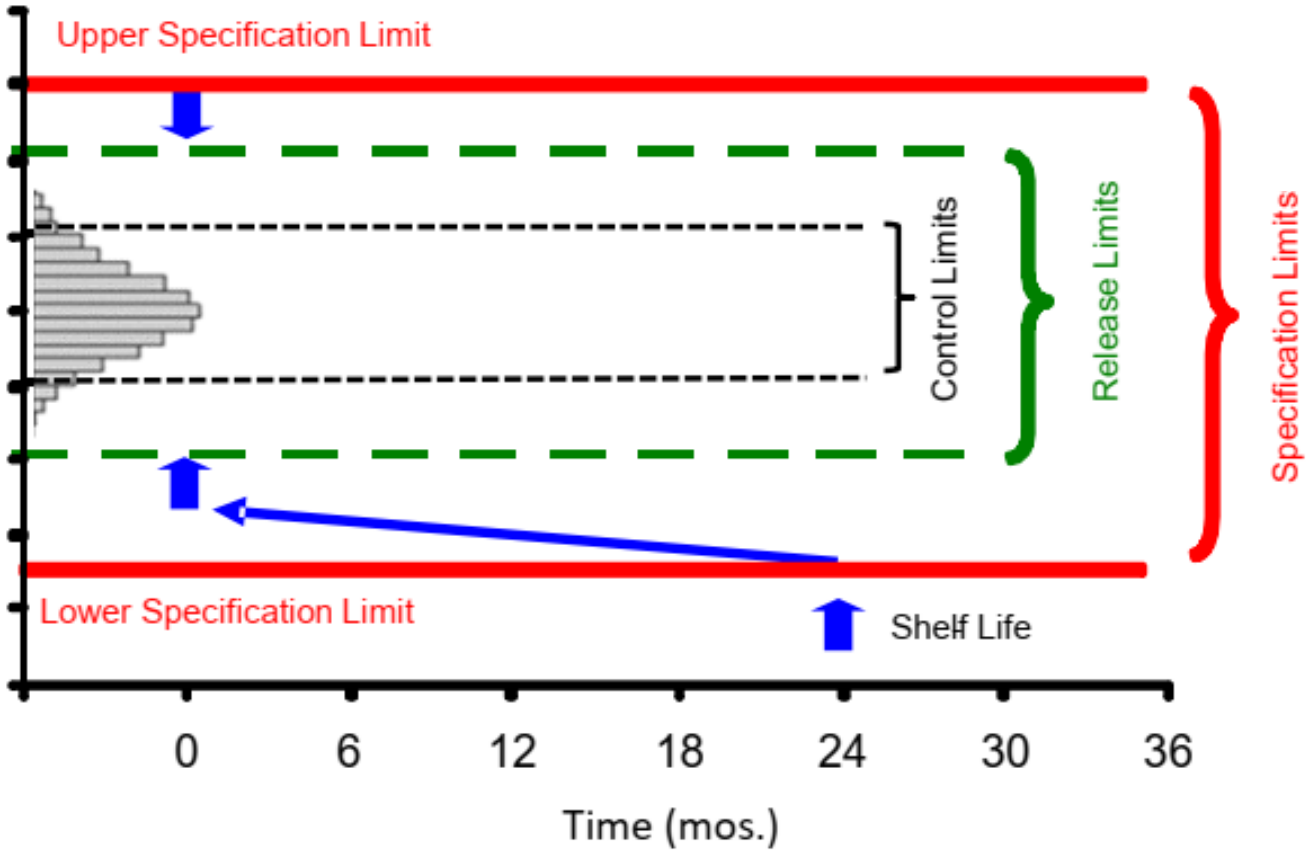
- Process controls, robust quality systems keep manufacturing processes under control, ***not*** *specifications*

- 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
  - Need change the belief that release specifications assure quality – they **confirm,** e.g.:
    - Sterility- **Material/process controls/design** result in a sterile product

Patient-centric specifications

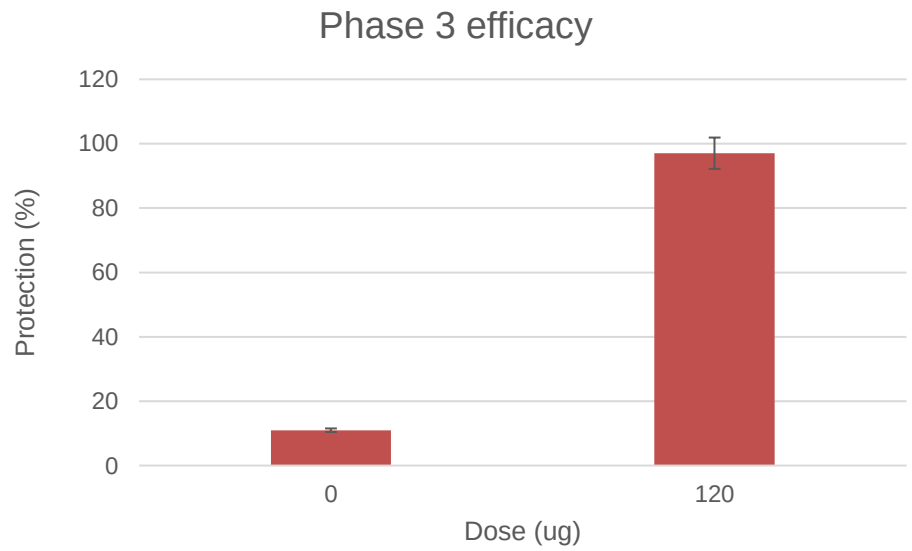
Manufacturing-based specifications tie the hands of both regulators and manufacturers!



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

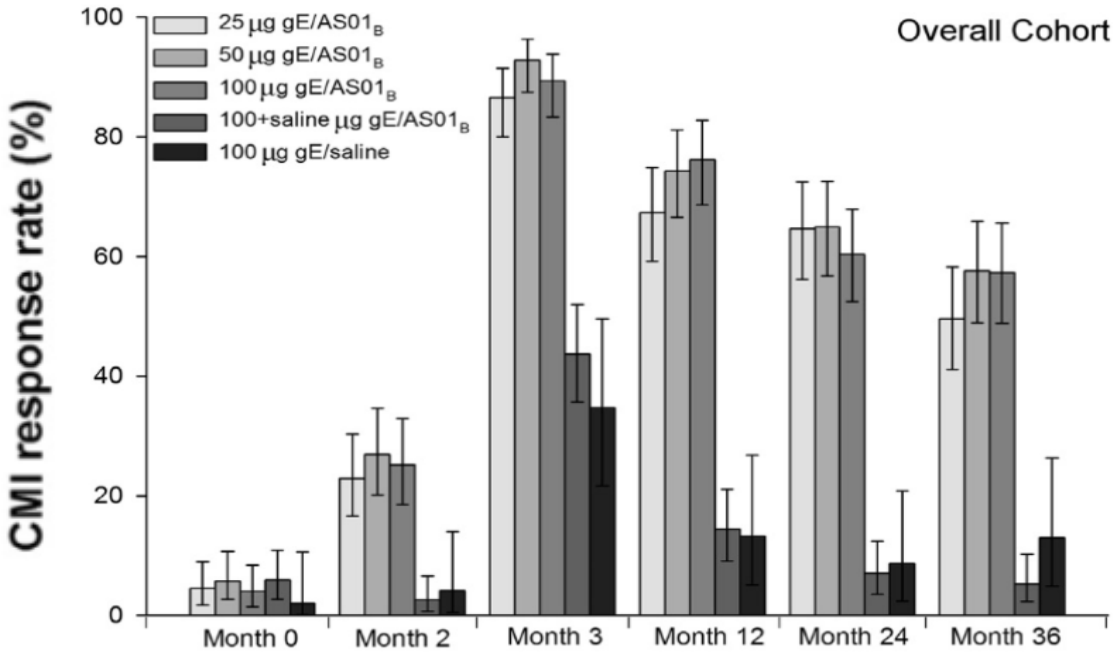
PCS case study: Shingrix

- 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

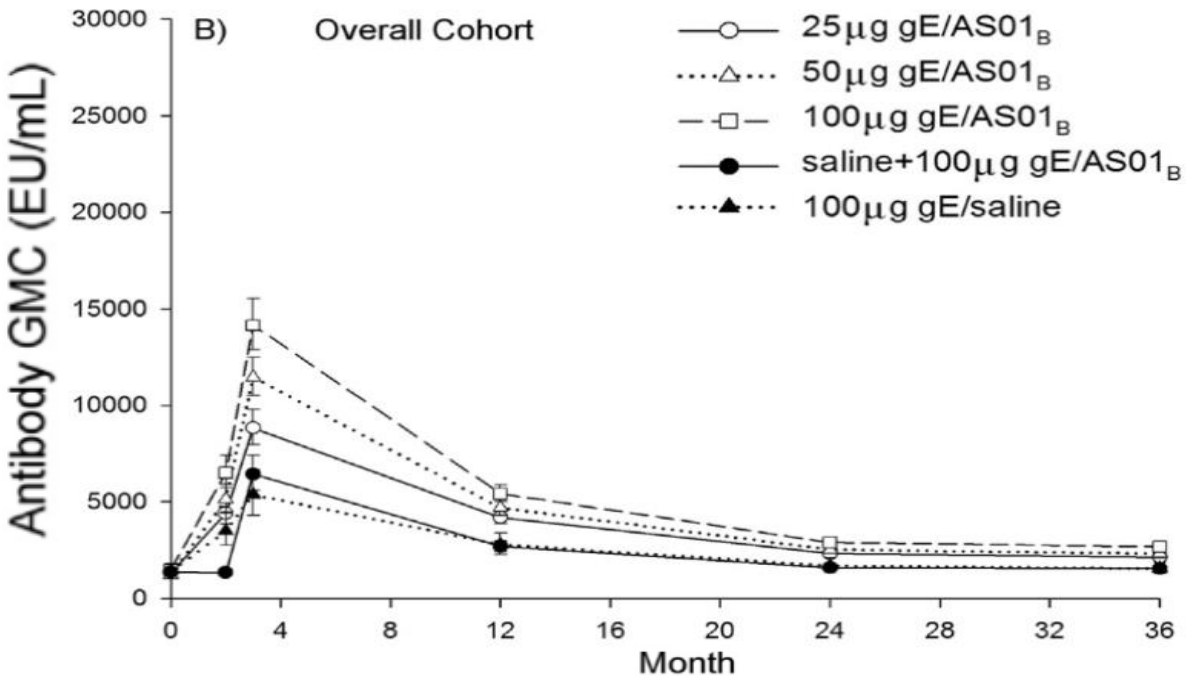


CMI

- 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

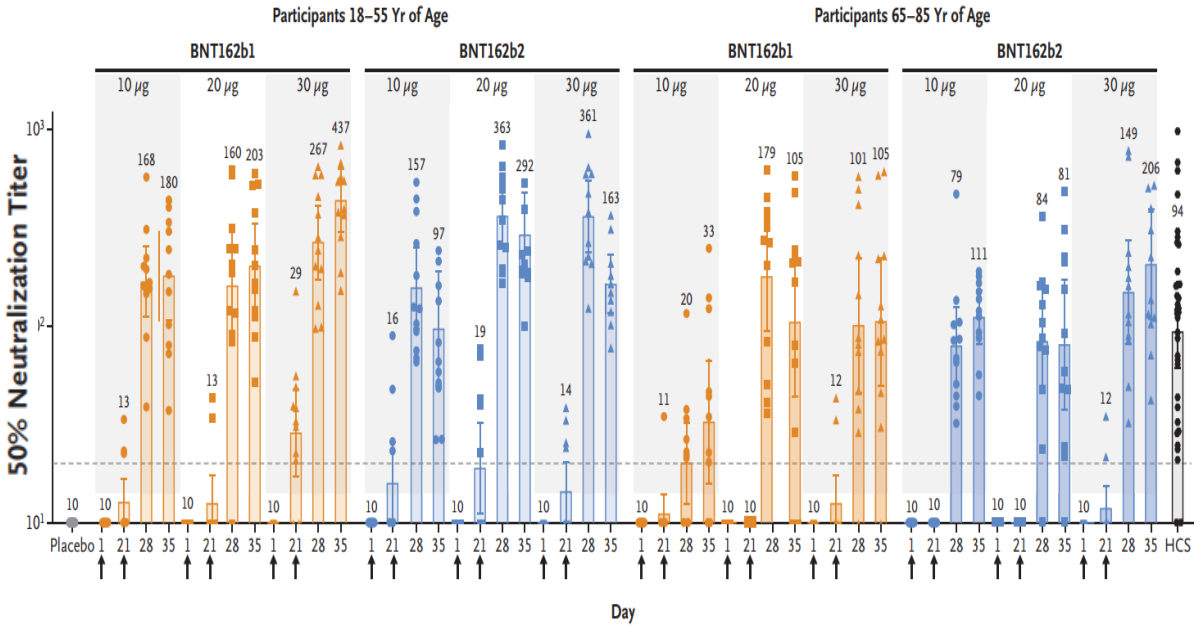
However, this was not an easy regulatory process for any of the parties, because the PCS product developed was not articulated to all agencies.

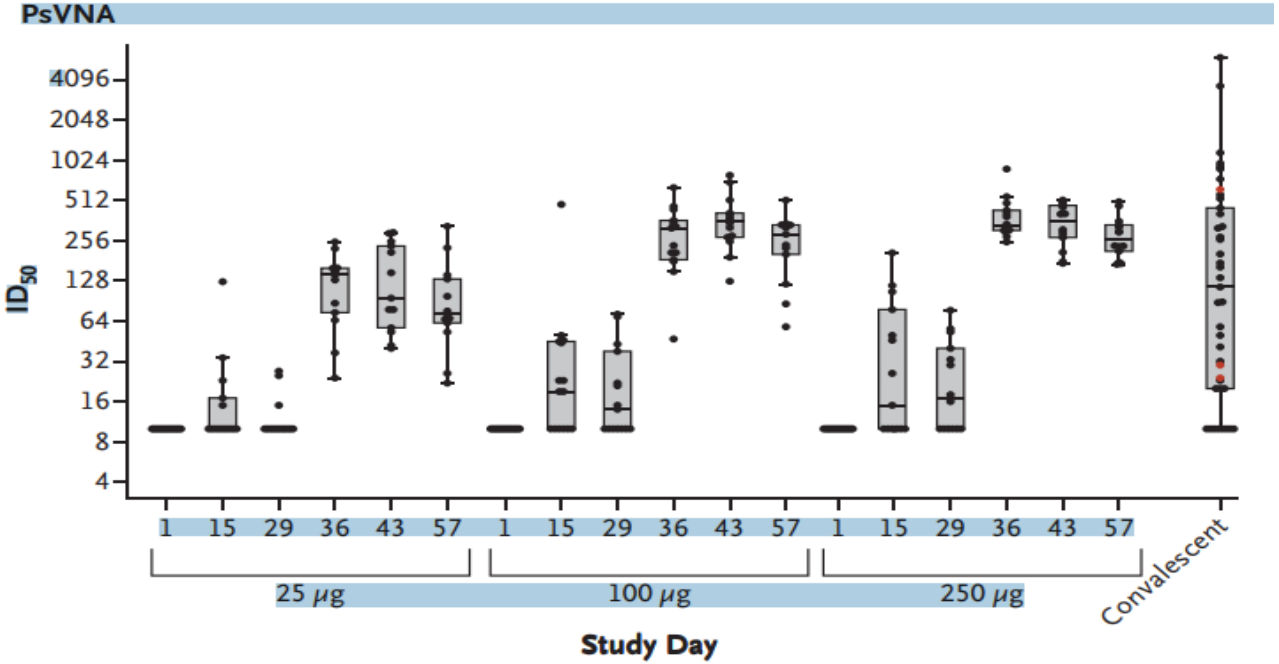
Case: COVID-19 mRNA vaccines

- 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

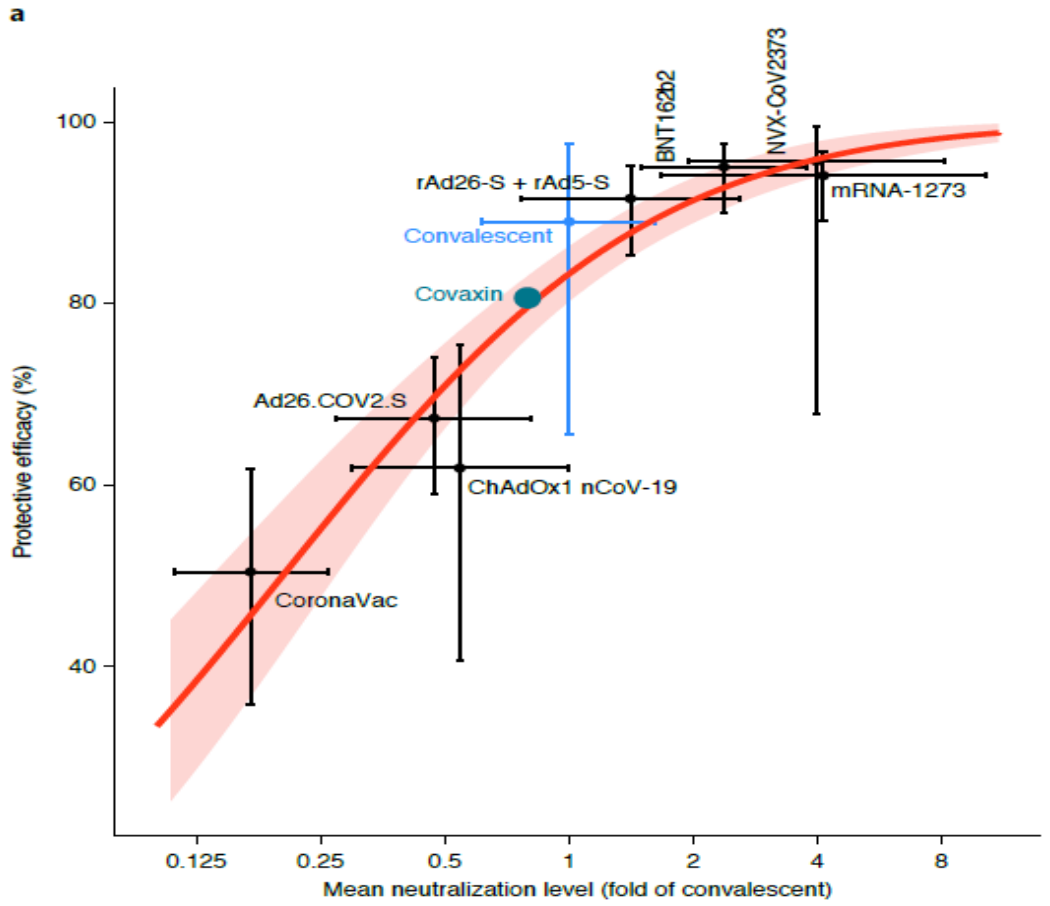
Case: COVID-19 mRNA vaccines

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

- Supported by preclinical studies

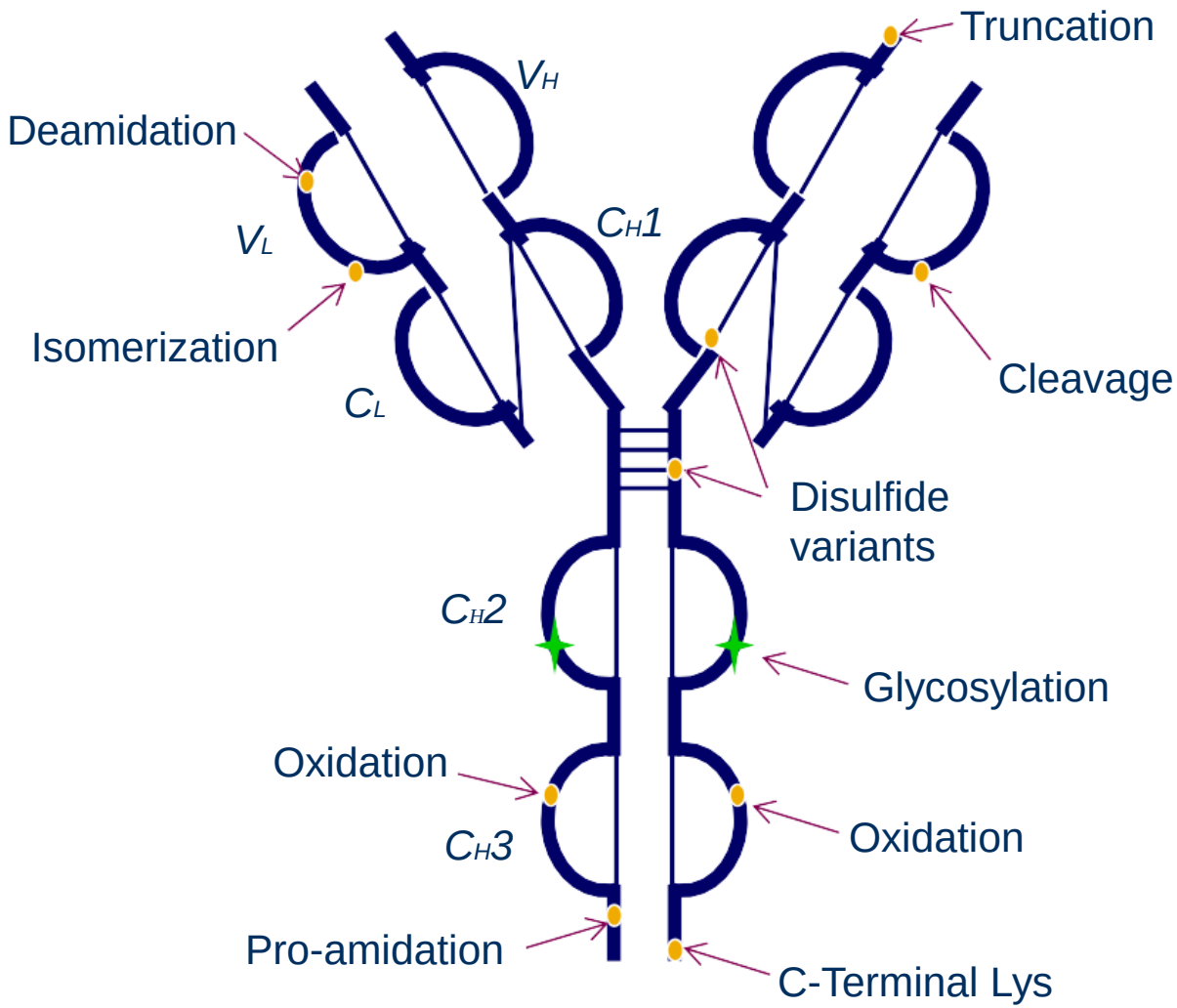
- Validated by work of Davenport group (Khoury et al., 2021)
  - Relevant across multiple platforms

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



What is Different about a Clinically Relevant Specification?

- "Clinically relevant specifications are based on risk to clinical performance, not what can be achieved by the process." (FDA, CDER)
- Allows appropriate use of risk and science-based strategies to establish tests and limits based on the overall control strategy as encouraged by current ICH guidance
- Monitors attributes of interest only
- Supported by the power of cross-product attribute clinical safety data
- Clinical experience including dose escalation studies and age of material at time of use



Adapted from D. Cowley, CASSS CMC Strategy Forum, 28 Jan. 2019

What can platforms can do for you?

What is platform technology?

- 21 U.S. Code § 356k - Platform technologies:
  - The term “platform technology” means a well-understood and reproducible technology, which may include a nucleic acid sequence, molecular structure, mechanism of action, delivery method, vector, or a combination of any such technologies that the Secretary determines to be appropriate, that the sponsor demonstrates—
    A. is incorporated in or utilized by a drug or biological product and is essential to the structure or function of such drug or biological product;
    B. can be adapted for, incorporated into, or utilized by, more than one drug or biological product sharing common structural elements; and
    C. facilitates the manufacture or development of more than one drug or biological product through a standardized production or manufacturing process or processes.

Sometimes platforms can speed development

- Good: Updating vaccines to new viral variants where sponsor has substantial applicable knowledge
  - **clear proof of concept, toxicology, common control approaches, stability profile, established non-clinical and clinical data for an approved product relevant to a new antigen**
    - **e.g., a different nucleic acid sequence for new COVID-19 VOC, or updated flu strain in an authorized platform**

- Bad: Sponsor has manufacturing experience but some control knowledge gaps
  - **Manufacturing processes translate, but control strategies don't**
    - **e.g., nucleic acid vs protein measurement**

- Ugly: Broad similarities to a product class, but little (or no!) manufacturing knowledge
  - **No experience with process development, control, but same molecule class**
    - **e.g., "someone else makes an mRNA vaccine, do we have to do proof of concept?"**

How can Platforms Speed Development

Process

- Validated unit operations (predictable CPPs, CQAs)
- Process improvement and scale-up experience

Safety

- Safety record of platform-related impurities
- Qualification of cell banks, reagents

Control

- Applicability of existing assay validations
- Stability

The caveat…

"Regulatory agencies [generally] license products, not platforms"

<u>Risk-based decisions are supported by data, not concepts</u>

A platform is only helpful if there's helpful data behind it!

Final thoughts

Potential benefits of PCS

For patients:

- Assurance of product quality
- Reduced likelihood of product shortages that may be caused by inappropriately narrow acceptance criteria
- Can potentially support more equitable product availability

Potential benefits of PCS

For regulators:

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

Potential benefits of PCS

For manufacturers:

- Fewer OOS, longer shelf-life, easier process/analytical improvement, lower-risk regulatory interactions, reduces regulatory burden if harmonized, 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 support and expedite future clinical and product development

Barriers to using PCS

- Lack of a of consensus regarding the value for both regulators and manufactures of PC **versus** 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 non-innovative pharmacopeia
- While PCS can be the framework for a harmonized specification, only interagency collaboration, **driven by manufacturers**, will yield a product specific globally harmonize specification. The industry practice of regulatory “divide and concur” should end.

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!