Whitepaper

Reference standards biopharmaceutical products - Do you have your reference standard program in place?

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Experts in Regulatory Affairs

White paper

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To meet the current expectation of the Health Authorities (HAs), which varies from country to country, companies developing and commercializing biopharmaceutical products should set up a reference standard (RS) program and carefully plan a change control strategy for post approval changes.

Definitions

In-House Primary Reference Standard: Per ICH Q7 [1], primary reference standard is defined as "a substance that has been shown by an extensive set of analytical tests to be an authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognized source, (2) prepared by independent synthesis, (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material." Specifically for biopharmaceutical products, rather than using an ultra-purified material as reference, ICH 6B states that an in-house primary reference standard is an appropriately characterized material prepared by the manufacturer from representative lot(s) for the purpose of biological assay and physicochemical testing of subsequent lots, and against which in-house working reference standard is calibrated.

In-House Secondary Reference Standard (also referred to as a working standard): Appropriately characterized material prepared from representative clinical or commercial lot(s) prepared to support routine testing of product lots for quality

control purposes, such as biological assays and physicochemical testing. It is always calibrated against a primary reference standard (either official or in-house, two-tiered approach[1]).

In-House Interim Reference Standard: Appropriately characterized material prepared from representative clinical or production lot(s) used for quality control purposes during the development stage of a product. It is not compared to an official or primary reference standard, but it is established based on appropriate demonstration of its inherent characteristics.

Official Reference Standard: According to ICH Q7 definition, an official RS is a primary reference standard obtained from an "officially-recognized source." Typically it is established by a public agency (e.g. WHO), government (e.g. NIST, NIBSC), or compendia (e.g., USP, Ph. Eur.), and is officially recognized as standard by individual regulatory authorities.

Reference standards for biopharmaceutical products

Reference standards are developed as part of the analytical control strategy. Due to the nature of biopharmaceutical products (amongst other, structurally complex, heterogeneous mixtures, inherent batch-to-batch variability, sensitive to manufacturing changes), a well characterized reference standard is essential to ensure consistency between different batches of Investigational Medicinal Product. Also the use of a reference standard will ensure the comparability of the product to be marketed with that used in clinical studies and provide a link between process development and commercial manufacturing [2]. Reference standards can help to provide solutions that support discovery, regulatory compliance, and process efficiency [3].

Compared to small molecule drugs, biopharmaceutical drugs have more complex structures and often cannot be fully characterized. Thus, quality determination of and quality control for biopharmaceutical drugs often require the application of multiple analytical approaches including physicochemical methods, assays that measure for potency, or a combination thereof.

The characterization of the RS should be performed with reliable state-of-the-art analytical methods, which should be sufficiently described in the Common Technical Document Module 3 quality documentation. Information regarding the qualification history and manufacturing process used to establish the RS should be provided. If available, an international or Ph. Eur. standard should be used as primary reference standard. However, it should be noted that when an international or Ph. Eur. standard is not available, an in-house RS should be established [2].

[1] A two-tiered approach, when qualifying new reference standards, is to prevent drift in the quality attributes. A two-tiered approach involves a comparison of each new reference standard with a primary reference standard so that it is linked to clinical trial material and the current manufacturing process.

In-house reference standards are used for various purposes amongst other:

- Comparative analytical methods:
  - Quantitative (e.g., calibrator for the determination of biological activity)
  - Qualitative (e.g., comparator for purity testing)
  - Performance control in assays to evaluate system suitability
- Batch release testing
- Stability testing
- Characterization studies
- Comparability assessments

ICH guidance

According to ICHQ7 [1] Primary reference standards should be obtained as appropriate for the manufacture of Active Pharmaceutical Ingredients (APIs). The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations. For biopharmaceutical drugs, primary reference standard is most often not available from an official recognized source. When this is the case an "in-house primary standard" should be established. Appropriate testing should be performed to establish the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

API of small molecule products is usually homogenous and very pure, the lot-to-lot reproducibility is high and tests are generally very precise and are able to detect with a high sensitivity the lowest level of impurities. The manufacturing processes for proteins however, produce heterogeneous material with a certain amount of lot-to-lot variability, tests are generally more variable (e.g. Bioassays) with often a lower sensitivity. Due to these differences ICH Q6B [4] describes specific definitions for in-house reference standards for biopharmaceutical products (see Definitions).

Reference Standard Program

HAs are expecting that a comprehensive reference standard program covering the lifetime of the product (preclinical through commercial) is in place [5]. The intent of this program is to ensure that there is a constant and consistent supply of RS.

The following protocols should be included in the program:

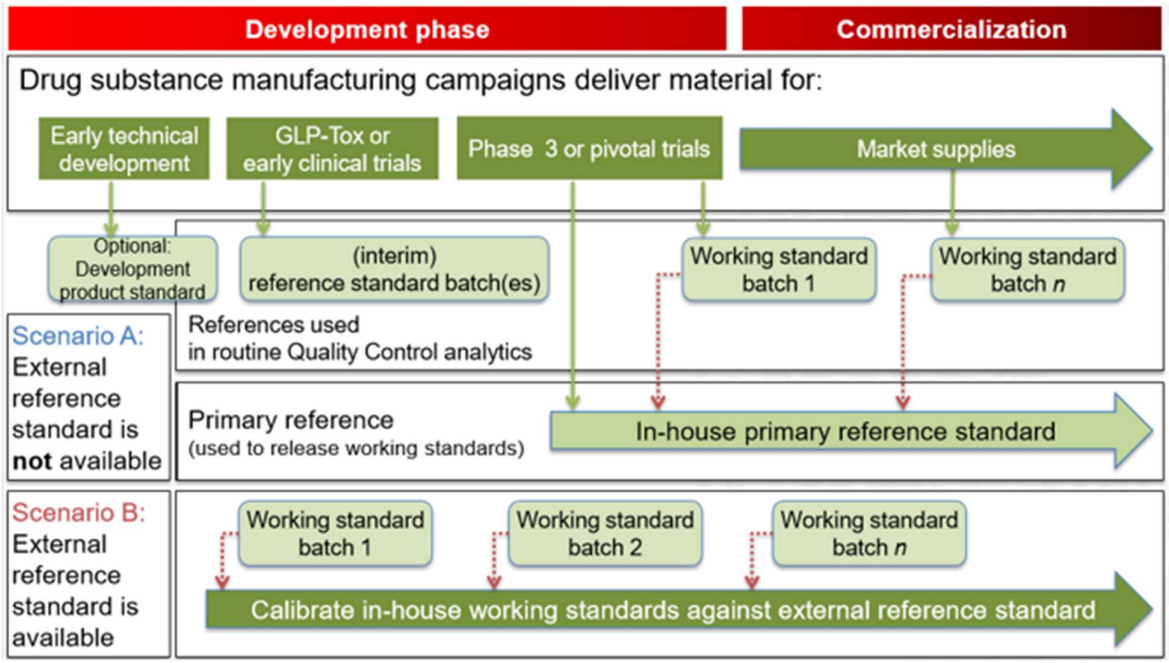
- Manufacturing and storage of the RS
    - As can be seen in figure 1 it is not expected that a RS is in place for use early in development. A plan for putting the RS system in place should be generated sufficiently early in development to ensure that an appropriate RS system can be implemented for licensure.
    - The selected drug substance material may be pooled from multiple lots, formulated, diluted (e.g. with placebo) or concentrated to a concentration best suitable to support all relevant analytical assays and to ensure prolonged stability of the reference standard [6].
    - The RS does not need to be filled under GMP, but under conditions controlled as well as possible to ensure optimum quality and integrity [6].
    - Sufficient quantities of a primary reference standard should be manufactured to maintain consistent product history, i.e. to minimize the need to have to replace the primary reference standard [6].
    - Storage containers and temperature do not have to be identical to the primary packaging of neither DS nor DP [6].
- Qualification of RS
    - In-house reference standards should be characterized by procedures including routine and beyond routine release testing as described in ICH Q6B [4]. Orthogonal methods for reference standard characterization should be considered. Additional testing could include attributes to determine the suitability of the reference standard not necessarily captured by the drug substance or product release tests (e.g., more extensive structural identity and orthogonal techniques for potency, purity and impurities) [7] and not relying solely on comparison testing to a previously designated RS.
- Stability testing of RS
    - Stability protocols for monitoring each lot of RS should be included in the RS program.
- Trending of RS
    - All trended parameters that are derived from the RS should be evaluated for a shift in assay results, especially following the implementation of a new RS lot [6].
- Manufacturing and qualification of a new RS

- It is not necessary to generate a new RS for every manufacturing change made during development. If the manufacturing change results in significant differences in the product, specifically in quality parameters that are compared against the reference (e.g., potency), a new RS would be necessary.

The RS program should make sure that:

- The new RS is qualified before the current RS is depleted or degraded
- The RS is suitable for its purpose
- The new RS represents the previous RS and the material used in pivotal clinical studies (at the applicable time in development)
- The RS is appropriately stable

Figure 1 Different types of reference standards evolving during development (Adapted from [8]*)*



Post approval submission approaches

For authorized products it is expected that updates to RS protocols or new RS are submitted per applicable HA guidance since a change in RS has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product.

When reviewing the guidance from different HAs, it is clear that there are different expectations for different countries. For example, when a new RS is introduced according to an approved quality protocol, the change types range from no

need to file (the new RS is covered by the quality system) to a prior approval submission. As these differences in regulatory expectations for RS post approval changes can have a big impact on product supply, a change control strategy should be carefully planned.

For the most up to date information regarding the HAs expectations, please consult the regulations and published guidance.

When you need help with the set-up of a reference standard program that is acceptable for HAs, don't hesitate to contact the regulatory experts of STARoDub BV.

References

[1] ICH Q7, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients," 2000.

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[5] S. Kennett, "Regulatory Expectations for the Use of Reference Standards during Development and Beyond," *C. Strateg. Forum- Ref. Stand. Ther. Proteins*, 2013.

[6] D. Schmalzing *et al.*, "Current Best Practices and Remaining Open Questions for Reference Standard Programs," *C. Strateg. Forum 2013, Gaithersburg, MD CASSS*, 2013.

[7] FDA, "Guidance for Industry, Analytical Procedures and Methods Validation for Drugs and Biologics," 2015.

[8] A. Mire-Sluis, N. Ritter, B. Cherney, D. Schmalzing, and M. Blümel, "Reference Standards for Therapeutic Proteins," *Bioprocess Int.*, 2014.

About Starodub

Reliable, Efficient and Knowledgeable

Starodub BV was founded in May 2014. The company started with one employee, the founder Valentyna Starodub. By today, our team has grown to round 20 employees and has a valuable network of specialized experts. We partner with (bio)pharmaceutical and medical device companies worldwide to ensure that regulatory requirements are met and business goals, such as quick market access and compliance, are achieved. Please check the Our services page to learn how we can support you with meeting your business goals.

Our lean and powerful team strives to be of added value to our clients. All employees are highly educated and obtained degrees in pharmacy, chemistry, biology or related. Our short reporting lines are key to finding the most efficient road to your success. One of our experts will be your primary contact and the team's collective knowledge and resources are available to give reliable advice and execute projects in the most efficient way. Together, we connect the dots and look beyond the scope of projects to make sure all aspects of importance are addressed.

At Starodub BV consistency and assurance of quality are considered as being highly important. A quality management system has been implemented and we strive to comply with GxP and ISO 9001/13485 constantly. In addition, we have an external board of control, acting as the sparring partner to set the optimal course for our company.

We strive to be a true partner to Our clients, who rate our services as ≥4.5 on a scale of 1 (poor) to 5 (excellent). This motivates us to maintain the highest professional standards and to implement continuous improvement.

About the Author

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Since 1990, I worked in the molecular diagnostic and pharmaceutical industry. Working in regulatory affairs, I have been involved in IND/IMPD registrations, MAA/BLA registrations and post-approval activities for Biotech products worldwide. I have also gained experience with quality, change control and compliance related issues. I am service oriented with an eye for detail and I think in possibilities and solutions.

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