Regulatory perspectives on setting relevant specifications in early development and throughout product life cycle

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Disclaimer

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Outline of presentation

• Specifications: tests and acceptance criteria
  – Definitions and supporting regulations
• Release and stability specifications
• Goals and challenges for specifications during early drug development
• Types of stability studies and their applications
  – Real-time stability and setting expiry date
  – Impurities and forced degradation studies
  – Excipient stability
  – Physiological stability
• Strategies for identifying CQAs for monitoring
• Risk assessment for relevant specifications
Specifications

Specification, as per § 314.3 and 600.10(kk), 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 means numerical limits, ranges, or other criteria for the tests described. § 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
Regulatory requirements for release testing

- 21 CFR 312.23(a)(7)(i) Identification and control of DS/DP
  - 
  - “(i)... sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug.”
  - “Final specifications for the drug substance and drug product are not expected until the end of the investigational process.”

- 21 CFR 211.165. cGMP / Testing and release for distribution
  - Reproducibility of test method and consistency of manufacture

- 21 CFR 610.1 Tests required prior to release for each lot

- 21 CFR 312.23 IND Content and Format
  - 312.23 (7)(ii); 312.23 (7)(iv)(a); 312.23(7)(iv)(b)
  - 21 CFR 610.61 Package Label
  - 21 CFR 601.12 Changes to an approved application
The goal of a release testing program throughout a drug’s developmental lifecycle

- To prevent unreasonable and significant risk of illness or injury to human subjects [21 CFR 312.42(b)(1)(i)]
- Provide sufficient information (about your product and process) to asses risk to human subjects [21 CFR 312.42(b)(1)(iv)]
Regulatory requirements for *stability* testing

- 21 CFR 211.166 cGMP / Stability Testing
  - “(a) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates.”
  - “Reliable, meaningful, specific methods”
  - Expiry dating, confirmed by licensure

- 21 CFR 312.23 IND Content and Format
- 312.23 (7)(ii); 312.23 (7)(iv)(a); 312.23(7)(iv)(b)
  - 21 CFR 610.61 Package Label
  - 21 CFR 601.12 Changes to an approved application
The goal of a stability program throughout a drug’s developmental lifecycle

- Maintain product quality, shelf-life, safety, and efficacy throughout preclinical and clinical testing [21 CFR 312.23(a)(7)(i)]
- Important tool to assess impact of change in manufacture, storage, or container on active ingredient and excipients in the final container-closure system [21 CFR 211.166(a)(4) and 610.15(a)]
- Confirmation of lot-to-lot consistency of manufacture [21 CFR 610.1, 610.12, 610.13, 610.14]
Stability Guidances

- FDA Guidance for Industry: Content and format of Investigational New Drug Applications (INDs) for phase 1 studies of drugs, including well-characterized, therapeutic, biotechnology-derived products (1995).
  - “although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly very limited.”
  - 21 CFR 312.23- “…information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies”
Stability Guidances

• FDA Guidance dedicated to stability of biotechnology products is needed and is a current agency goal
• ICH provides most focus on stability
  – Q5C
    • Designed for Biotech products: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
  – Q1A(r2); Q1B, Q1C, Q1D, Q1E
    • Designed for small molecules
    • Apply to Biotech as appropriate
Life Cycle of Analytical Tests and Acceptance Criteria

Pre-Clinical
- Selection
- Development
- Optimization

Phase 1
- Qualified methods
- Set tentative release/stability acceptance criteria
- Stability protocol to support clinical studies
- Comparability of preclinical and clinical material

Phase 2
- Optimization/qualification
- Refine lot release and stability criteria
- Set tentative validation acceptance criteria
- Delineate/initiate assay validation parameters

Phase 3 and BLA
- Full assay validation (strongly recommended for phase 3)
- Set release and stability specifications
- Set expiration date

Post-Licensure
- Trend analysis
- Performance review
- Method replacement (supplement)

Implement
Review
Validate
Optimize
Develop
Method
The preIND consultation program

- 21 CFR 312.82(a)

*Pre-investigational new drug (IND) meetings.* “Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.”

“Pre-IND interactions should be considered as preliminary communications based on early development information, and will generally take the form of written comments that may be supplemented by teleconferences or meetings as needed and appropriate. Additions or modifications to these communications may arise as additional information becomes available, during follow-up pre-IND interactions or when an IND is established.”

Contact the appropriate clinical division to get started.
Stability studies at different steps in manufacture and storage

• Early in development and as you identify your molecule’s CQAs, start your stability program before your prospective clinical study to catch any potential drift in CQAs

• Perform trend analysis of your ongoing stability protocol(s)

• During manufacturing process
  – Hold times, freeze-thaw steps, site transfer
  – Key intermediates and DS
  – DP in final formulation and container-closure

• Control of raw materials
  – Changes in raw material should not impact product quality
Role and timing of forced degradation/stress studies

• Confirm stability indicating capabilities of analytical test methods

• Earlier is better - get to know your product and best storage conditions
  – Phase 1 or 2 desirable
  – Phase 3 expected

• Temperatures, light, pH, chemicals (e.g., oxidation), agitation
Stability studies at different steps in manufacture and storage

• Stability of excipients
  – Polysorbates
  – Albumin
  – Preservatives (phenolic by-products)
  – Interactions with container-closure system
    (consider leachable/extractable testing?)
Stability studies at different steps in manufacture and storage

• As part of shipping validation
  – Choose appropriate range of conditions, outside of what’s expected
    • Heat (airplane on hot tarmac)
    • Agitation
    • Pressure
    • Freeze-thaw
    • Saline/pH

• During conditions of use
  – Infusion time
  – Light conditions and photosensitivity, room location (in the sun?)
  – Infusion solution (glucose; compatibility with i.v. bag?)
  – Home use (patient errors)

All relevant for YOUR process and YOUR product
The goals of your stability testing program prior to licensure

- Sufficient data to demonstrate stability under the proposed storage AND shipping conditions
- Panel of stability-indicating assays
- Expiration estimation (expected to evolve)
- Clinical trial and commercial scale
- Real time and accelerated/stressed (worst case scenario for CQAs)
- Conditions of use, where appropriate

See summary of July 2005 WCBP Stability Forum
(Gold sheet, October 2005)
Determining CQAs for testing:
Levels of protein structure

- Primary
- Secondary
- Tertiary
- Quaternary
Many proteins have multiple domains that confer correct function under appropriate physiological conditions.

- **Inhibitor Binding Domain (PAI)**
- **Fibrin Binding Domain (site-specific activation)**
- **Protease Domain (substrate plasminogen binding & activity)**
Power of protein analytics - which to use for stability studies?

**Amino acid sequence and modifications**: Mass spectrometry, chromatographic separation, peptide mapping

**Folding**: circular dichroism, Fourier transform spectroscopy, fluorescence, S-S bonds, calorimetry, H₂-D₂ Mass spectrometry, NMR

**Subunit interactions**: chromatography, S-S bonding

**Heterogeneity** of size, charge, hydrophobicity: chromatography, electrophoresis

**Glycosylation**
- N- & O-sites, antennae, high mannose
- Sialylation, terminal galactose

**PEGylation & isomers**: chromatography, peptide map

**Bioactivity**: cellular and animal bioassays; ligand binding (ELISA, surface plasmon resonance)

**Aggregation**: analytical ultracentrifugation, size-exclusion chromatography, field flow fractionation, microscopy

**Proteolysis**: electrophoresis, chromatography, mass spectrometry

**Impurities**: proteomics, immunoassays, metal & solvents analysis

**Sterility** (qPCR, bioassays, clearance)

**Immunogenicity** (Epitope mapping)
Product-related substances (variants): assess as part of stability protocol

- Effects of variants on bioactivity and bioavailability (PK/PD)
  - *In vitro vs in vivo*
    - Terminal sialic acid - little effect on receptor binding and bioactivity *in vitro* but controls product half-life *in vivo*
    - Glycosylation - decreases receptor binding and bioactivity *in vitro* but increases half-life
  - Full vs partial potency
  - Antagonistic activity
  - Toxicity (toxin-conjugated product)
  - Immunogenicity
The big questions for therapeutic proteins

How do you know when:

• have correct structure(s)?
• structural variants are present?
• structure has changed significantly?
• change in structure is important (clinically)?

To what extent can physicochemical and biological methods answer these questions?
Challenges during early development

• Which lots? How many?
• Important to put the tox lot on stability.
  – Can be used to support stability of lot to be used in clinical trial
• After significant changes to the process or use of a reprocessing or reworking step
  – Risk assessment
• Enough to know your product.
  – Expect to have few lots made before licensure
Implications for changes to the manufacturing process or product

• Stability protocol may need to be revised to assess product quality attributes previously resistant to change
  – *e.g.*, increased pH --> add tests for deamidation, oxidation
  – *e.g.*, higher protein concentration --> additional aggregates testing

• Part of establishing comparability as well as stability
Applications of a reference standard

- ICH Q6A, Q6B, and Q7: *Test Procedures and Acceptance Criteria* and Good manufacturing practice guidance for active pharmaceutical ingredients
- Reference standards (RS) for drug substances can be useful in validating specificity for an identity test.
- Stability of a reference standard and the use of an appropriate stable reference standard during stability testing of your DS/DP should be ensured.
- Follow storage, usage conditions, and handling instructions to avoid added impurities (e.g. aggregates) & inaccurate analyses relative to an inconsistent RS.
- Reference standards, including qualification test protocols, purity profile, stability protocols, are to be included in the BLA.
- In rare cases, some potency reference standards can be obtained form official sources (e.g. WHO).
- A reference standard could also be developed and used for assaying attributes not necessarily captured by the DS and DP characterization (e.g. impurity profile, system suitability).
Unique considerations for in vivo stability

- Physiological stability?
  - Is physiological stability critical for safety and efficacy? (e.g. intra-tumor or intra-lesion injectable)
  - Do you need to test your product’s stability for a predefined duration in a physiologically relevant buffer/medium?
  - What physiological factors contribute to the in vivo activity or degradation of your product? (e.g. metal co-factor, proteases)
  - Should physiological stability studies be part of your characterization and stability testing?
Product quality and a multi-disciplinary risk approach to “relevant” specifications?
Risk assessment considerations for specifications

- Differences in CQAs that are within specifications but outside of clinical experience may have unknown but potentially significant consequences.
- In some instances, meeting current specifications may not be sufficient to predict impact on clinical performance of product following manufacturing deviations (e.g. microbial contamination, immunogenicity).
- As product knowledge grows, critical quality attributes and appropriate limits may be identified and proposed (e.g. glycosylation, deamidation).
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

**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

Specific to your product, process, assay, indication, and patient population.
Risk assessment matrix for meaningful specifications?

<table>
<thead>
<tr>
<th>Clinical determinant</th>
<th>Product quality attribute 1</th>
<th>Product quality attribute 2</th>
<th>Product quality attribute 3</th>
<th>Product quality attribute 4</th>
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<tbody>
<tr>
<td>Clinical determinant A</td>
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<td>Clinical determinant B</td>
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<td>Clinical determinant D</td>
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Perform your own risk assessment and share relevant conclusions with the agency
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
- Human factor issues such as in-use stability
- Product meets official/pharmacopoeial standards, if applicable
Supportive evidence for relevance?

- In vivo human study data with representative lots
- Assay validation and manufacturing history
- Reference standard or pivotal trial material
- In vitro biochemical assessment such as QbD/DOE – start early
- Animal toxicology data with comparable lots -limited use in some instances
- Modeling and in-silico simulation studies such as with QSAR, ADME, IVIVC models – still evolving
- Leverage prior knowledge including from known SAR for molecule, structural analogs, family members, adverse event reports, and drug recalls- with appropriate scientific justification

A multi-disciplinary and individualized approach to justify the analytical and clinical relevance of your product specifications.
Take home messages

- Consider the complexity of your protein and the availability of multiple, appropriate analytical methods (Primary, Secondary, Tertiary, Quaternary, Aggregates)
- Need battery of complimentary methods to determine structure, function, purity, potency. Confirm stability indicating capabilities of analytical test methods.
- Different studies for different aspects of your product, manufacturing, storage, shipping, and usage
- In early development, the stability protocol is aimed at maintaining shelf-life, product quality, safety, and efficacy throughout preclinical and clinical testing time frames.
- Accelerated and stressed studies (temp, pH, ionic) to characterize and compare pre-/post-change lots
- The results of stability testing are used to determine appropriate storage conditions and expiration date at the time of licensure. The stability protocol should also be sufficient to support stability during the toxicological studies and the planned clinical studies.
- Start your stability program before your prospective clinical study to catch any potential drift in CQAs. Monitor and perform trend analysis of your real-time stability data.
- Control for attributes based on their biological and clinical significance.
- Linking your historical clinical success to your future safety and efficacy
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