IQ Consortium Biologics Working Group on Specification Setting Strategies

Juliana Kretsinger
Eli Lilly and Company
Who is the IQ Consortium?

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) is a technically-focused organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader R&D community.
The IQ Biologics Leadership Group has defined the following mission:

To identify challenges that are impeding the progress of biologic development, including mAbs, other protein therapeutics and vaccines, and share information on cross-industry best practices to proactively advance innovative, science and risk-based phase-appropriate strategies for process and testing controls, and justify approaches to enable alignment with regulatory bodies.

- Members include representatives from 21 companies
- The Biologics LG members have varied expertise
  - Drug Substance, Drug Product, and Analytical Development
  - Vaccines, mAbs, ADCs, and other biological products
Specification Working Group

- Members include representatives from 14 companies
- Early phase specification strategies were the first focus
  - Recent manuscript published in the Journal of Pharmaceutical Sciences
    - Juliana Kretsinger, et. al. Expectations for Phase-Appropriate Drug Substance and Drug Product Specifications for Early-Stage Protein Therapeutics
- Second effort is underway to define strategies for setting patient focused commercial specifications
  - Manuscript has been drafted and is under review within the group
# Acknowledgements

<table>
<thead>
<tr>
<th>Name</th>
<th>Company_Name</th>
<th>Early Specs WG</th>
<th>Commercial Specs WG</th>
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Early Phase Spec Survey

• Survey was prepared to gather information about current early phase specification practices and sent to all IQ consortium members in 2017.
• 14 questions focused on specifications for first in human (FIH) clinical trial materials
• 20 responses were received
  • 3 responses across all vaccines provided a limited dataset
• Full survey results are provided as supplemental material to the article
Use of Platform Specifications

Question 2: Do you utilize platform/template specifications to guide establishment of required test methods and specification acceptance criteria for early phase projects on the following molecule types?

- No applicable
- RNA Vaccines
- DNA Vaccines
- Viral Vector Vaccines
- Inactivated Vaccines
- Live Attenuated Vaccines
- Glycoconjugate Vaccines
- Protein Based Vaccines
- Antibody Drug Conjugates
- Fusion Proteins
- Antibody Fragments
- Bispecific Antibodies
- Monoclonal Antibodies

~80% use platform specifications
Similarities and Differences

- 55% indicated they had recently changed platform specification strategies based on regulatory feedback
  - 25% had not changed strategies, despite feedback
- 60% frequently (plus 20% sometimes) use report results as acceptance criteria for charge heterogeneity
- Compares to reference is most frequently used as a criteria for identity testing
  - Detailed criteria vary and are typically listed in the method
- Additional characterization testing of clinical batches is common
  - Some characterization results may be in regulatory submissions, but not all characterization testing and results are included
White paper outline

- Introduction
- Results of Survey
- Template Specification Proposal
  - mAb and ADC examples
- Justification of Specifications
  - Report results
  - Compares to reference
  - Characterization testing
- Conclusion

- Approach is to define minimal requirements.
  - More tests or tighter criteria may be standard at some companies, but the white paper focuses on aligned minimal requirements

<table>
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<tr>
<th>Quality Attribute</th>
<th>Analytical Procedure</th>
<th>Acceptance Criteria</th>
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<tbody>
<tr>
<td>Identity</td>
<td>List out method type (e.g. Peptide Map, IEX, ICE, ELISA)</td>
<td>Identification confirmed e.g. “Conforms to reference material”</td>
</tr>
<tr>
<td>Quantity Assay (e.g. Protein Content)</td>
<td>UV</td>
<td>Not less than xx.x mg/mL or specify range (see discussion section)</td>
</tr>
<tr>
<td>Potency</td>
<td>List out method type (e.g. Binding ELISA)</td>
<td>Not less than 50% and not more than 150% potency relative to potency of reference standard</td>
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<tr>
<td>Monomer Purity</td>
<td>SEC</td>
<td>Not less than 90.0%</td>
</tr>
<tr>
<td>Total Aggregates/High Molecular Weight Species</td>
<td>SEC</td>
<td>Not more than 5.0 %</td>
</tr>
<tr>
<td>Purity (Reduced)</td>
<td>Reduced CE-SDS</td>
<td>Not less than 90.0%</td>
</tr>
<tr>
<td>Total Fragments</td>
<td>Non-Reduced/Reduced CE-SDS</td>
<td>Report result or not more than x.x% 6</td>
</tr>
<tr>
<td>Purity (Non-Reduced)</td>
<td>Non-Reduced CE-SDS</td>
<td>Not less than 90.0%</td>
</tr>
<tr>
<td>Residual DNA</td>
<td>qPCR</td>
<td>Not more than xx ppb (value based on WHO limit of 10 ng/dose)</td>
</tr>
<tr>
<td>Residual Protein A</td>
<td>ELISA</td>
<td>Not more than x ppm</td>
</tr>
<tr>
<td>Residual Host Cell Proteins</td>
<td>ELISA</td>
<td>Not more than x ppm</td>
</tr>
<tr>
<td>Additional process related impurity (if applicable)</td>
<td>List method type</td>
<td>Not more than x ppm</td>
</tr>
<tr>
<td>Appearance/Description</td>
<td>Visual</td>
<td>Provide description (e.g. colorless to slightly brown/yellow solution)</td>
</tr>
<tr>
<td>Charge Heterogeneity</td>
<td>List method type (e.g. IEX, ICE)</td>
<td>Compares to reference</td>
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<tr>
<td>Main Peak</td>
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<td>Report results</td>
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<tr>
<td>Total Acidic Variants</td>
<td></td>
<td>Report results</td>
</tr>
<tr>
<td>Total Basic Variants</td>
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<td>Report results</td>
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<tr>
<td>Bacterial Endotoxins</td>
<td>USP &lt;85&gt;</td>
<td>Not more than x (or x.xx) EU/mg</td>
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<tr>
<td>Total Microbial Count</td>
<td>USP &lt;61&gt;</td>
<td>Not more than x CFU/x mL</td>
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<tr>
<td>pH</td>
<td>USP &lt;791&gt;</td>
<td>Not less than x.x and not more than x.x</td>
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1 Test should be evaluated for inclusion in stability studies. Microbial testing not recommended for frozen drug substance or samples held at accelerated conditions.
2 Limit = 10 ng/dose + (maximum clinical dose (X mg/kg) × patient mass (kg)).
3 Strategy of testing process residuals as in-process controls or performing a risk assessment may be considered (see discussion/justification section).
4 For early stage products a simple description is sufficient, however, if color and clarity are assessed then an additional description is not necessary.
5 USP compendia tests are listed as examples. Alternate compendia methods may be considered suitable.
6 Multiple approaches can be used to define limit, see discussion/justification section.
Commercial Spec Strategies

Mission

• Develop an industry aligned view on commercial specification setting best practices.
• Promote the use of science and risk-based justifications to support patient focused specifications.

Key Objectives

• Define terminology, tools and strategies for setting commercial specifications that are focused on the needs of patients, while including consideration of the needs of regulators and manufacturers

Deliverables

• Prepare a white paper on this topic for publication in a peer-reviewed journal
Factors in Specification Setting

- ICH Q6B identified key data sources used to establish and justify specification acceptance criteria
  - Data from lots used in clinical studies
  - Data from lots used for demonstration of manufacturing consistency
  - Data from stability studies
  - Relevant development data
  - Pharmacopeia Requirements
  - Prior Knowledge
  - Critical Quality Attribute Risk Assessments
  - In vitro Assessments

- ICH Q8, Q9, Q10, and Q11 provide additional information on definition of an overall control strategy that supports Quality by Design approaches
Key Definitions

• Clinically Relevant Specifications:
  • Specifications that are based on risk to clinical performance, not what can be achieved by the process (J Woodcock)

• Clinical Range/Experience:
  • Lots and their attributes that were used in clinical trials, may be additionally adjusted for dose, lot age, etc.

• Patient Focused Specifications:
  • Considers both the clinical range/experience and additional knowledge that links the specification to the patient
    • Knowledge includes product specific, relevant internal and public knowledge
    • Links to all stages of control strategy development from identification of attributes, attribute criticality assessment, attribute range establishment, through control strategy
## Goals vs. Reality

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<tr>
<th>Goal</th>
<th>Challenges</th>
<th>Common Practice</th>
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| Able to directly correlate each molecular attribute to its impact on safety and efficacy | • Multiple attributes confound any correlation  
• Clinical studies do not have statistical power to support these correlations | CQA risk assessments are based on clinical and nonclinical data from the molecule of interest, but also must rely on literature and platform knowledge |
| Able to precisely define the acceptable level of an attribute during clinical trials, then design process to ensure control | • Not ethical to expose patients to materials that could have reduced safety  
• Clinical materials with varying efficacy could compromise the clinical trial | Targets are set for each attribute based on the capability of the process to reduce CQAs and control variability for all attributes |
| Patient focused specifications ensure safety and efficacy, while allowing variability that does not impact patients | • Without the ability to define the true point of impact, criteria may be set based on the variability observed in clinical batches | Process and product variability are restricted by tighter limits than truly necessary to ensure safety and efficacy |
Began with a robust discussions on definitions and review of recent regulatory presentations and meetings on the topic

Aligned on the need to provide examples for the use of in vitro systems and prior knowledge

Defined the white paper approach & scope

General commercial specification setting approaches not just a paper on clinical relevance

Evaluating variants within clinical studies, or animal models, are less discriminating due to variability

Vaccines out of scope due to different considerations related to in vitro assay relevance as well as use of clinical data

Currently have a white paper draft, with authoring in progress
White Paper Outline

Introduction

Discussion

1. Appearance and Description (DS and DP)
2. Identity (DS and DP)
3. Potency (DS and DP)
4. Quantity (DS and DP)
5. General Tests & Additional Tests for Unique Dosage Forms (DS and DP)
6. Process related Impurities (DS)
7. Purity/ Product related impurities (DS and DP)

Case Studies
Highlight

- Control of product-related substances and impurities requires understanding of the attribute to support risk assessment approach
  - Based on molecule specific data and prior knowledge
- Justification for acceptance criteria ranges beyond clinical experience examine potential for patient impact requires:
  - Bioactivity is typically assessed by testing isolated or enriched variant samples in relevant bioassays
  - PK can be assessed by evaluating the plasma concentration of variants within in vivo samples or relative FcRn binding for mAbs
  - Immunogenicity can be evaluated by in silico tools, in vitro models, or based on low anti-drug antibody response in clinical trials
  - Safety assessments require an understanding of the overall safety profile of the product. Can sometimes leverage higher exposure in early-phase clinical trials and toxicology studies
Conclusion

➢ Patient-focused specifications that link directly to patient needs are the target for both industry and regulatory agencies
  ➢ In the absence of information that supports this linkage, worldwide health authorities have sometimes required specification acceptance criteria limited to clinical experience

➢ IQ Biologics Specification Working Group includes representatives across the biologics industry
  ➢ First manuscript with guidance on early phase platform specification approaches was published this month in Journal of Pharmaceutical Sciences
  ➢ Second manuscript is in draft to provide guidance on commercial specification setting strategies with case study examples to support the use of prior knowledge and in vitro studies
Discussion Points

• Case studies shared at multiple conferences over the past few years have demonstrated opportunities for justifying ranges beyond clinical experience
  • Have standard practices been identified that can be implemented broadly or are these efforts reserved for limited attributes that are identified as high risk and challenging to control?
• Often specifications for biologics are set for collections of attributes (eg. HMWP, acidic variants, and basic variants)
  • Can focusing on individual high risk attributes enable better control where needed and greater flexibility for lower risk attributes?
  • What are the associated analytical challenges to enable control for individual high risk attributes?