Pharmaceutical Reference Standards: Overview and Role in Global Harmonization

3rd DIA China Annual Meeting

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What is a Pharmaceutical Reference Standard?

A highly purified sample of a particular compound that has been characterized so that an accurate content can be stated.

Used as the basis for quantitative and qualitative testing.

If 100%, then 90%
Reference Standard Materials

Flame sealed glass ampoules with argon headspace

Glass bottles with Teflon lined screw caps

Crimp sealed lyophilized vials
Reference Standard Uses

Quantitative calibration
Identity comparison
Test of system suitability
Peak marker
Fingerprinting
Visual comparison
Types of Reference Standards

Reference Standard

- Company Reference Standard
  - Primary Reference Standard
  - Secondary Reference Standard
  - Other Reference Standard

- Laboratory-based Reference Standard

- Official Reference Standard
  - Primary Reference Standard
Reference Standard Role in Pharmaceutical Testing
The Role of Reference Standards in a Pharmaceutical Control System

Reference Standards are developed as part of the **analytical control strategy** for each drug product.

Each reference standard has a **control strategy** of its own.

Reference Standards play a **central role** in assuring the **quality** of medicines for patients during cGMP testing and release activities.
Simplified Product Control Strategy

Specifications
What the measurement means...

Methods
How to measure...

Reference Standards
Basis of the measurement...

Process
What to measure...

When to measure...
Reference Standard Control Strategy

Specifications

Methods

Process
Regulations Governing RS Operations

Food and Drug Administration (FDA)
- CFR Title 21 – Food and Drugs GMP, 211.194(c), 211.160(b)(1) and 299.5(c)
- ICH Guidelines Q7, Q6B
- Various FDA Guidance Documents
- FDA regulatory observations (Warning Letters, 483’s)
- United States Pharmacopeia

European Agency for the Evaluation of Medicinal Products (EMEA)
- EU GMP 32, Annex 18 (transcription of ICH Q7)
- EU Quality Guideline 32 (regulatory submission requirements)
- ICH Guidelines Q7, Q6B
- European Pharmacopoeia

Japan Ministry of Health Labor and Welfare (MHLW)
- Japan Pharmacopoeia Technical Information (JPTI) 1995, section 2
- ICH Guidelines Q7, Q6B
- Japan Pharmacopoeia
Additional Sources of Guidance

ISO Guidelines 31, 32, 34

WHO Technical Report Series (TRS) 885, 902, and 908

Published Warning Letter Citations

Benchmarking of Findings at Other Firms

Audit Near Misses

Internal QA/QC Audits
## Reference Standard vs Drug Product

<table>
<thead>
<tr>
<th>Reference Standard</th>
<th>GMP for Human Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intended use – laboratory control</td>
<td>1. Intended use – human dosing</td>
</tr>
<tr>
<td>2. Limited regulatory requirements</td>
<td>2. Extensive regulatory requirements</td>
</tr>
<tr>
<td>3. Limited registration commitment</td>
<td>3. Extensive registration commitment</td>
</tr>
<tr>
<td>4. Closed system of users</td>
<td>4. Open system of patients</td>
</tr>
<tr>
<td>5. Infrequent manufacturing</td>
<td>5. Routine manufacturing</td>
</tr>
<tr>
<td>6. Overprotective packaging</td>
<td>6. Packaging optimized for cost</td>
</tr>
<tr>
<td>7. Overprotective storage</td>
<td>7. Storage optimized for convenience</td>
</tr>
<tr>
<td>8. Sterility typically unimportant</td>
<td>8. Sterility typically vital</td>
</tr>
<tr>
<td>9. Documentation is critical!</td>
<td>9. Documentation is critical!</td>
</tr>
<tr>
<td>10. <strong>S I S p Q</strong>: Strength and Identity are most critical</td>
<td>10. <strong>S i s P Q</strong>: Safety and Purity are most critical</td>
</tr>
</tbody>
</table>

**S, I, S, p, Q**: Strength, Identity, Safety, Purity, Quality
Reference Standards are an integral part of a pharmaceutical product control strategy

Reference Standards have their own unique control strategy

There are some external regulations and more external guidance associated with pharmaceutical reference standards

Reference Standards are not drugs (have a different intended use) and thus have unique attributes

*Reference Standard Quality Systems must be designed with regulations, guidance, unique attributes, and intended use in mind*
Reference Standard Quality Systems
Lilly RS Quality System

Global Quality Standard – Reference Standards

Local Procedures

- Establishment and Maintenance
- Acquisition and Management of Materials and Components
- Production Records
- Finishing Operations
- Inventory Management
- Storage Facility Requirements
- Processing, Dispensing, Transferring, and Shipping
- Complaints and Withdrawals
- Quality Unit Responsibilities

M. Borer, May 2011, 3rd DIA China Meeting

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Example: Reference Standard Characterization

Reference standard characterization must be customized to support its specific intended use

ICH Q3a, IV

• Reference standards used in the analytical procedures for control of impurities should be evaluated and characterized according to their intended uses.

WHO, Annex 3, Technical Report Number 885,3

• It is necessary to consider all data obtained from testing the material by a wide variety of analytical methods. When taken as a whole, this will ensure that the substance is suitable for its intended use. The extent of the analyses required depends on the purpose(s) for which the chemical reference substance is to be employed, and may involve a number of independent laboratories.

ISO 34, 4.1.1

• It should be recognized that a reference material needs to be characterized mainly to the level of accuracy required for its intended purpose
Example: Inventory Management

Material receipt

Inventory segregation
  • Active, Inactive, Hold

Material moves

Cycle counting

Disaster recovery

Removal from inventory
Global Harmonization
Example: Legal Basis for United States Pharmacopeia

According to the FD&C Act Section 501 and 21CFR299(c), a drug marketed in the United States must comply with compendial standards


A drug or device shall be deemed to be adulterated

(b) If it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium. Such determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium,…

§299.5 Drugs; compendial name.

(c) A statement that a drug defined in an official compendium differs in strength, quality, or purity from the standard of strength, quality, or purity set forth for such drug in an official compendium shall show all the respects in which such drug so differs, and the extent of each such difference.
For each of the following, the firm should have written and approved procedures and documentation resulting therefrom…

- reference standards; source, purity and assay, and **tests to establish equivalency to current official reference** standards as appropriate
Eastman Chemical Company

- Review of procedures for handling Reference Standards showed that Triacetin working standards are **not compared to or qualified against the USP** Triacetin RS. Current and draft SOPs for handling reference standards in general do not clearly indicate what tests or methods of qualification are to be used for each standard material, or specify how the expiry/re-certification date is established; instead it allows any chemist discretion in these matters.
Reference Standard
Harmonization Goals

The same dose of medicine for every patient around the world

No difference in property values of a Reference Standard only due to measurement variability
The Challenge for a Global Manufacturer

How to maintain equivalency with multiple national standards?
Example: Small Molecule API

Student t-test results in a P-value of $3.5 \times 10^{-5}$, rejecting the null hypothesis that the mean values are equivalent.

Comparing ratio of the solution concentration to the peak area on a single HPLC setup

0.84%
Example: Peptide Drug Product

Shifts in control chart correlate with new compendial reference standards.
Ways to Demonstrate Equivalency

Comparative Assay

Establish a Secondary RS using the Compendial RS as a Primary RS per the ICH Q7 definition

![Diagram showing the process of establishing a Secondary RS using the Compendial RS as a Primary RS.]

- **Assigned Value**
- **Standard**
- **Sample**

Official RS

Secondary RS
Ways to Demonstrate Equivalency

Mass Balance

Assign the in-house RS by another means (e.g., mass balance) and show that this assignment is equivalent to comparative assay results versus the compendial standard(s) (e.g., mass balance is within the 95% confidence interval)
Why Establish an In-house RS?

Pre-compendial support
• Compendial RSs are not available during development and early commercialization

Global supply chain
• An in-house RS can be shown equivalent to more than one Official RS

Reliable supply
• It is unacceptable to halt manufacturing waiting for an Official RS to be re-supplied

Control of frequency of batch replacement
• Official RS batches might be replaced frequently which reduces long-term consistency

Usage rate
• Agencies typically cannot supply the volume of RSs required by the pharmaceutical industry

Intended use
• An in-house RS can be shown compatible with intended uses beyond monographs

Site-to-site consistency
• When global manufacturing sites use the same RS, there is more assurance or consistency

Cost
• In-house RSs are less expensive to maintain, especially when there are multiple Official standards
Future Challenges

The difficulties associated with characterization of biomolecule reference standards make harmonization of multiple compendial reference standards a challenge.

No way to fully define the Potency via physiochemical testing, so the Primary RS defines biological activity.

but

The Primary RS has no basis for comparison, so monitoring for change in Potency is hampered.

and

Bioassay methods are typically highly variable, making it difficult to measure small changes.
Conclusions

Reference Standards are an essential part of cGMP pharmaceutical manufacturing

Reference Standards are not drugs and thus have a unique intended use and unique attributes

Reference Standard Quality Systems must be designed with regulations, guidance, unique attributes, and intended use in mind

It is a challenge to maintain multiple regional official standards that are equivalent, especially for biomolecules

Global compendial agencies and manufacturers should work together to maintain equivalency