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

Jason Fernandes, Ph. D.
Health Canada
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Declarations

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The views and opinions expressed herein do not represent the official policy or perspective of Health Canada.
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 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\textsubscript{B} adjuvant.
  - **Phase 3 efficacy:**
    - Placebo-controlled (1:1)
    - 2 doses (50 ug gE + AS01\textsubscript{B})
    - Primary endpoint: reducing risk of herpes zoster & postherpetic neuralgia
    - [https://doi.org/10.1056/NEJMoa1603800](https://doi.org/10.1056/NEJMoa1603800)

- **Phase 2 dose ranging:**
  - 2 doses 25, 50 or 100 µg gE in AS01\textsubscript{B}
  - 1 dose 100 µg gE in AS01\textsubscript{B}
  - 2 doses of 100 µg gE in saline.
  - [https://doi.org/10.1016/j.vaccine.2014.01.019](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
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
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, Th₁/Th₂, 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/NEJMoak0222483
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
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

Case: COVID-19 mRNA vaccines
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 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
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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