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Pharmaceutical Reference Standards: Overview and Role in Global Harmonization

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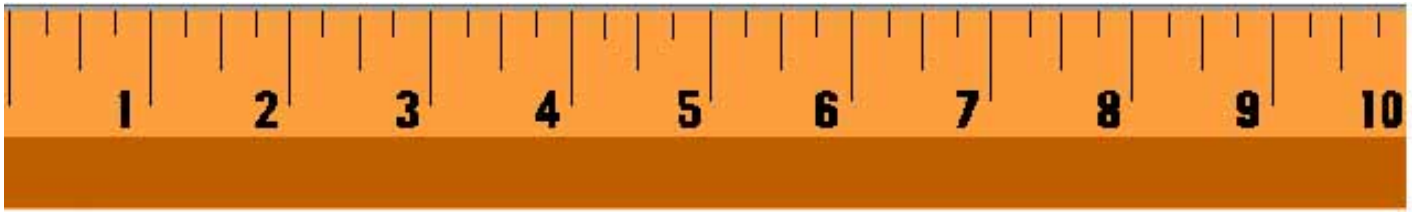
Lilly

Answers That Matter.

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 Information

Certificate

Protocol

Reference Standard Lot Evaluation
Publishable Chromatograms, Thermograms,
Strip Charts, Photos, etc.
REQUIRED

Protocol for the Evaluation of LY686017, Lot RJ9I730004025A

Reference Standard Profile

Effective Date: March 29, 2006
Expiry Date: March 28, 2007
Compound: 123456
Revision: 8

ıme: Compound A
t Number: RS01234

efined Potency: 100% on an "as-is" basis.

andling: Refer to current MSDS for handling and caution information.
orage: Tightly closed amber glass bottle at controlled room temperature, 15 to C.

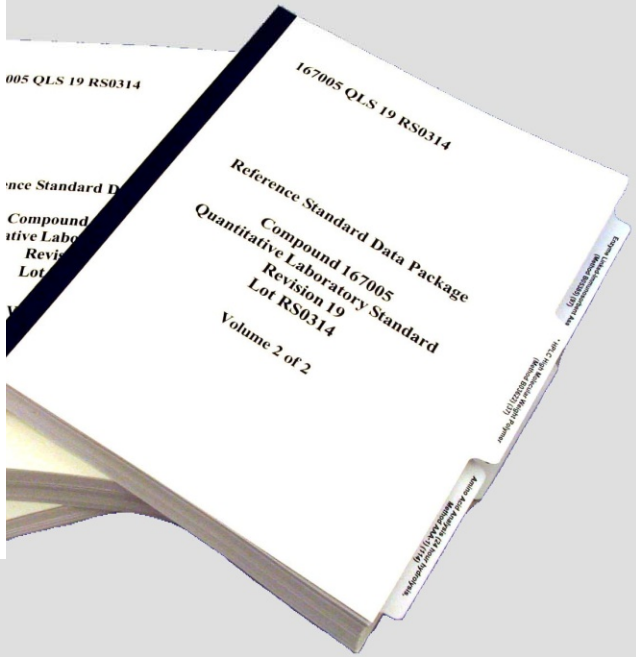
olution: Lot RS01234 was evaluated as a secondary standard in March 2006 vs. SP lot H and PhEur lot 1.

Tests	Results
LC Assay (Method ACB123)	100.1 % vs. USP lot H (n=18)
LC Assay (Method ABC123)	99.9 % vs. PhEur batch 1 (n=18)
LC Related Substances (Method C234)	0.06 % total related substances detected (n=2)
mental Analysis	C: Theory 69.05, Found 69.30%; H: Theory 7.04%, Found 7.15%; N: Theory 4.05%, Found 4.20%; Cl: Theory 15.25%, Found 15.27%
ay Pattern (Method CDE123)	Pattern compares favorably to the previous pattern for this lot; material is crystalline (n=1)
Spectrum (USP)	FT-IR spectrum compares favorably with that of USP lot H, PhEur batch 1, and the previous spectrum for this lot (n=1)
IR Spectrum (USP)	Spectrum is consistent with the structure and compares favorably to that of the previous standard (n=1)

sed March 7, 2006

ished By – John S. Smith
ied By – Leeroy A. Franklin

Data Package



Reference Standard Uses

Quantitative calibration

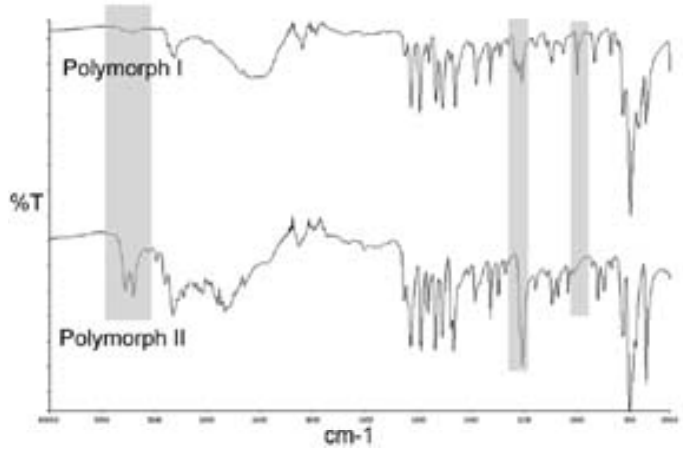
Identity comparison

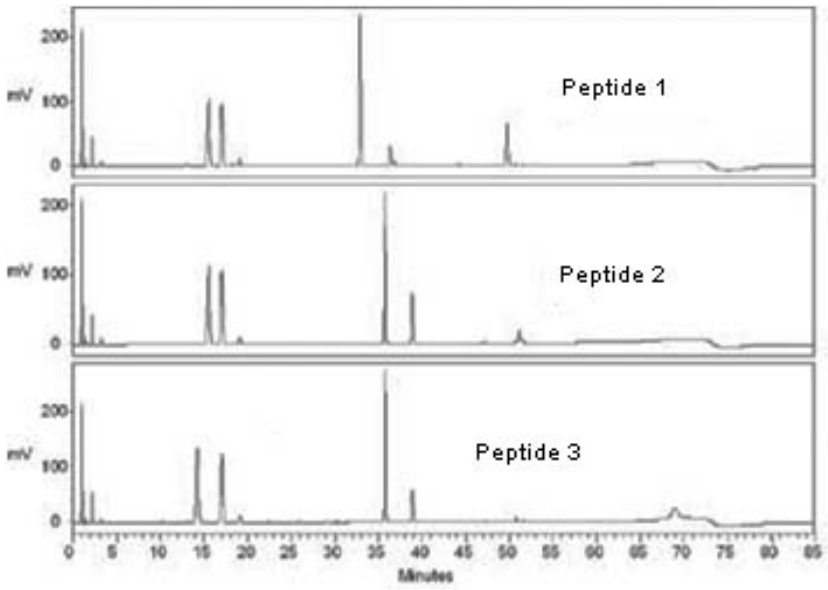
Test of system suitability

Peak marker

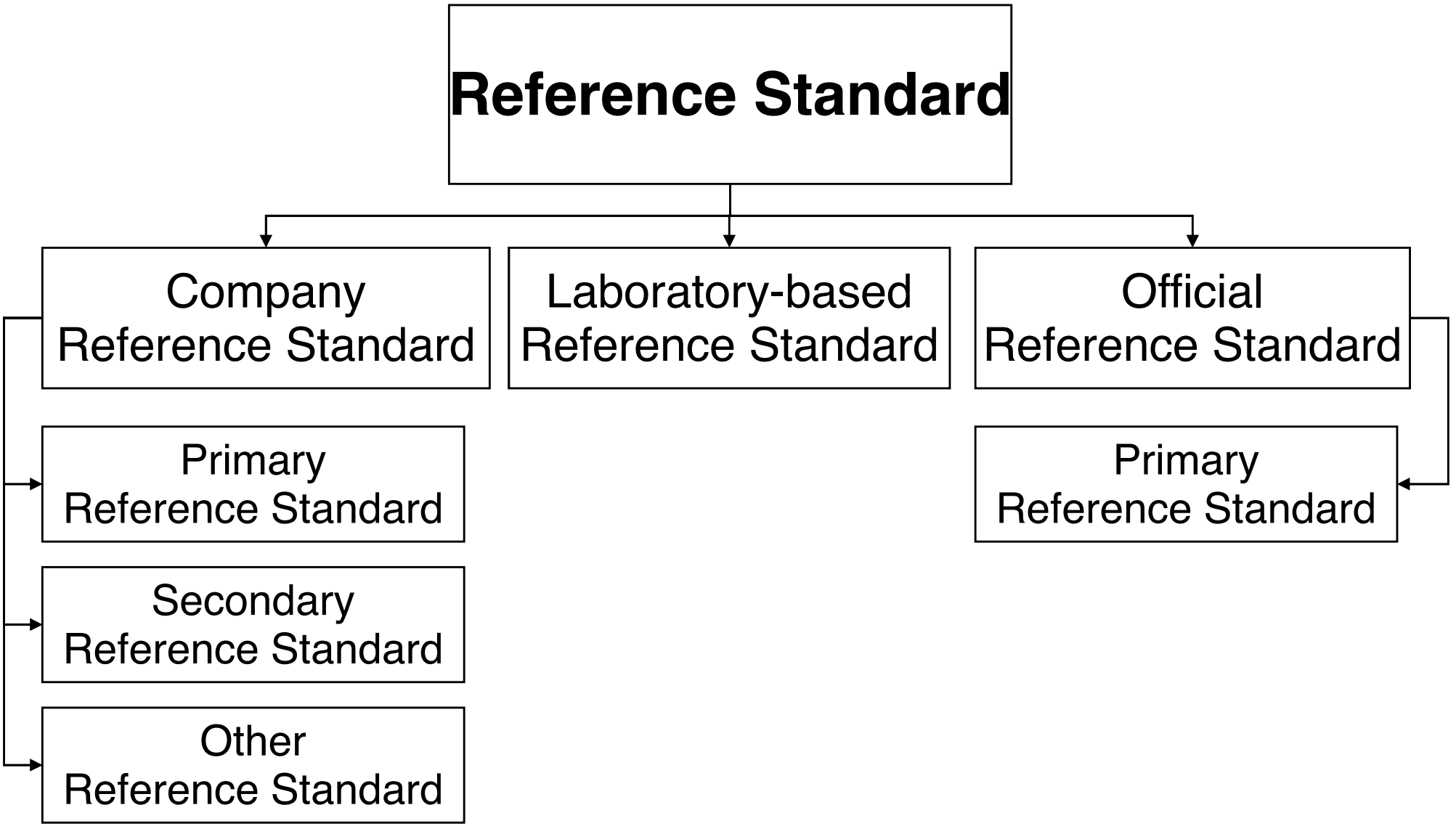
Fingerprinting

Visual comparison





Types of Reference Standards



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…

What to measure…

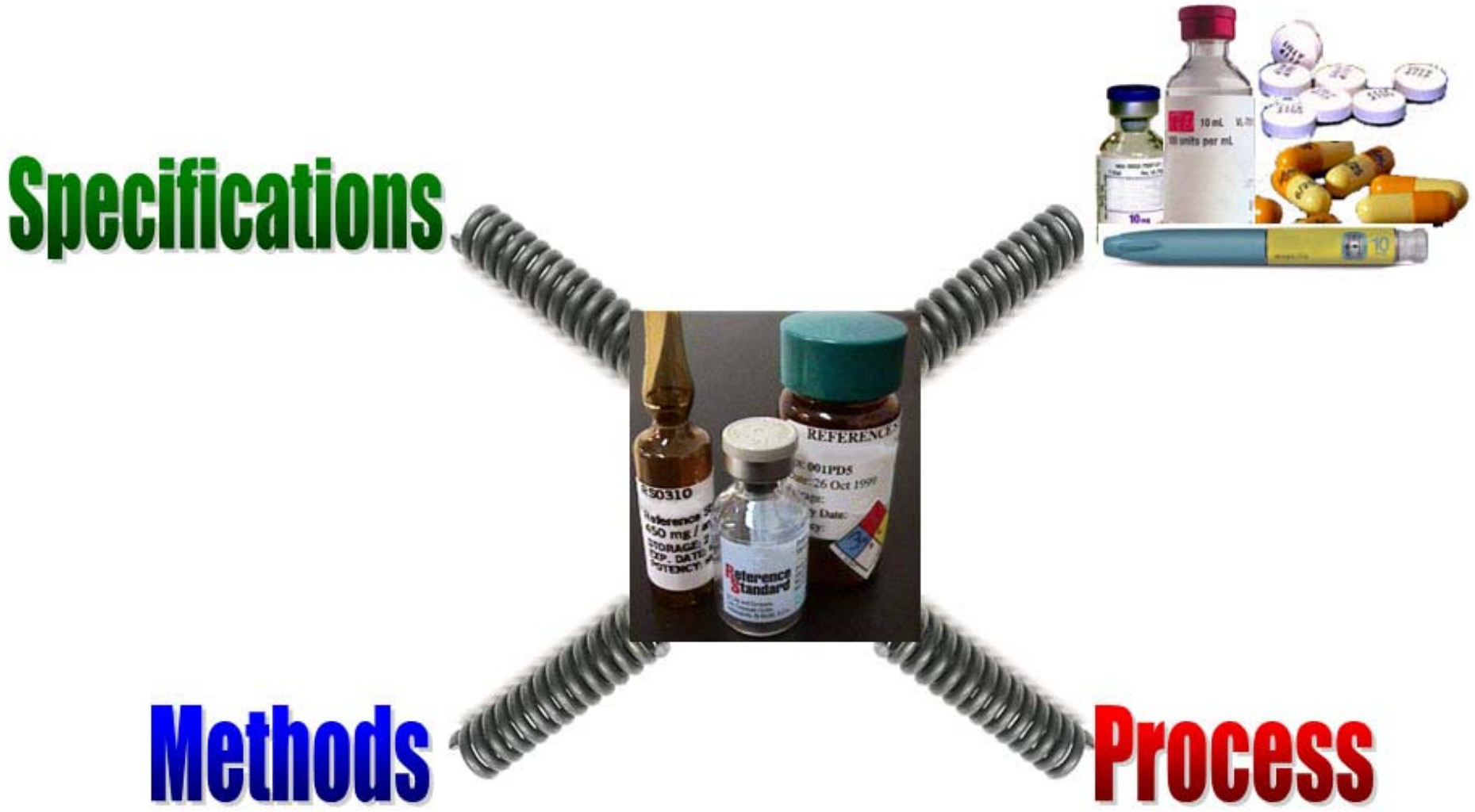
Reference Standards

Basis of the measurement…

Process

When to measure…

Reference Standard Control Strategy



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

Reference Standard

1. Intended use – laboratory control
2. Limited regulatory requirements
3. Limited registration commitment
4. Closed system of users
5. Infrequent manufacturing
6. Overprotective packaging
7. Overprotective storage
8. Sterility typically unimportant
9. Documentation is critical!
10. **s I S p Q** : Strength and Identity are most critical

GMP for Human Consumption

1. Intended use – human dosing
2. Extensive regulatory requirements
3. Extensive registration commitment
4. Open system of patients
5. Routine manufacturing
6. Packaging optimized for cost
7. Storage optimized for convenience
8. Sterility typically vital
9. Documentation is critical!
10. **S i s P Q** : Safety and Purity are most critical

Safety, **I**dentity, **S**trength, **P**urity, **Q**uality

Summary

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**

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

FD&C Act SEC. 501. [21 U.S.C. 351]

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.

Verified in Guidance to Inspectors

Compliance Program Guidance Manual
for FDA Staff: Drug Manufacturing Inspections
Program 7356.002

- PART III – INSPECTIONAL
- C. System Inspection Coverage
- LABORATORY CONTROL SYSTEM

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

Verified by 483 Observations

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

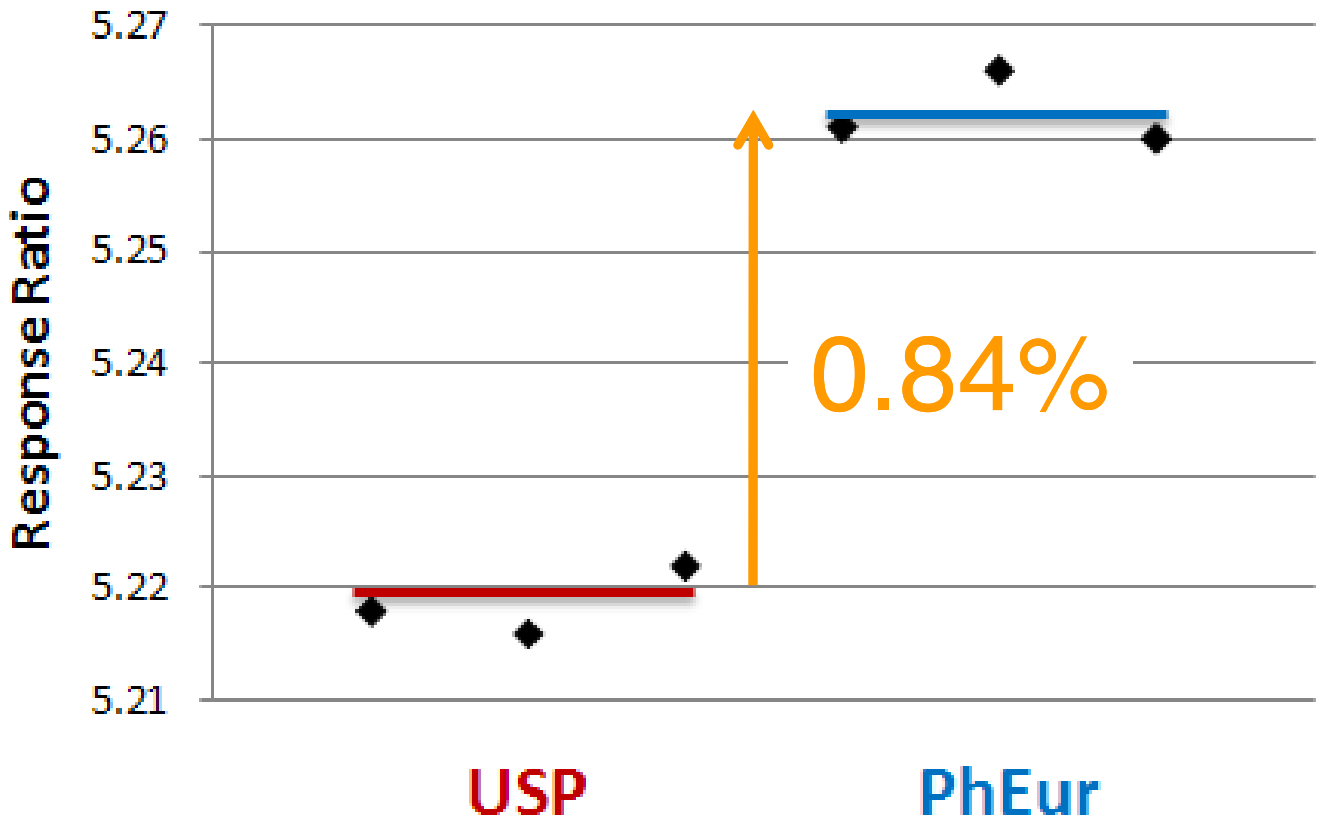
The Challenge for a Global Manufacturer

How to maintain equivalency with multiple national standards?

Example: Small Molecule API

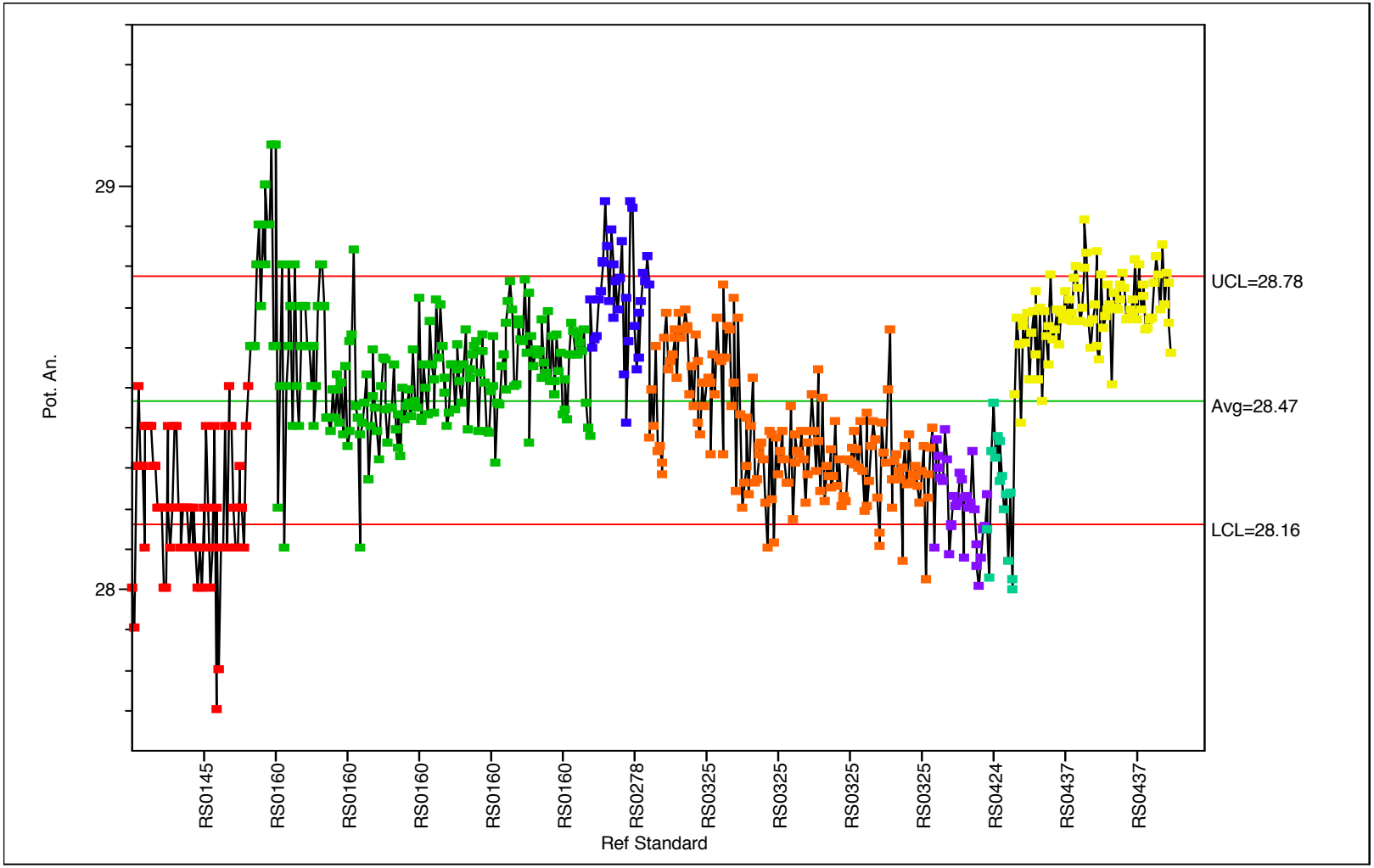
Student t-test results in a P-value of 3.5×10^{-5}, rejecting the null hypothesis that the mean values are equivalent

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



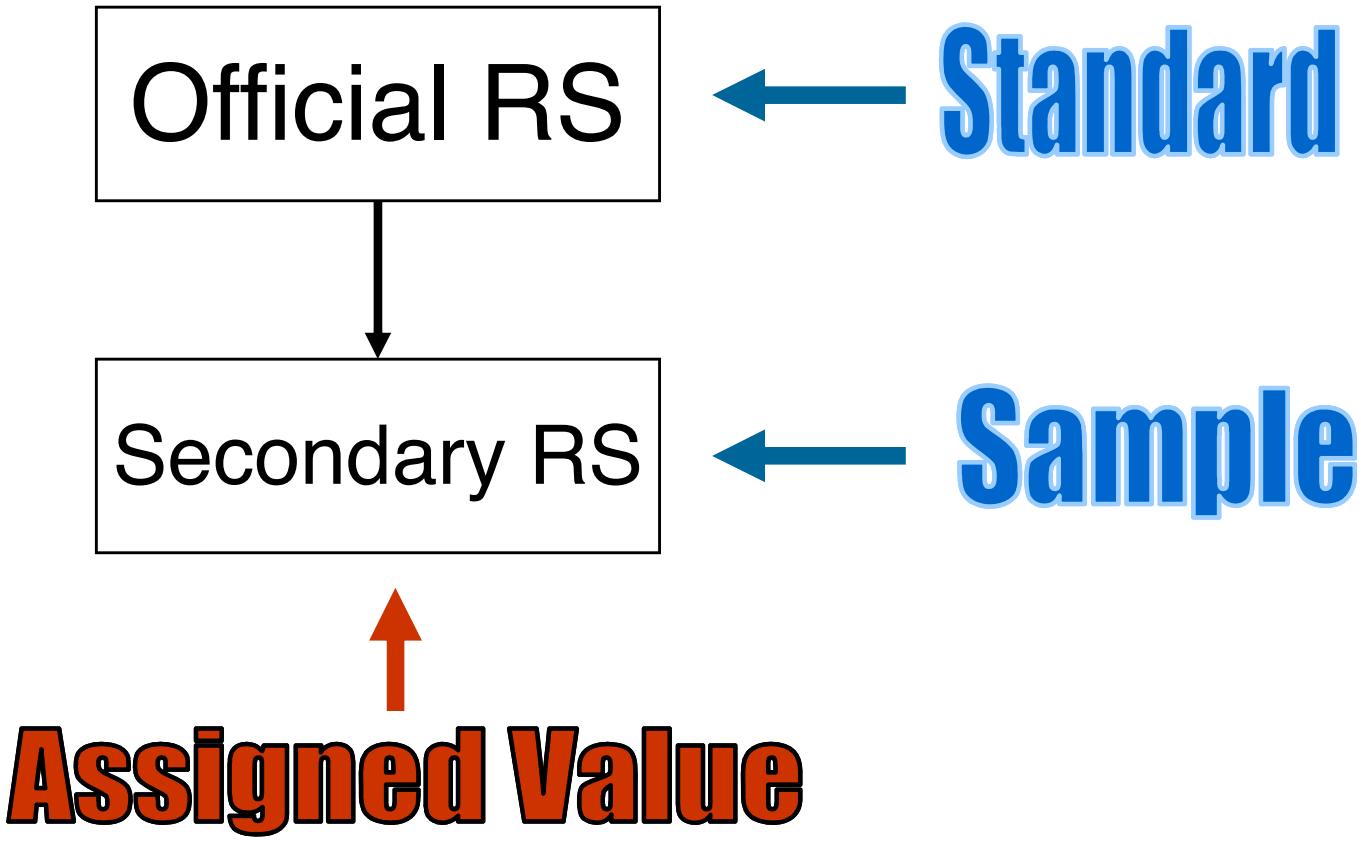
Example: Peptide Drug Product

Shifts in control chart correlate with new compendial reference standards



Ways to Demonstrate Equivalency
Comparative Assay

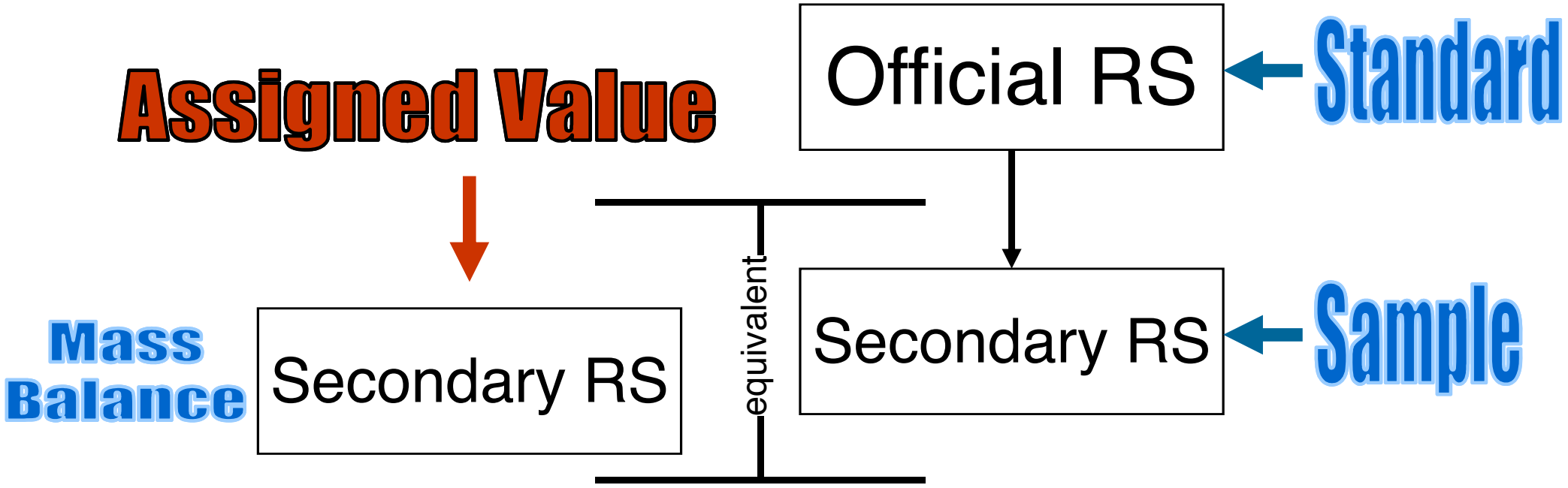
Establish a Secondary RS using the Compendial RS as a Primary RS per the ICH Q7 definition



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