Regulatory perspective on setting clinically relevant specifications

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Disclaimer

The views and opinions expressed should not be used in place of regulations, published FDA guidance, or discussions with the Agency.

Some case studies are hypothetical
Specifications

• Specification, as per 21 CFR 314.3 and 21 CFR 600.10, means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a product.
  – Acceptance criteria mean numerical limits, ranges, or other criteria for the tests described. 21 CFR 210.3(a)(20) extends this definition to include rejection criteria and unacceptable quality level
  – Test method
• Linking your historical clinical success to your future safety and efficacy
• ICH Q6B
Justification of specifications

Basic expectations:
• Linked to a manufacturing process
• Account for the stability of DS/DP
• Linked to preclinical and clinical studies
• Linked to analytical procedures

What to look for:
• Data with pivotal clinical trial lots
• Data with other representative GMP lots
• Batch analysis (with statistics)
• Assay validation data and assay capabilities – is the proposed lot within the validated range of the assay?
• Manufacturing history since licensure
• Reference standard material
Factors that may contribute to the relevance of specifications

• Establishment of an acceptable risk/benefit profile in the target population
• Assurance that the product will deliver a therapeutically reliable performance throughout its lifecycle with respect to safety and efficacy
• Product specifications for CQAs must be set to deliver the desired clinical performance
• Reflective of product-specific chemistry
• Assay capability and assay variability
• Manufacturing history
• Dosing specific issues such as in-use stability
• Product meets official/pharmacopoeial standards, if applicable
Types of release tests (ICH Q6B)

- **Drug Substance:**
  - Appearance and description (color, physical state, etc)
  - Identity (specific for drug and based on unique properties of drug)
  - Purity (combination of methods, charge-based/size-based)
  - Impurities [process-related (e.g. HCP, media components) and product related (e.g. variants)]
  - Potency (related to the proposed mechanism of action)
  - Quantity (usually based on protein content by mass)

- **Drug Product:** In addition to above –
  - Quantity (dosing related)
  - General tests (e.g. pH, osmolarity)
  - Microbial tests (sterility)
  - Additional testing for specific dosage forms (e.g. pre-filled syringes)
Evolution in FDA’s approach to pharmaceutical quality

- Definition of adequate quality: delivers clinical performance described in drug label and is not contaminated

- Clinically relevant specifications are based on risk to clinical performance, not what can be achieved by process

- Clinically relevant manufacturing standards: deviation should have clear link to risk of substandard clinical performance

— Janet Woodcock, CDER, evolution in FDA’s approach to pharmaceutical quality
ICH Q8, Q9, Q10, Q11

• allow use of science and risk based approaches that can potentially justify establishment of limits beyond those based solely on clinical exposure
• Quality by Design (QbD)
Quality Target Product Profile-QTPP

• A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy

• ICH Q8(R2) definition

• Elucidation of QTPP requires determination of Critical Quality Attributes (CQA)
CQAs are product specific

- Each product has unique properties that should be understood to establish proper controls

- Risk assessment tools can be used to identify and rank parameters with potential to have an impact on product quality

- Impact of product and process related impurities to Efficacy, safety, PK, PD, immunogenicity

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CQAs

• Definition:
  – A physical, chemical, biological, or microbial property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8)

• Designation:
  – By definitive data from clinical sources
  – preponderance of evidence from several sources including clinical, in vitro, and animal data
  – prior knowledge including published information of impact on PK/PD, potency, immunogenicity, and safety
Considerations for identifying CQA’s

• Focus is on patient protection:
  – “the protection of the patient by managing the risk to quality should be considered of prime importance” – ICH Q9
  – Scientific rationale and quality risk management processes are used to reach a conclusion on what are critical quality attributes and critical process parameters for a given product and process
  – Quality attribute criticality is based on severity of harm and does not change as a result of risk management
  – The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk

• Process parameter criticality
  – Linked to parameter’s effect on any critical quality attribute

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Product Understanding: Determining CQAs

- Attributes are assessed for clinical impact as the severity of harm to safety and efficacy:
  - the range of a candidate CQA is evaluated in different batches and scored for impact on activity, PK/PD, safety, immunogenicity
- Attributes are ranked based on strength of data used to assess impact and extent of residual uncertainty either in consequences or likelihood
- Impact and residual uncertainty determine where an attribute is on the criticality continuum
- Process capability and detectability should not be considered as primary drivers in the attribute risk assessment, but should be considered in the final control strategy
Assurance of QTPP requires a robust control strategy

- A control strategy is a planned set of controls, derived from current product and process understanding, that assures process performance and product quality – ICH Q10
- To deliver consistent product quality and minimize risk to patient safety and product efficacy
- To generate process and product understanding and identify sources of variability
- To provide an opportunity to shift controls upstream and minimize the need for end product testing
- To support control of the process such that the variability (e.g. raw materials) can be compensated for in an adaptable manner
- Consideration should be given to improving the control strategy over the lifecycle: in response to assessment of data trends over time and other knowledge gained. Product approval based on limited numbers of product lots and usually small number of patients
Control strategies for biotech products

- Control of raw materials
- Control of cell banks
- In-process testing
- Control of drug substance
- Reference standards
- Control of drug product
- Stability testing specifications
- Release testing specifications
- Validated manufacturing process
- Current good manufacturing practices
- Risk analysis Trending
Product quality attributes and determinants of clinical performance

Product Quality attributes:
• Strength/potency
• Purity (including impurities)
• Content uniformity
• Sterility and bioburden (including viral contaminants)
• Endotoxins/pyrogens
• Excipients

Specific to each product, process, assay, indication, and patient population

Determinants of clinical performance:
• Therapeutic index
• Time to onset of clinical effect
• Time to loss of clinical effect
• Duration of therapy (acute/chronic)
• Need for titration
• Washout/elimination period
• Pro-drug or metabolites
• Presence of toxic impurities
• Presence of adventitious agents
• Inter-patient/intra-patient variability
• Consequences of therapeutic failure
• Immunogenicity
CDER - collaborative review

• OPQ/OBP has discussions with OND (medical officers, clinical pharmacology, nonclinical reviewers)
• Link product quality data (CQAs) to efficacy and safety data
• Adverse events, immunogenicity
• Narrow therapeutic index
• Other product specific examples
Case study #1

- Recombinant protein – enzyme
- Sialic acid = CQA
- Sialic acid levels were linked to PK (half-life): lower sialic acid correlates to faster clearance
- Two lots in early clinical development had lowest sialic acid content
- Lots used in pivotal clinical study had highest sialic acid
- Subsequent manufacturing experience indicates variability in sialic acid content
- Initial proposal for wide acceptance criteria, but tightened range based on current manufacturing capability
- Limited understanding of process
- PMC to develop control strategy around sialic acid levels to reduce variability
Non-CQAs

- Examples of Mab quality attributes with minimal or no known impact on safety or efficacy:
  - C-terminal lysine
  - C-terminal proline amidation
  - Some process-related impurities below a well defined limit (e.g. DNA, elemental impurities)
Case study #2

• Charge variants for monoclonal antibody
• Additional characterization of acidic peaks indicate species are non-CQAs (such as deamidation in non-CDR region) with no impact to potency
• Sponsor was able to justify acceptance criteria 15% wider than clinical lots
Considerations for monoclonal antibodies with effector functions

<table>
<thead>
<tr>
<th>Therapeutic Ab type</th>
<th>Class I: cell-bound antigen stable upon Ab binding. MOA involving Fc effector function (ADCC, CDC, ADCP)</th>
<th>Class II: cell-bound antigen. MOA not involving Fc effector function</th>
<th>Class III: soluble antigen. MOA not involving Fc effector function (blocking)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG1 and IgG3</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>IgG1 and IgG3 with Fc mutations to enhance Fc functionality</td>
<td>High</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Afucosylated IgG1</td>
<td>High</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>IgG1 and IgG3 with Fc mutations to reduce Fc functionality, or aglycosylated IgG1 and IgG3</td>
<td>Not applicable</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>IgG2 and IgG4; IgG2 and IgG4 with Fc mutations to reduce Fc functionality, or aglycosylated IgG2 and IgG4</td>
<td>Not applicable</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Jiang et al., Advances in the assessment and control of the effector functions of therapeutic antibodies. Nature Reviews\Drug Discovery Feb 2011.)
Considerations for IgG1

• Cell bound antigen: target a receptor where primary MoA is to block ligand from binding, activating, and signaling downstream

• High potential for effector function – potential secondary MoA

• The % efficacy due to ligand binding vs % efficacy due to ADCC may be unknown

• Include specifications to monitor effector function: both functional and binding assays
Case study #3

- Monoclonal antibody, IgG1
- MoA (including CDC, ADCC, ADCP) is not well understood
- CDC is the proposed potency assay
- Process validation batches were consistently lower in CDC activity than the pivotal clinical study material, may be due to differences in glycosylation
- Variability in CDC and ADCC activity observed after manufacture of pivotal clinical study materials, root cause unknown
- Added control of glycosylation and ADCC assay to release testing
- PMC to confirm new manufacturing process controls

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Case study #4

- Monoclonal antibody, IgG1
- Proposed wide acceptance criteria for charge variants on stability (acidic peak, ~60%)
- Claim charge variants are non-CQAs
- However, within acidic peak a new deamidation site was identified and characterized to impact potency (ADCC)
- Studies indicate increase in deamidation when exposed to high temperature
- Sponsor tightened acceptance criteria for charge variants (acidic peak, ~30%) on stability
- Alternative strategy: add assay (such as peptide mapping) to monitor deamidation levels at this specific site
Considerations for Expedited development

- Under IND broader acceptance criteria may be allowed
- At time of BLA approval, specifications are tightened based on clinical and manufacturing experience
- Limited manufacturing experience, few lots, small number of patients
- Ongoing clinical studies under IND allow for opportunity to obtain clinical data at wider attribute ranges
Case study #5

- Monoclonal antibody
- PAS to revise release and stability specifications - IsoAsp
- CR due to lack of data to link proposed DS and DP shelf-life limits to clinical experience
- Sponsor was able to demonstrate levels of IsoAsp did not impact safety using additional lots manufactured for ongoing clinical studies under IND to support additional indications
Re-evaluation of specifications

- New understanding of product attributes relevant to safety and MoA emerges
- Manufacturing process capabilities mature and refine
- Target product profile is expanded or altered (e.g., route of administration)
Alternatives to Release Testing

• Spiking studies to demonstrate removal of HCP & DNA
• Move testing to in-process with rejection limit (PS80)
• After significant manufacturing experience, you may have data to support removal of certain attributes in DS release/stability testing but retain DP release/stability testing
Considerations for biosimilars

- The goal of a biosimilar development program is not to independently establish the safety and efficacy of the proposed biosimilar product but rather to prove its biosimilarity to the reference product.
- Important to obtain sufficient number of lots to capture the variability of the reference product.
- Ideally, lots should be selected across the shelf-life of the product.
- Lots sourced within a limited time-period might not capture the variability associated with the reference product.
Case study #6 - biosimilar

• ~3% difference in protein concentration between the biosimilar and reference product

• Sponsor had to tighten the controls for the DP manufacturing process

• Revise protein concentration release specification to more closely match the actual content of the reference product
Case study #7 - biosimilar

- Lower ADCC activity than reference product
- Correlates with differences in FcγRIIIa binding
- Residual uncertainty with regards to similarity
- Role of ADCC remains uncertain in indication
- Small sample size of lots
- Evaluate additional lots of biosimilar and reference product for ADCC activity, and tightened specifications for FcγRIIIa binding
Prior knowledge

• Information to be included in the submission for prior knowledge:
  • Source of prior knowledge
  • Relevant data
  • Justification of its relevance/applicability
  • eCTD section: 3.2.S.4.5 and 3.2.P.5.6
Knowledge from Literature

- Asn deamidation, Asp isomerization (IsoAsp) occur in vivo
- IgG2 disulfide structure is dynamic in vivo
  - linkages interconvert in circulation - IgG2-A, A/B, B
- IgG4 forms “half antibodies”
- May be important to confirm impact of isoforms with your specific product
Case study #8 – prior knowledge

- Proposed ~8% (charge variants, pre-peak) for stability
- Worst-case clinical experience estimated to be ~3%
- Stability data ~4% highest observed in lots
- Sponsor argued that knowledge gained from other monoclonal antibodies – same subclass IgG with (~16% of attribute) to support safety
- Safety experience in oncology patient population does not extrapolate to non-oncology indication
Take home messages

• Objectives of the use of prior knowledge are faster drug development and enhanced manufacturing efficiency
• Prior knowledge is leveraged and used to confirm data rather than building data/process from scratch
• Critical: understanding that each product has unique properties that should be understood in order to establish appropriate IPC, controls of input of materials, DS and DP specs
• Main concern: risks associated with over-reliance on prior knowledge
• Use of prior knowledge to support applications should not change the expectations of assurance of quality
Take home messages

Optimal use of prior knowledge in application requires:

• Clear distinction of what is prior knowledge and what is product specific knowledge
• Information to be placed in supportive eCTD sections with links to facilitate navigation
• Justification and demonstration of the relevance and applicability of prior knowledge to the new product
Thank you!

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