PHARMACEUTICAL REFERENCE STANDARDS

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Session 1 – Presentations (Part 1) Regulatory Aspects
Pharmaceutical Reference Standards
Regulatory Aspects
Assessors view point: Expectations and findings in dossiers

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Overview

• Types and use
• Expectations
• Findings
• Future challenges
• Conclusion
• Backup slides with definitions
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Types of Reference Standards/ Materials

• Chemical origin
• Biotechnological origin e.g.
  – Special case: Biosimilarity
  – Cell Therapy-Gene Therapy
• Herbals
• Radiopharmaceuticals

• Calibration of equipment (GMP)
Reference Standards/Materials: General Considerations

- Use for
  - Assay,
  - Identification,
  - Purity tests.
  - Analytical validation [e.g. accuracy, system suitability (e.g. chromatographic systems)].
- Quality: appropriate to its use.
- Characterised and evaluated for its intended purpose by additional procedures other than those used in routine testing.

Reference Standards/Materials

- References:
  - Different guidelines (ICH/CHMP)
  - Pharmacopoeias
  - WHO
- Primary Reference Standard
- Working Standard calibrated against the primary reference standard
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Establishment of a chemical Reference Standard (assay active substance)

• Primary reference standard.
  – Selected batch with batch number
  – Full characterization
• Working standard can be assigned against the primary reference standard
Primary Reference Standard (example)

- JLR (C_aH_bN_cO_dHClH_2O)
  batch: 27349
- Appearance: white powder
- Melting point: 160.8°C
- Elucidation of structure
  - IR – spectrum
  - _1^H – NMR spectrum
  - _13^C – NMR spectrum
  - Mass spectrum
  - UV spectrum

Primary Reference Standard (example)

- Purity
  - Rel. impurities: imp. A: not detected (< LOQ)
    (HPLC / % w/w) total: 0.1
  - Rel. impurities: imp. B: not detected (< LOQ)
    (CE w/w) imp. C: not detected (< LOQ)
    total: not detected (< LOQ)
  - Sulphated ash: 0.05 (%w/w)
  - Solvent content: 0.03 (HS) (% w/w)
  - DSC: 99.85%
Primary Reference Standard (example)

- **Assay**
  - Water content (KF): 5.47 % (w/w) (n=6, rsd=0.29) (theor. = 5.49)
  - Chloride content: 5.65 % (w/w) (n=6, rsd=0.18) (theor. = 5.60)
  - Non aqu.titration: 100.1 % (w/w) (n=6, rsd=0.39)

Primary Reference Standard (example)

- **Assignment of Potency:**
  - Water content: value close to theor.
  - Chloride content: value close to theor.
  - Assay (n.a.titr.): 100.1 % (w/w)
  - Rel. impurities: 0.1 % (w/w)
  - Sulphated ash: 0.05 % (w/w)
  - Solvent content: 0.03 % (w/w)
  - Result: 100-(0.1+ 0.05 + 0.03) = 99.8%
    Confirmation by DSC: 99.85%
- **Assigned potency:**
  JLR (CaHbNcOd.HCl.H2O) = 99.8 w/w (batch 27349)
Establishment of a Chemical Reference Standard (impurities)

- For identification purposes (routine)
  - In-situ generation of impurities acceptable
- For quantification purposes
- Correction factor needed when impurity determined versus test substance.

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- **Findings**
  - Future challenges
  - Conclusion
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Reference standards for chemicals

• Normally there is no big concern regarding the characterization of chemical reference standards in application files.

Reference standards for biologics

• Mainly used for potency assays.
• BRP or WHO standards often used as primary standard when available
• Recalibration or correction may be necessary when change of reference standard lot (e.g. EPO)
Example of Monoclonal antibody

• No harmonized method or standard currently available for Mab functional assays (e.g. ADCC, CDC…)
• In-house assays developed across companies
• Difficulty to set harmonized requirements

Example of Biosimilars

• Several institutions working on biological reference standards
• Biosimilar principle: reduction of non-clinical and clinical data package, with possibility of extrapolation of indications, if demonstrated to be highly similar to a reference medicinal product
• Could Reference standard replace Reference Medicinal Product?
  – NO
  – But could facilitate review of some attributes if harmonised (e.g. potency)
  – Standards for system suitability? Feasible?
Example of IVIg / SCIg

- Increase in Thrombo-Embolic Events for some Immunoglobulin medicinal product
- FXIa: risk factor +++
- Revision IVIg and SCIg monographs to evaluate removal capacity of thrombosis generating agents
- Difficulty to select a sensitive and robust assay (e.g. thrombin generation assay)
- No standardized method or reference product…

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NIRS and Standardization/Calibration Draft EU guideline

- NIRS procedures have a wide range of complexity.
- NIRS can be simple ie used without calibration models:
  - Direct comparison of representative spectra of the substance being examined and a reference substance for qualitative chemical or physical identification purposes.
  - Conformity checks (also called trend analysis) for monitoring of unit operations such as blending or drying etc.

NIRS and Standardization/Calibration Draft EU guideline

- NIRS can also generate complex data, which can only be interpreted by the use of multivariate data analysis and calibration models.
- These models are developed using carefully selected and representative samples, which have in turn been qualified by a reference analytical method, using analytical reference standards.
- In this case, NIRS is developed along with reference analytical method such as HPLC, GC, UV or any other compendial methods
- Typical applications are assay, content uniformity and identity tests (modelling approach).
- Maintenance of calibration models is crucial for NIRS procedures lifecycle
The iterative nature of NIRS/draft CHMP guideline

Future challenges for biologicals

- Harmonize methods and standards for potency and functional assays
- Establish useful standards for biosimilars?
- Development of standards for Advance Therapy Medicinal Products?
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Conclusion

• Reference substances or materials are an important part in an application file.
• However no major issue (chemicals): very seldom a concern in an application file.
• It is understood that whenever available, international standards are used.
  – European Pharmacopoeia
  – WHO
• Home standards must be fully characterised
• PAT applications: further discussion needed
Thanks to Lina Ertlé (ANSM)

Thanks for your attention

Backup slides
Common Technical Document - Quality

• 3.2.S.5 Reference Standards or Materials (name, manufacturer)
  Information on the reference standards or reference materials used for testing of the drug substance should be provided.

• 3.2.P.6 Reference Standards or Materials (name, dosage form)
  Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in “3.2.S.5 Reference Standards or Materials”. Reference ICH Guidelines: Q6A and Q6B

Q6A: Specification

• 2.11 Reference standard
  A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. It should have a quality appropriate to its use. It is often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing. For new drug substance reference standards intended for use in assays, the impurities should be adequately identified and/or controlled, and purity should be measured by a quantitative procedure.
Definition

In-house Primary Reference Material:
An appropriately characterised material prepared by the manufacturer from a representative lot(s) for the purpose of biological assay and physicochemical testing of subsequent lots, and against which in-house working reference material is calibrated.

In-house Working Reference Material:
A material prepared similarly to the primary reference material that is established solely to assess and control subsequent lots for the individual attribute in question. It is always calibrated against the in-house primary reference material.

Q3A/Q3B: Impurities

- Analytical Procedures (Extract)
Organic impurity levels can be measured by a variety of techniques, including those that compare an analytical response for an impurity to that of an appropriate reference standard or to the response of the new drug substance itself. In cases where the response factors of the drug substance and the relevant impurity are not close, this practice can still be appropriate, provided a correction factor is applied or the impurities are, in fact, being overestimated.
Q6B: Specification

• 2.2.1 Reference standards and reference materials
  – Where an international or national standard is available and appropriate, reference materials should be calibrated against it.
  – For new molecular entities, it is unlikely that an international or national standard will be available.
  – 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.

Q6B: Specification

• 2.2.1 Reference standards and reference materials
  – 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.
International Symposium on Pharmaceutical Reference Standards

Session 1
Inspectors Viewpoints - Expectations and Findings in GMP Inspections

3-4 September 2012, Strasbourg, France
Dr Thomas Hecker
Inspector, EDQM

Regulatory background:
EU GMP Part I Chapter 6*)

6.19 Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They should be prepared in accordance with written procedures.

*) Currently under revision
Regulatory background: EU GMP Part II Chapter 11

11.17 Primary reference standards should be obtained as appropriate for the manufacture of 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 recognised source are normally used without testing if stored under conditions consistent with the supplier’s recommendations.

11.18 Where a primary reference standard is not available from an officially recognized source, an “in-house primary standard” should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

Reference Standard, Primary

A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognised source, or (2) prepared by independent synthesis, or (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.

Reference Standard, Secondary

A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.
Regulatory background: European Pharmacopoeia

EUROPEAN PHARMACOPOEIA 7.0

01/2006.51200

5.12. REFERENCE STANDARDS
This chapter is published for information.

1. INTRODUCTION
‘Reference standard’ is used in this chapter as a general term covering reference substances, reference preparations and reference spectra.

2. TERMINOLOGY
Primary standard. A standard shown to have suitable properties for the intended use, the demonstration of suitability being made without comparison to an existing standard.
Secondary standard. A standard established by comparison with a primary standard.

Inspection of QC Facilities
What is Question 1 related to reference standards?
What is consequently Question 2 related to reference standards?
After a feeling of relief if the answers are positive, what is Question 3 of the inspection team?

What are the storage conditions?
Finally, what is the $64k Question?
11.19 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.

D22. [Major] There was no clear comprehension regarding the GMP requirements related to establishment and usage of reference standards evidenced by the following observations:

a. Secondary standards have not been qualified against primary standards from official sources, i.e. the SST specificity standard was provided by the company’s customer - [Redacted] Pharmaceuticals.

b. The current method to determine related substances was not consistent with the analytical method validation, as for the latter one the impurity mixture was prepared by the company and the current practice is to use a mixture supplied by [Redacted].

c. There was no traceability that the single impurity E (R009978) secondary reference standard was appropriately re-qualified by the supplier [Redacted].

[EU G MP Part II, Nos. 11.17, 11.19]

D18. [The qualification of the working standard AND [Redacted] 2012 was not performed against the primary/official standard for racemic [Redacted].]

[EU GMP Part II, 11.18, 11.19]

Company’s response: The qualification of working standard AND [Redacted] was performed against the primary standard for racemic [Redacted] on March 24, 2012. In addition, the Quality Control staff was retained in the SOP-CC-1-016 “Standards and Reference substances” from March 17 to 20, 2012 to prevent recurrence. A review of all working standards qualifications has been performed and no other such instances were identified.
Miscellaneous Issues

- Qualification of Non-Ph. Eur. primary reference standards
- Specific transport conditions such as dry-ice shipment (e.g. Hepatitis C Virus RNA)
- Hazardous substances such as CRS that could cause an explosion (e.g. Isosorbide dinitrate)
- Availability problems of impurities

Everything should be made as simple as possible, but not simpler.
(Albert Einstein)
Pharmaceutical Reference Standards at FDA

Review and CGMP

Jon Clark  FDA\CDER\OPS
Associate Director for Program Policy

Organization Detail

CDER Director
(Janet Woodcock)

CDER Office of Compliance
(Enforcement/GMP)
Generic Drugs
OGD

CDER Office of Pharmaceutical Science
(CMC Review)
New Drugs
ONDQA
Biotech
OBP
Research
OTR
(St. Louis + WO)

Research

04/09/2012
Translations

• “Dossiers” = “Applications”
• “Assessors” = “Reviewers”
• CGMP Inspection = CGMP Inspection
  – USA
    • Investigators conduct Inspections

Synonyms

• Reference Standards
• Reference Materials
• Laboratory Standards
• Analytical Standards
• Standard Reference Materials
Application Review (Assessment)

• User determines suitability for use
  – Includes specificity
    • Identification testing
    • Potency (assay) testing
  – API
    • Orthogonal testing to confirm chemical structure
    • Impurity profile
    • Qualification protocols
    • Storage requirements

CGMP

• Conditions of storage
• “In-date” usage or established “Use by”
  – Documented within procedures
• Confirmation of stock solution stability
• Records of standard solution preparation
• Watch for evidence of records copying
• Reference standards errors should include an investigation
Traceability

- Establish traceability of measurement results
  - An unbroken chain of calibrations to specified references
  - Establish measurement uncertainty
  - Secondary (working) standards are allowed
    - Need to trace to primary
    - Should measure added variability
  - Replacement of primary standard
    - Need to establish suitability for use
    - Should prevent drift of standard

Domestic Sources

- Manufacturer self source
  - Structure elucidation
  - Manufacturing summary
  - FDA may request sample
- USP
  - Certificate of Analysis
- NIST (National Institute of Standards and Technology)
  - Certificate of Analysis
  - Standard Reference Materials
  - NIST Policy on Metrological Traceability
    - [http://www.nist.gov/traceability/nist_traceability_policy_external.cfm](http://www.nist.gov/traceability/nist_traceability_policy_external.cfm)
Other Sources

- European Pharmacopoeia
- Japanese Pharmacopoeia
- World Health Organization
- Third Party Suppliers
- User needs to establish suitability

FDA Documents

- Guide to Inspection of Pharmaceutical Quality Control Laboratories
  - [www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074918.htm](http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074918.htm)
  - Q & A on CGMP #4
    - [www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm)
- Guidance for Industry – Analytical Procedures and Methods Validation
Harmonized Guidelines

- International Conference on Harmonization (ICH)
  - Q6A
    - Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
  - Q6B
    - Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biological Products
  - Q7
    - Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Q6A: Specifications

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Q7: API cGMP (1 of 2)

- Reagents and standard solutions should be prepared and labeled following written procedures. Use by dates should be applied, as appropriate, for analytical reagents or standard solutions.
- Primary reference standards should be obtained, as appropriate, for the manufacture of 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.

Q7: API cGMP (2 of 2)

- Where a primary reference standard is not available from an officially recognized source, an inhouse primary standard should be established. Appropriate testing should be performed to establish fully 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.
Dissolution Calibration

• Mechanical Calibration of Dissolution Apparatus
  – Allows for use of enhanced mechanical calibration to meet CGMP requirement
  – In lieu of:
    • Reference Standard Tablets
    • Performance Verification Tablets

Emerging Needs

• Automated manufacturing methods
  – Calibration for Process Analytical Technology sensors
  – Matrix of materials
  – Matrix changed from batch to batch
    • Intentional change
    • Unintentional change
• Real Time Release Testing (RTR)
• Advanced analytics
  – LCMS
  – NMR
  – Chemical Imaging
Summary

- Reference Standard recommendations for FDA are spread through different documents
- Recommendations seem consistent within FDA and among harmonized documents
- Emerging needs may require new thinking