Regulatory Expectations for the Use of Reference Standards during Development and Beyond

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Outline
In-house Reference Standards

Existing guidance

Expectations
RS program, suitability for purpose, well characterized, qualified, stable, protocols

Observations from past submissions and challenges faced
ICH Q6B (Specifications) – March 1999

Two-Tiered System

“At the time of submission, the manufacturer should have established an appropriately characterized in-house primary reference material, prepared from lot(s) representative of production and clinical materials. In-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material. Where an international or national standard is available and appropriate, reference materials should be calibrated against it. While it is desirable to use the same reference material for both biological assays and physicochemical testing, in some cases, a separate reference material may be necessary. Also, distinct reference materials for product-related substances, product-related impurities and process-related impurities, may need to be established. When appropriate, a description of the manufacture and/or purification of reference materials should be included in the application. Documentation of the characterization, storage conditions and formulation supportive of reference material(s) stability should also be provided.”
“A reference standard (i.e., primary standard) may be obtained from the USP/NF or other official sources (e.g., CBER, 21 CFR 610.20). If there are questions on whether a source of a standard would be considered by FDA to be an official source, applicants should contact the appropriate chemistry review staff. When there is no official source, a reference standard should be of the highest possible purity and be fully characterized.”

“A working standard (i.e., in-house or secondary standard) is a standard that is qualified against and used instead of the reference standard.”

“A reference standard that is not obtained from an official source should be of the highest purity that can be obtained by reasonable effort, and it should be thoroughly characterized to ensure its identity, strength, quality, purity, and potency. The qualitative and quantitative analytical procedures used to characterize a reference standard are expected to be different from, and more extensive than, those used to control the identity, strength, quality, purity, and potency of the drug substance or the drug product. Analytical procedures used to characterize a reference standard should not rely solely on comparison testing to a previously designated reference standard.”
“Generally, this characterization information should include:

• A brief description of the manufacture of the reference standard, if the manufacturing process differs from that of the drug substance. Any additional purification procedures used in the preparation of the reference standard should be described.

• Legible reproductions of the relevant spectra, chromatograms, thin-layer chromatogram (TLC) photographs or reproductions, and other appropriate instrumental recordings.

• A detailed description of the analytical procedures used to characterize the reference standard.”

“For biotechnological/biological product reference standards, the recommendations on characterization information above [small molecule testing] may apply and should be considered. However, additional and/or different tests would be important to assess physicochemical characteristics, structural characteristics, biological activity, and/or immunochemical activity. Physicochemical determinations may include isoform, electrophoretic, and liquid chromatographic patterns, as well as spectroscopic profiles. Structural characterization may include a determination of amino acid sequence, amino acid composition, peptide map, and carbohydrate structure. Biological and/or immunochemical activity should be assessed using the same analytical procedures used to determine product potency. These can include animal-based, cell culture based, biochemical, or ligand/receptor-binding assays. While these tests may be needed for complete characterization of certain reference standards, specific recommendations for validation of biological and immunochemical tests are not contained in this guidance document.”
For drug applications for new molecular entities, it is unlikely that an international or national standard will be available.

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"Also, distinct reference materials for product-related substances, product-related impurities and process-related impurities, may need to be established. When appropriate, a description of the manufacture and/or purification of reference materials should be included in the application. Documentation of the characterisation, storage conditions and formulation supportive of reference material(s) stability should also be provided."
“Before a mAb is studied in humans…”

“A properly qualified in-house reference standard with known characteristics, specificity, and potency, and that is stored under appropriate conditions and periodically tested to ensure its integrity, should be used for lot-to-lot comparisons. Reference standards should be updated as a product evolves but should be finalized by the start of phase 3 trials. Appropriate standard operating procedures (SOPs) should be developed for qualification of a new reference standard.”
The guidance does not apply to ... protein drug products derived from natural sources or produced by the use of biotechnology, or other biologics.

“Where a recognized national or international standard ... is available, the manufacturer’s reference material and/or working standard should be qualified against this standard. A national or international reference standard may not be available .... In this case, the sponsor can select a batch of drug substance to be used as a reference material, against which initial clinical batches would be tested before their release. Preferably, the sponsor would establish a working standard even at the initial stage of drug development. For the purpose of this guidance, a working standard is a reference material that has been further characterized beyond the standard batch release tests. The protocol for establishing the working standard should be submitted in an information amendment. However, the results from the testing to establish the working standard can be reported in an annual report.”

“When a reference material is fully characterized, it would become the manufacturer’s primary reference material. The manufacturer can continue to establish new working standards that are qualified against that primary reference material.”

“If a national or international standard is not yet available, the sponsor should establish its own primary reference material during phase 3 studies. The manufacturer can continue to use the working standard from phase 2 or can establish a new working standard for lot release.”
Committee for Medicinal Products for Human Use (CHMP)
Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials
EMA/CHMP/BWP/534898/2008  18 February 2010

“This guideline outlines the requirements for the data to be presented on the biological, chemical and pharmaceutical quality of Investigational Medicinal Products (IMP) containing biological/biotechnology derived substances.”

“Due to the nature of biologically/biotechnology derived products a well characterised reference material is essential to ensure consistency between different batches of IMP but also to ensure the comparability of the product to be marketed with that used in clinical studies and to provide a link between process development and commercial manufacturing. The characterisation of the reference material should be performed with reliable state-of-the-art analytical methods, which should be sufficiently described. Information regarding the manufacturing process used to establish the reference material should be provided.”

“If available an international or Ph.Eur. standard should be used as primary reference material. However it should be noted that the use of an international or Ph.Eur. standard might be limited to certain defined test methods, e.g. biological activity.”
Two Tiered System

Primary RS and Secondary/Working RS that is qualified using the Primary RS

Not expected to be in place for use early in development

Should be carefully considered early in development

A plan for putting this system in place should be generated sufficiently early in development to ensure that an appropriate RS system can be implemented for licensure.
Two Tiered System

Observation and challenge: The sponsor did not have an appropriate RS program in place during development (or at the time of licensure).

For the licensed product –
The sponsor did not have a sufficient supply of RS used during the pivotal clinical studies to designate this the primary RS.
The sponsor did not have a sufficient supply of material used during the pivotal clinical study to generate a RS from this material.
We expect the commercial RS to be representative of the pivotal clinical study material to ensure that the commercial lots are representative of the pivotal clinical study material.
The sponsor needed to develop a mechanism by which a new lot of material could be qualified as a commercial RS.

There was sufficient pivotal study material (that had been stored under appropriate conditions) to allow a new lot of material to be qualified against the pivotal study material, at least for product quality attributes that are critical for the intended purposes of the RS.

Multiple PAS were required to get this RS program approved.
When to Manufacture and Qualify a new RS

A new RS is **not** necessary for every manufacturing change made during development. (If additional RS is needed, this may be an appropriate time to qualify a new RS.)

A new RS would be necessary only if the manufacturing changes resulted in significant differences in the product, especially in quality parameters that are compared against the reference (e.g., potency). (This should not be a frequent occurrence and would also require careful consideration regarding acceptability of the manufacturing change.)

Report the new RS to the IND.
When to Manufacture and Qualify a new RS

Observation and Challenge: Many RS manufactured during development; apparently one RS qualified against the previous RS

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<th>RS</th>
<th>Process</th>
<th>Qual. RS</th>
<th>Potency 1</th>
<th>Potency 2</th>
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Qualification of RS

Expectations for RS qualification/characterization change over the course of development.

Qualification needs to demonstrate suitability for purpose.

– Purpose is more than just acting as a comparator for lot release/stability.
– RS is used for evaluating system suitability, assay/plate acceptance, method validation, assay trending, etc.
– A single RS may be used for assessment of DS and DP, even if DS and DP are not identical formulations.

“…FDA’s review of Phase 1 submissions will focus on assessing the safety of the Phase 1 investigations, FDA’s review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.”

21 CFR 312.22(a)
Qualification of RS

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Understanding of critical quality attributes changes throughout development. Additional characterization may be needed as development continues. This understanding may alter the level of qualification needed for different attributes.

The need for accuracy (e.g., for potency and protein concentration) increases as development proceeds. Additional independent determinations (over those required for routine testing) should be added at later stages of development.
RS Qualification Protocols

More than simply the DS/DP specifications

**Sufficient controls must be in place to prevent product quality drift.** This is true for both clinical and commercial RS; tighter control would be expected late in development and throughout the licensed product lifecycle.

The protocols should describe the purposes of the RS, and the qualification requirements should be derived to ensure that the RS is suitable to meet those purposes.

Acceptance criteria should be set for all product quality attributes that are evaluated.

Talk given by Barry Cherney at IABS/FDA Reference Standards for Therapeutic Proteins: Their Relevance, Development, Qualification and Replacement (2011)

“Of late, we have frequently requested withdrawal of these protocols.”

Requesting withdrawal of RS protocols is still occurring.
RS Qualification Protocols

Observation and Challenge:
No protocol included in the BLA, only statements such as “release testing of reference standard lots will be performed per the drug product specifications” and there would be “additional testing and acceptance criteria for characterization”

This is not sufficient for a BLA.

- Prior to licensure, we requested confirmation that an approved protocol would be implemented before release of a new RS. The protocol would need to be submitted to the BLA as a PAS.
- In the initial PAS submission, the data provided showed that a product quality parameter did not meet its acceptance criterion. The sponsor did not consider how this might affect aspects such as when RS is used for system suitability/assay/plate acceptance or comparison to the RS. Along with other issues, this resulted in a CR prior to eventual approval.

(Note, if a commitment is made during the BLA review, there should be follow through.)
RS Qualification Protocols

Observation and Challenge:
BLA with insufficient RS protocols (selection, qualification, overall program)

Initial requirement: 75-125% relative potency
Subsequent requirement: 90-110% relative potency

A two tiered system was not in place.
As noted in one IR sent to the sponsor, after 4 generations, an acceptable range of 90-110% would allow for an effective change in the lot release/stability specification acceptance criteria from:
- 60-140% to upper or lower limits of 204% or 39% for the bioassay
- 65-135% to upper or lower limits of 197% or 43% for binding assay.

This was not considered sufficient control to prevent drift.

The number of evaluations initially proposed did not provide sufficient statistical power to alleviate the issues resulting from variability of the potency assays. Additional independent determinations were implemented prior to approval.

Continued on next slide
RS Qualification Protocols

Observation and Challenge:
BLA with insufficient RS protocols (selection, qualification, overall program)

It was considered that for tests other than potency, the RS serves as a system suitability control.
- A comparison to RS is used for identity and the charge variant assay for this product.
- RS is used in many characterization tests that are performed as part of the proposed RS qualification and are performed during other aspects of the product life-cycle (e.g., comparability assessments).

The protocols were withdrawn from the BLA prior to approval with the intention to resubmit RS protocols as a PAS. Agreement on the protocols could not be reached within the initial PAS review timeline, which led to the withdrawal of all protocols and the approval of a single lot of RS. The second PAS was approved after multiple IRs and protocol updates.
RS stability and requalification

Under IND, there will be limited information regarding long-term stability of the RS. RS should not be stored under conditions that are permissive for degradation.

Observation and Challenge:
Original IND submission- Storage of RS at 2-8°C
- Resulted in requests for additional data/details and in additional scrutiny of all data submitted to the IND

Data supporting stability of the RS under the intended storage conditions should be provided for licensure.
- Note that potency results comparing RS to itself may not be sufficient. Raw data (e.g., IC_{50} or equivalent) may be useful.

Stability protocols for monitoring each lot of RS should be included in the RS program.
Reference Standard Program

A complete RS program covering the lifetime of the product (preclinical through commercial) should be in place for all products.

This program should include, but is not limited to, protocols that define:
- When a new RS should be manufactured and qualified
- How a potential RS lot is identified
- RS manufacturing/storage
- RS qualification
- RS stability
- RS trending

This program should ensure that:
- New RS is qualified before the current RS is depleted or degraded
- RS is suitable for its purpose
- New RS represents the previous RS and the material used in pivotal clinical studies (at the applicable time in development)
- RS is sufficiently stable

There should be a constant, consistent supply of RS.

For licensed products, RS protocols/new RS to be implemented without an approved protocol in place are expected to be submitted as a PAS, since a change in reference standard has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product.
Acknowledgements

Kathleen Clouse

DMA colleagues