

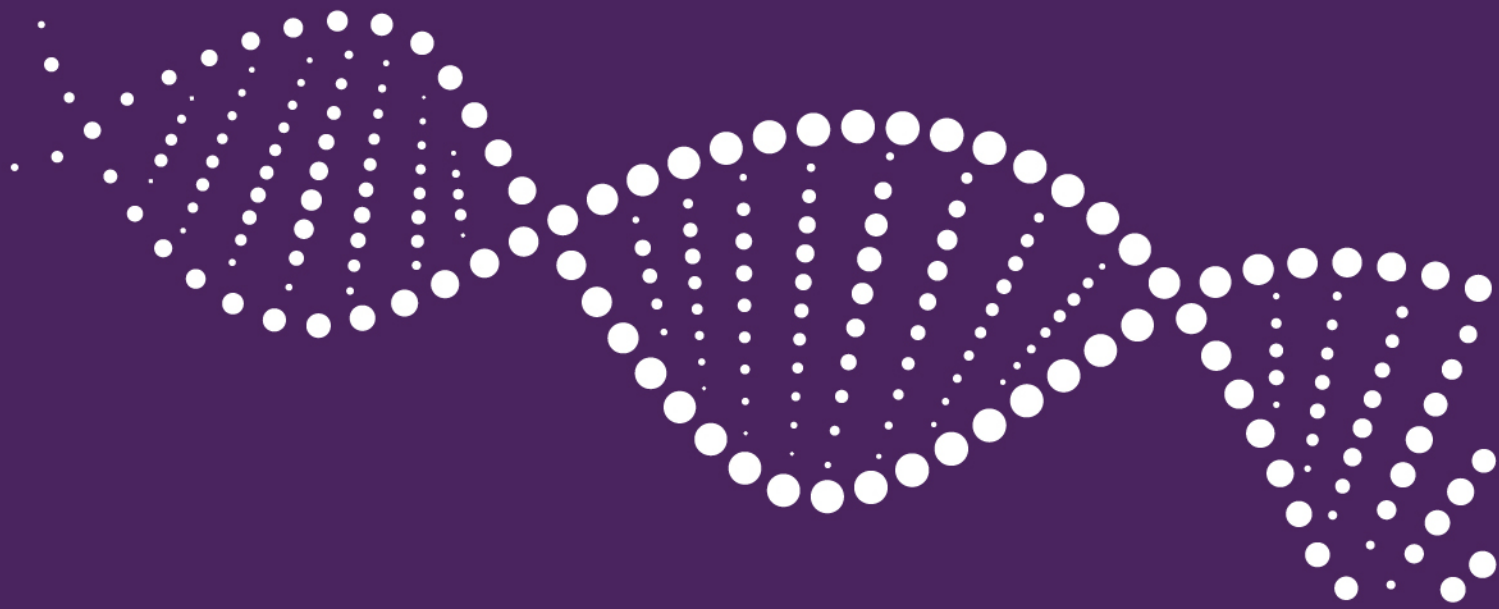
Considerations While Setting Specifications for Vaccines

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Specifications

- *“Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.”*
- *“Specifications are one part of a total control strategy designed to ensure product quality and consistency.”*
- *“Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization and should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.”*

--ICH Q6B

Justification of Specifications

In order to set specifications for the quality attributes for commercial manufacturing of vaccines, several factors must be considered:

- Existing Requirements**
 - **Monographs / Pharmacopeia**
- Prior Experience with Specifications for Similar Products**
- Clinical Experience**
- Process Capability**
- Stability Influence**
- Range Studies Performed During Development**

Existing Requirements of Monographs / Pharmacopeia

- **Specific Product Monographs**
 - Example: EP Monograph for Meningococcal Group C Conjugate Vaccine
 - Specifications for some attributes:
 - Residual Protein, Nucleic Acid in polysaccharide list specific limit
 - For Other Attributes, acknowledgment that limits must be set for the particular product
 - Molecular Size, Free Saccharide, etc.
- **General Chapters**
 - Example: USP Sterility
- **“Obligatory Attributes”**

Prior Experience with Specifications for Similar Products

- **Licensed specifications for similar or related products**
- **Pfizer's experience with conjugated protein : polysaccharide vaccines, and even pneumococcal polysaccharide vaccine before that, for example has provided valuable experience between products.**
 - **This experience also informs other areas of clinical experience and process performance**
- **Specifications used for Phase 3 clinical material production and process validation also will be a consideration during licensure**

Clinical Experience

- Longstanding expectations for linkages between clinical experience and specification ranges
- More recent enunciation of definition and discussion of clinically relevant specifications when FDA / CDER launched Office of Pharmaceutical Quality (OPQ)
 - “Clinically relevant specifications” can be defined as a set of criteria and acceptance ranges to which drug products should conform in order to deliver the therapeutic benefit indicated in the label. Clinically relevant specifications, according to this definition, offer a way to predict how well drug products will perform under real-life, real-use conditions.

Yu, L. and Woodcock, J. (2015) FDA Pharmaceutical Quality Oversight.
International Journal of Pharmaceutics 491, 2-7

Clinical Experience...

But What does it look like?

- Batches with measured attributes at the extreme edges of the specification ranges for all quality attributes?
i.e. a Min-Max approach?
- Practical considerations dictate this may not be possible for all quality attributes of even simple biologic products, let alone for a complex, multi-antigen vaccine.
 - Typically a relatively small number of lots are produced in order to support clinical studies
 - Large number of variables in multi-component vaccines
 - Some attributes are correlated
 - For example, for some serotypes of protein : polysaccharide conjugates:
 - » higher % Free Saccharide (FS) values correlate with
 - » higher Saccharide-to-Protein Ratio (SPR).
 - » Therefore, producing a “high-% FS, low-SPR” conjugate, would require process adjustments, or even entirely new process steps.

Clinical Experience...

But What does it look like?

- Data from earlier clinical lots or studies, perhaps prior to lock-down of final process and product formulation, may provide additional variability that can be useful in developing product knowledge.
 - For a particular polysaccharide-protein conjugate process that was still being refined over the clinical development program, percentage of free saccharide (%FS) levels of 4-42% were measured at release for various clinical batches.
 - Formulations with each of these conjugates, irrespective of the %FS in the intermediate monovalent bulk conjugates, were found to be highly immunogenic in infants.
 - Within the range of %FS values in the monovalent conjugate concentrate lot at release, the serotype specific antibody response was found to be independent of the percentage of free saccharide.

Clinical Experience...

But What does it look like?

- Data from earlier clinical lots or studies, perhaps prior to lock-down of final process and product formulation may provide additional variability that can be useful in developing product knowledge – A 2nd example:

- Given that, in infants, the immunologically active component of conjugate vaccine is comprised of only the conjugated saccharide:

$$\text{Dose of conjugated poly} = \text{Total polysaccharide} \times (1 - \% \text{FS})$$

- Therefore, in a dose ranging study that evaluated 0.5, 2, and 5 µg doses, the delivered dose of conjugated polysaccharide:

$$0.50 \mu\text{g dose with } 10\% \text{FS} \approx 2.0 \text{ mcg dose with } \sim 78\% \% \text{FS}$$

- Although diminished, a significant antibody response was demonstrated with this 0.5 µg vaccine dose for all serotypes.

Clinical Experience...

But What does it look like?

- General expectations for clinical consistency trials, along with time required to progress from FIH to Phase 3 suggest that often at least 3-5 lots will go into clinical studies. Clinical consistency trials are powered to assess equivalence or non-inferiority between different lots.
 - From these individual observations, one can create a statistical model of what has been used in the clinic and what future production is likely to be.
 - Considerations include of within-lot sample variability, lot-to-lot variability and test method variability.

Mean \pm X * SD
Tolerance Interval
Confidence Limits
Other?

Clinical Experience...

But What does it look like?

- Other situations may not be as clear as some shown, but...
- Can still look for signals of correlation between levels of attributes and measures of performance. Where none are observed, inferences that expansion slightly outside the observed ranges will still behave similarly.
- Would not generally promote purposefully making more variable (“dirty”) batches
 - At what point is process not representative?
 - If your knowledge suggests a preferred state, is it ethical to purposefully make clinical material in a suboptimal way?
- Inferences of similarity between some materials might be justified, even while some uncertainty remains

Easier	More Difficult
Same Carrier Protein	Different Carrier Protein
Similar Linkages	Different Chemistry
Similar Antigen	Different Antigen

Process Capability

- **Generally relies on an assumption that the variability observed within production of development, scale-up and validation batches will be representative of the normal, expected common-cause variation which is likely to be observed during routine production.**
- **As such, a statistical model represents the test results one would expect from a stable, in-control process.**
- **Consideration of process capability to ensure capability to consistently supply material.**
- **Strong clinical experience, that definitively ensures delivery of the therapeutic benefit may justify specs significantly wider than process capability.**
- **More limited clinical experience and small production data sets lead to situations where greater uncertainty remains and re-evaluation of specifications, after additional experience may be called for.**

Stability Influence

- **Effect of changes to product attributes during storage must be taken into account.**
- **Consider setting release limits within the shelf-life limits to ensure product remains in specification throughout it's shelf life.**
- **Carefully evaluate stability behavior relative to age of intermediates, drug substance, or drug product used in clinical studies. This evaluation may provide additional understanding of the true clinical experience of the vaccine.**

Range Studies Performed During Development

This factor is primarily a consideration for intermediates.

Experimental data provides evidence that downstream quality attributes are met when the attributes for the upstream intermediate are within a proven acceptable range.

Example:

- Molecular Size of Polysaccharide Intermediate may influence the Conjugate Drug Substance
- In laboratory experiments, it is possible to manipulate molecular size of the polysaccharide and perform comprehensive experiments to demonstrate how the quality attributes of the conjugate drug substance are impacted

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- Clinical Experience**
- Process Capability**
- Stability Influence**
- Range Studies performed during development**

Justification of Specifications

- Clinical experience has to be considered in the context of these other factors, including prior knowledge.
- Simply considering min and max of observed test results for clinical batches is rarely sufficient for setting of specifications.
- Where clinical experience is definitively wider than process capability, specifications may remain wider than process capability assessment alone, based on the ability to deliver the therapeutic benefit indicated in the label.
- Where uncertainty remains regarding the ability of the specification to ensure delivery of the therapeutic benefit, judgement and risk assessments may be required to assess the most appropriate path forward and more frequent re-assessment may be appropriate.

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