February 15, 2007

Global Validation Requirements

The Principles of ICH, FDA, USP, Ph. Eur., JP

Presented to: PDA New England Chapter

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Topics

- Sources
- Contents by Method Type
  - Biological
  - Chemical
  - Biotechnological
  - Physical
- Validation/Verification Concepts
- References

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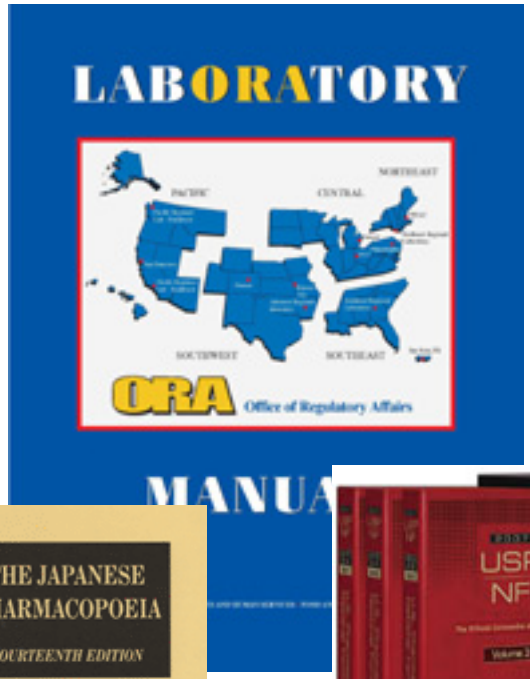
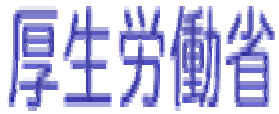
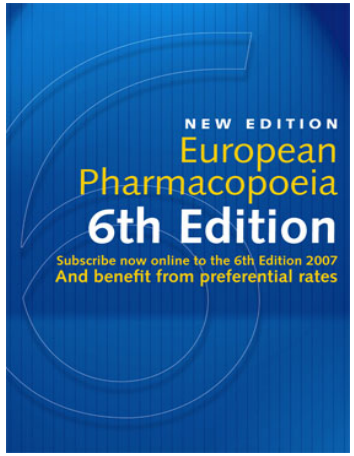
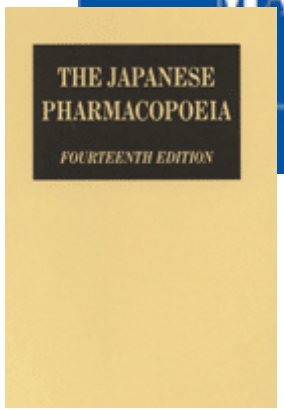
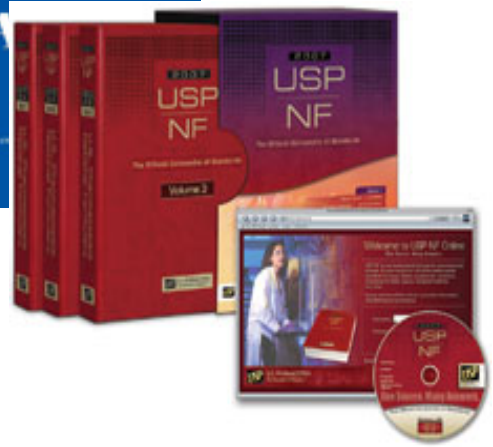
Sources of Information











Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

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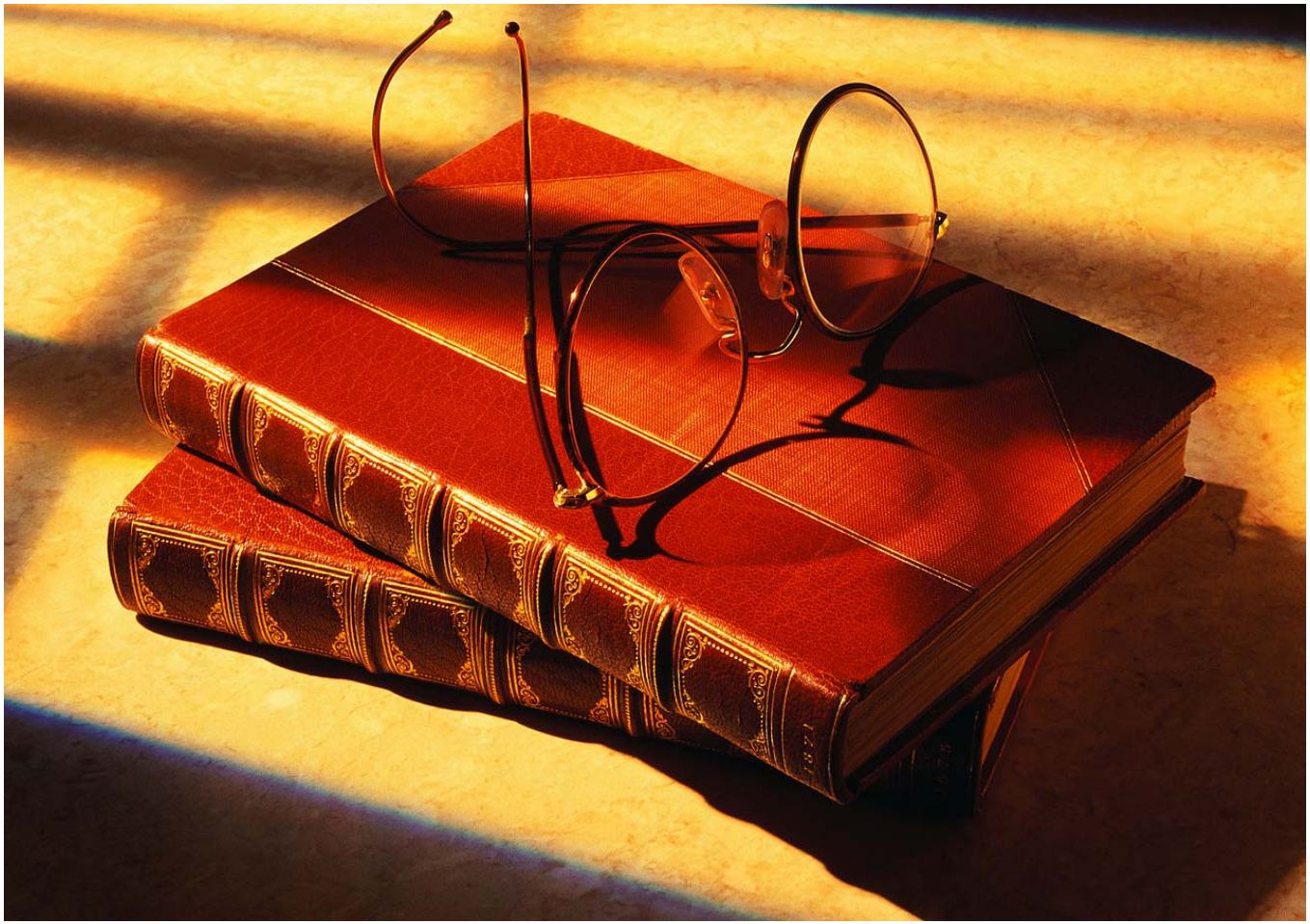
Contents of the Documents



Biological Methods

Test	ICH	USP	Ph. Eur.	JP	FDA
Antimicrobial Effectiveness	Q6	yes	yes	yes	yes
Sterility	Q6	yes	yes	yes	yes
Microbial Limits	Q6	yes	yes	yes	yes
Bacterial Endotoxin	Q6	yes	yes	yes	yes
Pyrogen	no	yes	yes	yes	no
Rapid Micro Methods	no	yes	yes	no	PAT

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USP and Ph. Eur. Harmonized Cultures

Aerobic bacteria	
Staphylococcus aureus	ATCC 6538, CIP 4.83, NCTC 10788, NCIMB 9518
Bacillus subtilis	ATCC 6633, CIP 52.62, NCIMB 8054
Pseudomonas aeruginosa	ATCC 9027, NCIMB 8626, CIP 82.118
Anaerobic bacterium	
Clostridium sporogenes	ATCC 19404, CIP 79.3, NCTC 532 *or* ATCC 11437
Fungi	
Candida albicans	ATCC 10231, IP 48.72, NCPF 3179
Aspergillus niger	ATCC 16404, IP 1431.83, IMI 149007

Alternative to *Staphylococcus aureus* is *Bacillus subtilis* (ATCC 6633)

Alternative to *Pseudomonas aeruginosa* is *Micrococcus luteus* (*Kocuria rhizophila*), ATCC 9341

Alternative to *Clostridium sporogenes*, when a nonspore-forming microorganism is desired, is *Bacetroides vulgatus* (ATCC 8482)

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Home Pages of Culture Collections in the World

- http://wdcm.nig.ac.jp/hpcc.html
- 521 culture collections in 66 countries
  - IP: Institut Pasteur
  - ATCC: American Type Culture Collection
  - NCIMB: National Collections of Industrial Food and Marine Bacteria
  - CIP: Collection de L'Institut Pasteur
  - NCT: National Collection of Type Cultures
  - NCPF: National Collection of Pathogenic Fungi
  - IMI: CABI Bioscience Genetic Resource Collection
  - JCM: Japan Collection of Microorganisms

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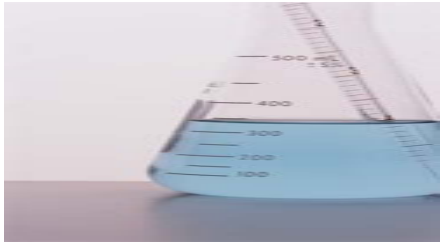
Analytical (Chemical) Methods



Parameter	ICH	USP	Ph. Eur.	JP	FDA*
Specificity	yes	yes	no	yes	yes
Accuracy	yes	yes	no	yes[1]	yes
Precision: Repeatability	yes	yes	no	yes[3]	yes
Precision: Intermediate precision	yes	yes[2]	no	yes	yes
Precision: Reproducibility	yes	yes	no	yes	yes
Detection Limit	yes	yes	no	yes	yes
Quantitation Limit	yes	yes	no	yes	yes
Linearity	yes	yes	no	yes	yes
Range	yes	yes	no	yes	yes
Robustness	yes	yes	no	yes	yes

[1]Also called Trueness [2]Also called Robustness [3]Also called Intra-assay precision
*Recognizes ICH

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Table 1: Validation Parameters by Type of Method

Type of Method Validation Parameter	ID	Impurities: Quantitation	Impurities: Limit	Cleaning	Assay	Specific Tests
Accuracy	-	+	- [3]	+	+	+ [9]
Precision Repeatability Intermediate Precision	- -	+ + [1]	- -	+ - [3]	+ + [1]	+ [9] + [9]
Specificity [2]	+	+	+	+[6]	+[8]	+ [9]
Detection Limit [4]	-	- [3]	+	+ [7]	-	-
Quantitation Limit [5]	-	+	-	+ [7]	-	-
Linearity [10]	-	+	-	+	+ [11]	-
Range	-	+	- [3]	+	+	-
Robustness	-	+	-	- [3]	+ [12]	+ [9]
Surface Recovery	-	-	-	+	-	-
Stability Indicating	-	+	-	-	+ [12]	-
Solution Reagent Stability [13]	-	+	+	+	+	+ [9]
Reference Standard / Control Evaluation	+ [9]	+ [9]	+ [9]	+ [9]	+ [9]	+ [9]

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Table 1: Footnotes

- 1. In cases where reproducibility has been performed, intermediate precision is not needed.
  - Assumes better estimate of precision interlab
- 3. May be needed in some cases
  - As determined by development scientist and VRB
  - e.g., detection limit per certain regulatory requests
- 6. At a minimum, assay response must be characteristic of the analyte of interest and must be sufficient to distinguish the analyte from the matrix.
  - Must run appropriate controls during validation
  - Controls may be required during method use

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Table 1: Footnotes for titration assays

- 8. Lack of specificity for an assay for release may be compensated for by impurities testing.
- 11. Linearity is not required for titration assays where the process represents a mole for mole chemical reaction.
- 12. Robustness and stability indication not required for titration assays.

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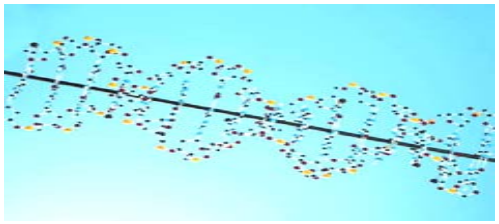
Biotechnological Methods



Parameter	ICH	USP	Ph. Eur.	JP	FDA
Viral Clearance	Q5A(R1)	Yes	Yes	Yes	See ICH
DNA Analysis	Q5B	Yes	Yes	No	See ICH
Stability	Q5C	Yes	Yes	No	See ICH
Cell Substrate Characterization	Q5D	Yes	Yes	No	See ICH
Methods for Batch Release	Q2(R1), Q5C, Q6B	Yes	Yes	No	See ICH

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Physical Methods

- Sample independent/Technique dependent
- Relies on calibration of instrumentation
- Relies on analyst training
- Examples:
  - Melting Point
  - Loss on Drying
  - Residue on Ignition
  - Particulate Matter

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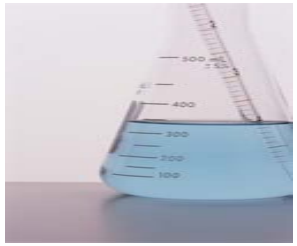
Method Type / Reference	Biological	Chemical	Physical	Biotech
				
ICH	Yes	Yes	No	Yes
USP	Yes	Yes	No	Yes
Ph. Eur.	Yes	No	No	Yes
JP	Yes	Yes	No	Limited
FDA	Yes	Yes	No	Yes

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Pharmacopoeial Method Validation/Verification Concepts

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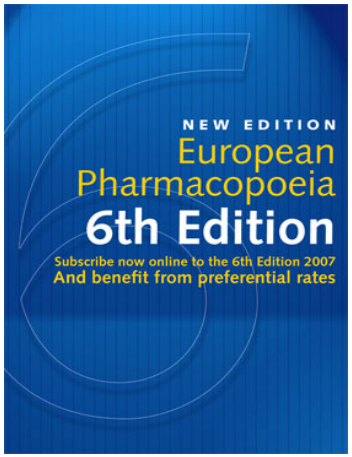
Question: Are Compendial Methods Validated?

Answer: Yes

Response: Prove it.

From the Ph. Eur.

- The procedures for the tests and assays published in the individual monographs have been validated according to current practice at the time of their elaboration for the purpose for which they are intended.



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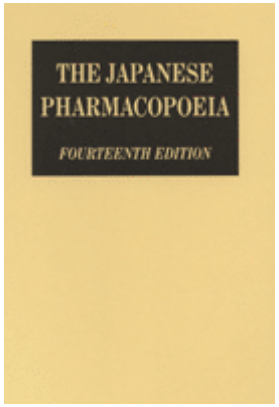
From the JP

- When an analytical procedure is to be newly carried in the Japanese Pharmacopoeia, when a test carried in the Japanese Pharmacopoeia is to be revised, and when the test carried in the Japanese Pharmacopoeia is to be replaced with a new test according to regulations in General Notices, analytical procedures employed for these tests should be validated according to this document.



From the USP

- Recognizing the legal status of *USP* and *NF* standards, it is essential, therefore, that proposals for adoption of new or revised compendial analytical procedures be supported by sufficient laboratory data to document their validity.

From the USP (continued)

- The text of this information chapter harmonizes, to the extent possible, with the Tripartite International Conference on Harmonization (ICH) documents *Validation of Analytical Procedures* and the *Methodology* extension text, which are concerned with analytical procedures included as part of registration applications submitted within the EC, Japan, and the USA.

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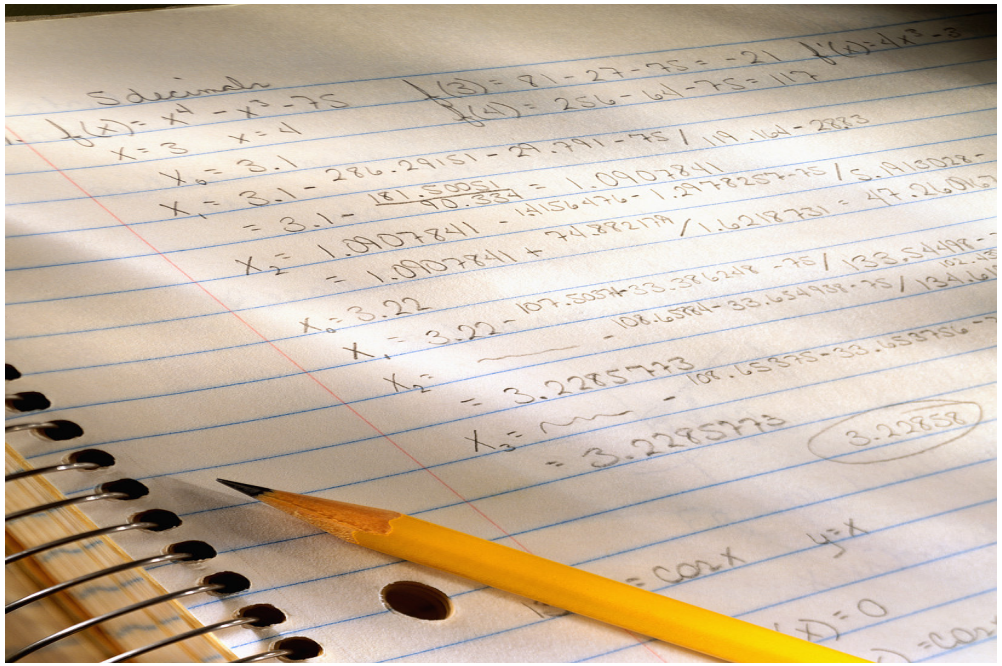
From the FDA

Federal Food, Drug and Cosmetic Act - Section 501.[351](b)

- Synopsis: Assays and specifications in monographs of the United States Pharmacopeia and the National Formulary constitute legal standards.

CFR 211.194(a)

- a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays…..



CFR 211.194(a)(2) - Laboratory Records

- If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists, Book of Methods,\1\ or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice.

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From ICH Q6

Pharmacopoeial Tests and Acceptance Criteria

- References to certain procedures are found in pharmacopoeias in each region. Wherever they are appropriate, pharmacopoeial procedures should be utilized.
- Where harmonization has been achieved, an appropriate reference to the harmonized procedure and acceptance criteria is considered acceptable for a specification in all three regions. For example, after harmonization sterility data generated using the JP procedure, as well as the JP procedure itself and its acceptance criteria, are considered acceptable for registration in all three regions.

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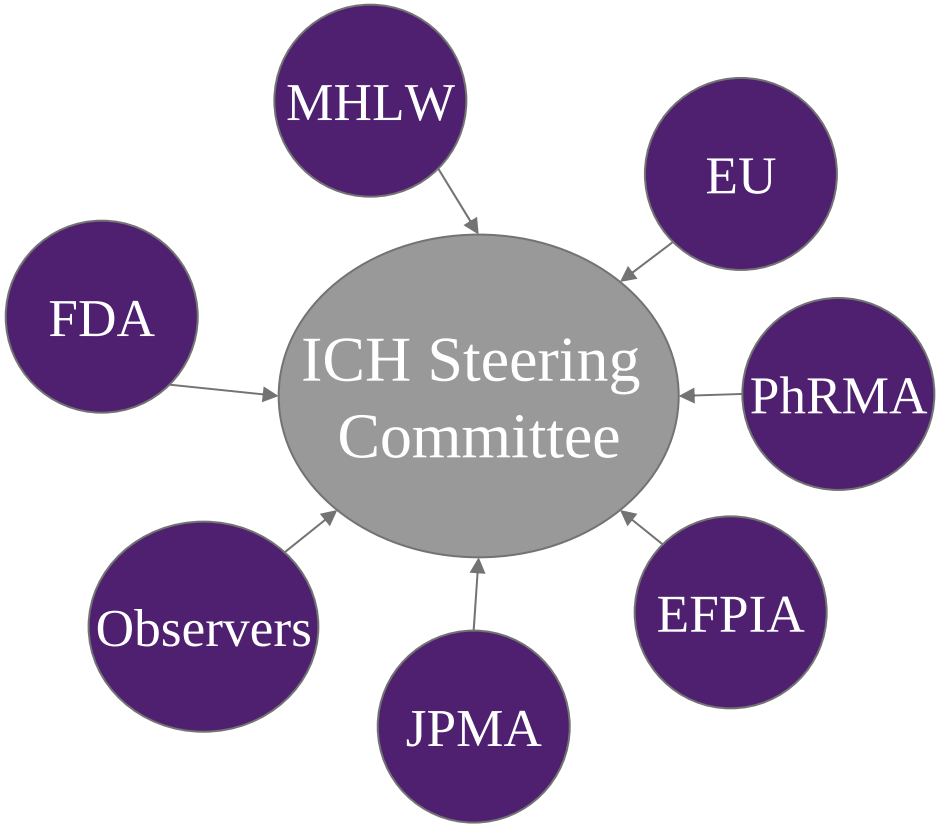
ICH Structure



Verification Concept
CFR 211.194(a)(2) - Laboratory Records

- The suitability of all testing methods used shall be verified under actual conditions of use.
- Currently unaddressed
- USP Proposed General Chapter <1226>

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The References

- ICH
  - www.ICH.org
  - Q2(R1): Validation of Analytical Procedures
  - Q3A(R2): Impurities in New Drug Substances
  - Q3B(R2): Impurities in New Drug Products
  - Q3C(R3): Impurities: Guideline for Residual Solvents
  - Q4, Q4A, Q4B: Pharmacopoeias
  - Q5A(R1), Q5B, Q5C, Q5D, Q5E: Quality of Biotechnological Products
  - Q6A, Q6B: Specifications

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The References (continued)

- FDA
  - www.fda.gov
  - CBER Guidance Documents
  - CDER Guidance Documents
  - ICH References
  - Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products and Medical – 12/1987

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The References (continued)

- USP
  - www.usp.org
  - USP 30-NF 25 (2007)
  - <1223>, Validation of Alternative Microbiological Methods
  - <1225>, Validation of Compendial Procedures
  - <1227>, Validation of Microbial Recovery from Pharmacopeial Articles
  - <1226>, Verification of Compendial Procedures
- Biotechnological Series
  - <1043>, <1045> to <1050> and <1052> to <1057>
  - <111> Design and Analysis of Biological Assays

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The References (continued)

- JP 14th Edition
  - http://jpdb.nihs.go.jp/jp14e/
  - Microbial Attributes of Nonsterile Pharmaceutical Products
  - Mycoplasma Testing for Cell Substrates used for the Production of Biotechnological/Biological Products
  - Validation of Analytical Procedures

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The References (continued)

- Ph. Eur.
  - http://online.pheur.org/entry.htm
  - 5.1.7.Viral Safety
  - 5.1.6.Alternative methods for control of microbiological quality
  - 5.1.4. Microbiological Quality of Pharmaceutical Preparations

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The References (continued)

- Other References
  - TGA: Starting Material Analytical Procedure Validation
  - MHRA: http://www.mhra.gov.uk
  - EMEA: http://www.emea.eu.int

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Thank You

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