



U.S. PHARMACOPEIA
The Standard of Quality[®]

Spirit of Voluntarism

IPAC-RS 2006 Conference Inhalation & Nasal Drugs: the Regulatory Landscape

November 6-8, 2006

Role of Pharmacopeial Monographs and Other Finished Product Testing under the Quality by Design Paradigm



Roger L. Williams, M.D.
Chair, Council of Experts



Topics

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- u The Old
- u The New
- u The New at USP: General
- u The New at USP: Aerosols





CMC Guidances: May 18, 2006

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u Withdrawn

- 4 Drug Substance (Draft 2004)
- 4 Drug Product (Draft 2003)
- 4 Stability (Draft 1998)
- 4 BACPAC I (February 2001)
- 4 BACPAC II (Not Started)
- 4 Also 'old' red guidances (2)

u ICH Preferred

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FDA BA/BE Guidances

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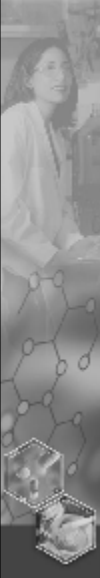
- u General Guidance
- u Criteria Guidance
- u Bioanalytical Guidance
- u Biopharmaceutics Classification System Guidance
- u Food-Effects Guidance
- u Nasal Drug Products
- u Oral Inhalation Drug Products (delayed)
- u Topically Applied Drug Products (withdrawn)
- u Dissolution Testing of Immediate Release Solid Oral Dosage Forms (final)
- u Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (final)

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Topics

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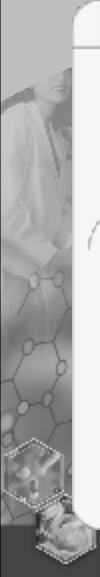
- u The Old
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- u The New at USP: General
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GMPs for the 21st Century/Quality Initiatives

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FDA's GMP's for the 21st Century/ICH Quality Approaches

Antecedents Documents

- U.S. Presidential/Congressional Commission on Risk Assessment and Risk Management (2007)
- FDA, Managing the Risks from Medical Products Use (1999)
- ISO Guide 51: Safety Aspects Guidelines for Their Inclusion in Standards (1999)

Q9: Quality Risk Management

Post-Approval Change

- 314.70
- Guidance: Changes to an Approved NDV/NDM
- Comparability Documents (2 NDV/NDM)

Research & Development



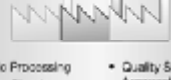
QR: Product Development Report

Regulatory Authority



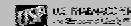
- QMDC, Risk-based Quality Assessment System
- Quality Systems Framework for Internal Activities

Manufacturing



- Aseptic Processing
- Powder Blends
- PAT
- Risk-based Approval for Prioritizing Inspections
- Quality Systems Approach to Pharmaceutical cGMP's
- Part 11: Electronic Records

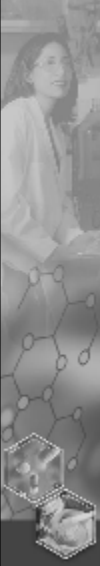
Dispute Resolution





GMPs for the 21st Century

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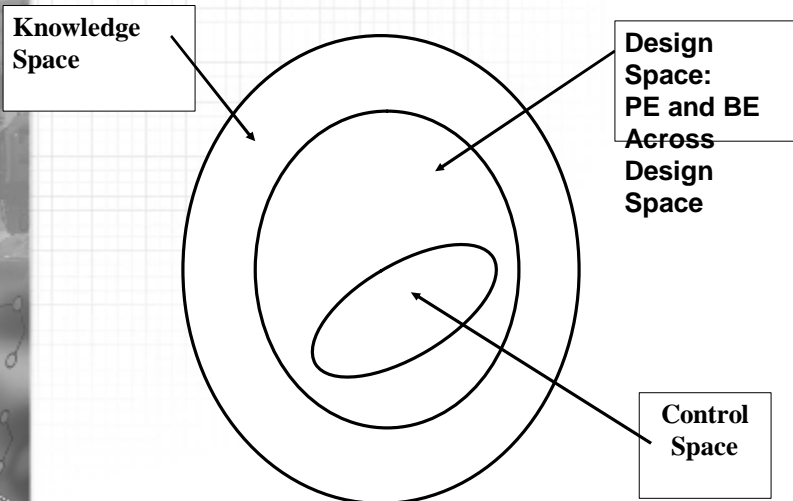
- u FDA's GMPs for the 21st Century Initiative
- u Challenges in traditional CMC program
- u Pharmaceutical Quality Assessment System (PQAS) in the 21st Century
- u What is Quality by Design (QbD)
 - 4 Dosage Form Development
- u Pharmaceutical Quality Assessment System (PQAS) - Implementation
- u CMC Pilot Program
- u Benefits and Regulatory Flexibility
- u Conclusions

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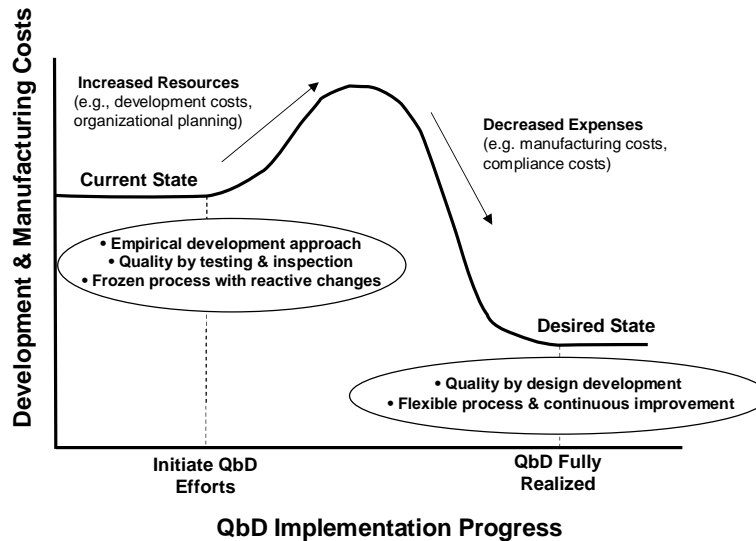
Design Space* and Equivalence

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* Jeffrey J. Blumenstein et al, Pfizer, adopted from J. Berridge PQRI Mar 2005 Conference November 2006

Cost and Benefit of QbD



New Approaches

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- u Data and Research Intensive
- u Private
- u Untested (Hypothesis: a product made according to QbD and PAT is better quality than a product made to invariant manufacturing and end product testing)
- u Public health impact of regulatory flexibility (reduced FDA review/inspections, reduced end product testing)
- u PE and BE maintained?—uncertain
- u OOS Guidance
- u USP: meets the requirement



Topics

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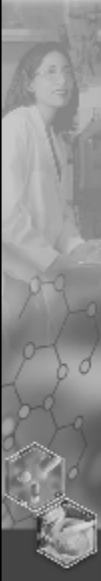
- u The Old
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- u The New at USP: General
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USP Is Changing

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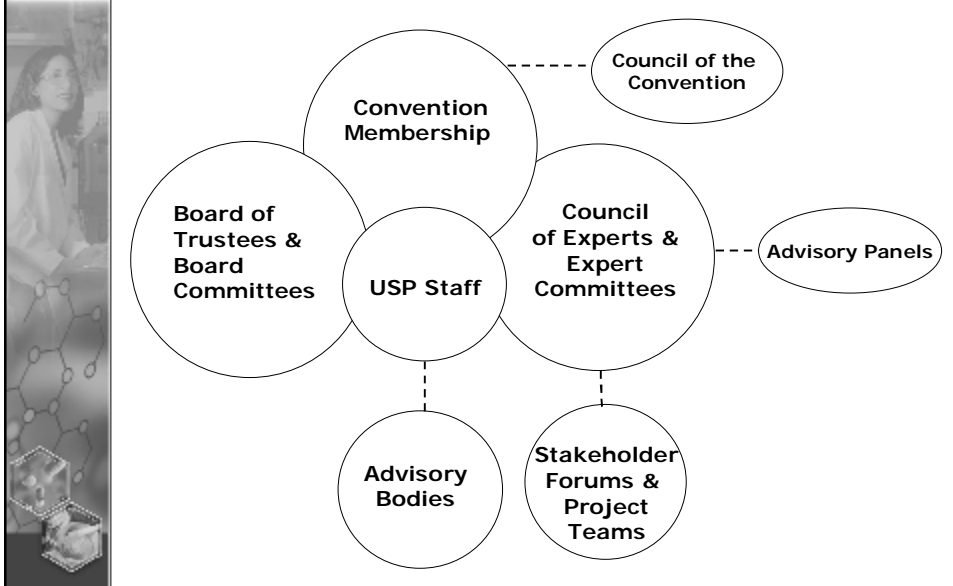
- u Volunteers
- u Monograph Acquisition
- u Redesign
- u Science

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USP Governing and Advisory Bodies

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USP's Volunteers

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- ┌ USP has more than 1,000 USP Volunteers
 - └ 58 Expert Committees
 - 41 Standards (newly approved FCC)
 - 17 Information
 - └ 500 Council of Experts and Expert Committee Members
 - └ 250 Advisory Panel Members

 - └ Plus hundreds of Stakeholder Forum and Project Team volunteers



Expert Committee Member Demographics

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Sector	Standards	Information	Total
Academia	24%	54%	29%
Consultant	9%	1%	8%
Government	12%	10%	12%
Industry	37%	6%	31%
Medical Practice	4%	20%	7%
Other (self employed, institutes, journalists, nonprofits)	14%	9%	13%
Totals	100%	100%	100%

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52 Volunteers are from 26 Other Countries

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u Argentina	1	u Italy	1
u Austria	1	u Jordan	1
u Belgium	1	u Mexico	1
u Brazil	2	u Norway	1
u Canada	17	u Peru	1
u China	2	u Puerto Rico	1
u Denmark	1	u Panama	1
u France	1	u Russian Fed	1
u Germany	3	u S. Africa	1
u Hungary	1	u S. Korea	1
u India	4	u Sweden	1
u Ireland	1	u Switzerland	3
u Israel	1	u UK	2

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Advisory Panels

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- u 41 Advisory Panels
 - 4 Two have concluded:
 - Medical Gases
 - Naming of Biotechnology-Derived Products
 - 4 One did not start
 - Global Documentary Standards
- u Executive Committee Advisory Panels
 - 4 Resolution 3 Advisory Panel
 - 4 Food Chemicals Codex Advisory Panel

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Stakeholder Forums

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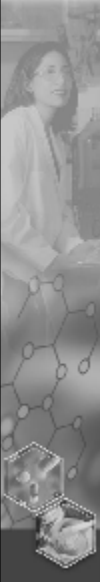
- u Domestic
 1. Prescription-Non-Prescription Stakeholder Forum
 2. Biologicals and Biotechnology Stakeholder Forum
 3. Dietary Supplement Stakeholder Forum
 4. Compounding Stakeholder Forum
 5. Patient Safety Stakeholder Forum
 6. USP Consortium of Pharmaceutical Research Centers
 7. Food Chemicals Codex Stakeholder Forum

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Project Teams

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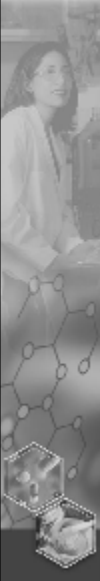
1. Compendial Calculations
2. Compendial Process Improvements
3. General Chapters
4. General Notices
5. Inorganic Impurities/Heavy Metals
6. Residual Solvents
7. *USP-NF* Monographs
8. Full-length Vaccine Monographs

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USP Is Changing

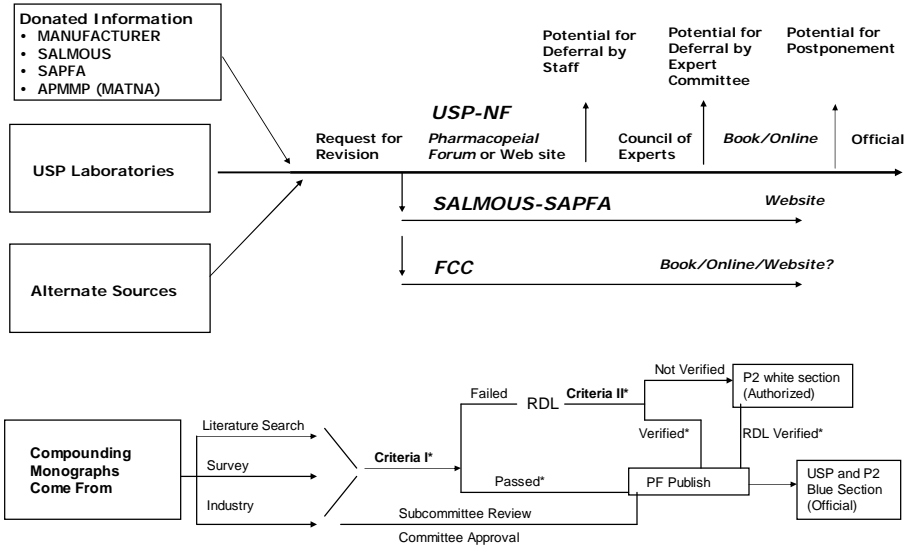
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- u Volunteers
- u Monograph Acquisition
- u Redesign
- u Science

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USP Monograph Acquisition: Approaches and Process September 2006



NOTE: * It must be approved by expert committee or subcommittee before monographs go to the next step.



USP Is Changing

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- u Volunteers
- u Monograph Acquisition
- u Redesign
- u Science



How Will the Content Be Organized?

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Volume 1	Volume 2	Volume 3
<ul style="list-style-type: none">• Full Table of Contents• General Chapters Table of Contents• Front Matter• USP General Notices• General Chapters• Reagents• Reference Tables• Dietary Supplements• Excipients• NF General Notices• NF Monographs• Full Index	<ul style="list-style-type: none">• Full Table of Contents• General Chapters Table of Contents• USP General Notices• USP Monographs• A-L• Full Index	<ul style="list-style-type: none">• Full Table of Contents• General Chapters Table of Contents• USP General Notices• USP Monographs• M-Z• Full Index

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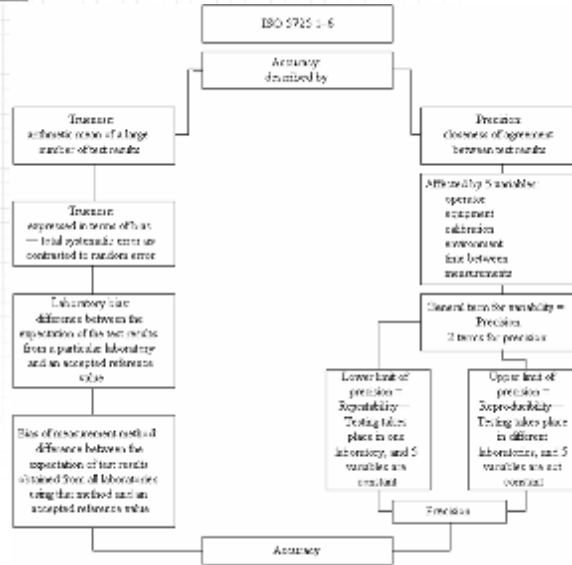
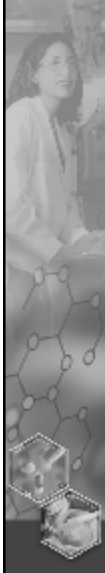
<ul style="list-style-type: none">u Volunteersu Monograph Acquisitionu Redesignu Science

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ISO 5725 1-6

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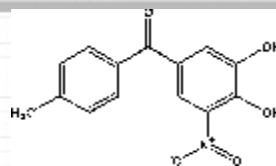


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Example CERTIFICATE OF ANALYSIS Example USP TOLCAPONE RS/CRM (3,4-dihydroxy-5-nitrophenyl)(4-methylphenyl)-methanone

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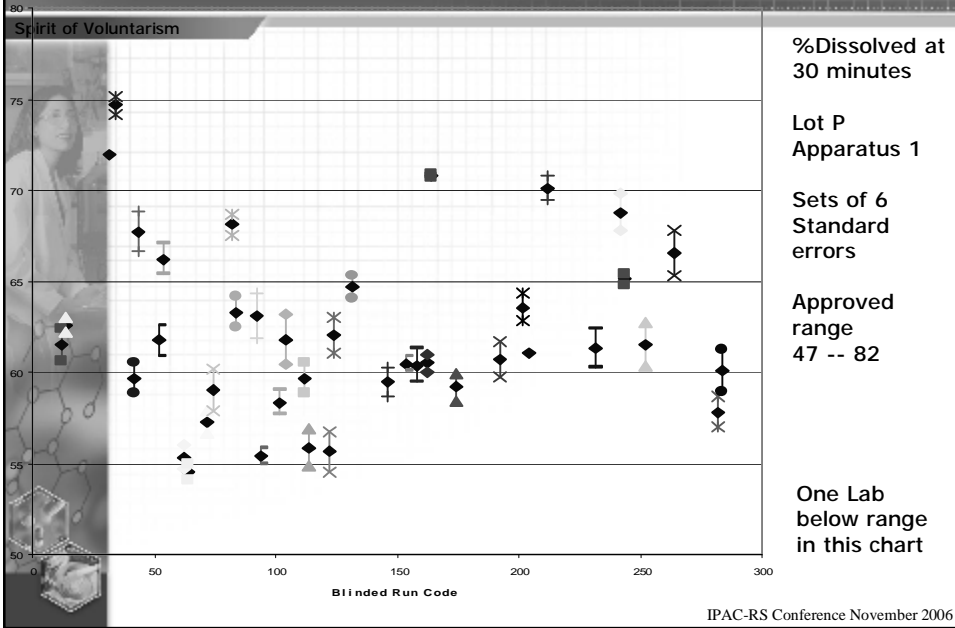
Produced and Certified by: U. S. Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852
Technical Service: 301-816-8129

Catalog Number: 1670207
Lot: F0D280
Nominal Package Size: 200 mg
Molecular Formula: $C_{14}H_{11}NO_5$
Molecular Weight: 273.24
Appearance: Clumpy, bright yellow powder
Storage: Controlled room temperature, protect from light
CAS Number: [134308-13-7]
Release Date: October 2004
Certified Value: 0.999 mg/mg +/- 0.001 mg/mg on the As Is Basis (95% Confidence Level)

NOTE: Uncertainty values are provided for informational purposes only. They are not to be used for Compendial or legal purposes. IPAC-RS Conference November 2006



Collaborative Study: Physical Standard (USP Prednisone Tablets Lot P)



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Structure of the Council of Experts

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2005-2010 Council of Experts

COUNCIL OF EXPERTS EXECUTIVE COMMITTEE

STANDARDS EXPERT COMMITTEES Collaborative Groups



INFORMATION EXPERT COMMITTEES

MEDICARE MODEL GUIDELINES
EXPERT COMMITTEE

18 EXPERT COMMITTEES

16



Aerosols Expert Committee

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- u Chair
 - 4 Anthony Hickey, Ph.D., D.Sc.
- u Members
 - 4 Paul D. Curry, Jr., Ph.D.
 - 4 Harris Cummings, Ph.D.
 - 4 Bo L. Olsson, Ph.D.
 - 4 Guirag Poochikian, Ph.D.
 - 4 John K. Simons, Ph.D.
 - 4 Charles Thiel, B.A.
 - 4 Caroline Vanneste, B.Sc.
- u Liaison – Kahkashan Zaidi, Ph.D.



Aerosols EC WorkPlan (2005-2010)

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u **Short-term (1-2 years) Goals**

- u Resolve issues related to medical gases monographs.
- u Finalize first draft of the monograph on tetrafluoroethane.
- u Add microbial limit test specification for oral inhalers to GC <601> ----- **Draft in Progress.**
- u Develop new monograph on lactose for inhalation (**Draft in progress**)

u **Long-term (3-5 years) Goals**

- u Develop criteria for particle size testing for nasal sprays (**In Progress**).
- u Reporting and qualification thresholds for leachables in orally inhaled and nasal drug products.

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Aerosols EC WorkPlan (2005-2010)

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- u **21 Official Monographs**
- u **17 Official Monographs in PF (Revisions)**
- u **4 New Monographs in PF**
- u **Develop 27 New Monographs**

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Nomenclature Expert Committee

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u [Drug]

- 4 Inhalation Aerosol Product
- 4 Lingual Aerosol Product
- 4 Nasal Aerosol Product
- 4 Topical Aerosol Product
- 4 Metered Topical aerosol Product
- 4 Inhalation Solution for Nebulization
- 4 Inhalation Suspension for Nebulization
- 4 Solution Concentrate for Inhalation
- 4 Suspension Concentrate for Inhalation
- 4 Power for Inhalation Solution
- 4 Inhalation Spray Product
- 4 Lingual Spray Product
- 4 Nasal Spray Product
- 4 Topical Spray Product

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Taxonomy-Categories of Dosage Forms

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First-Tier Category
Route of Administration

Second-Tier Category
Dosage Form (e.g., general type of dosage form)

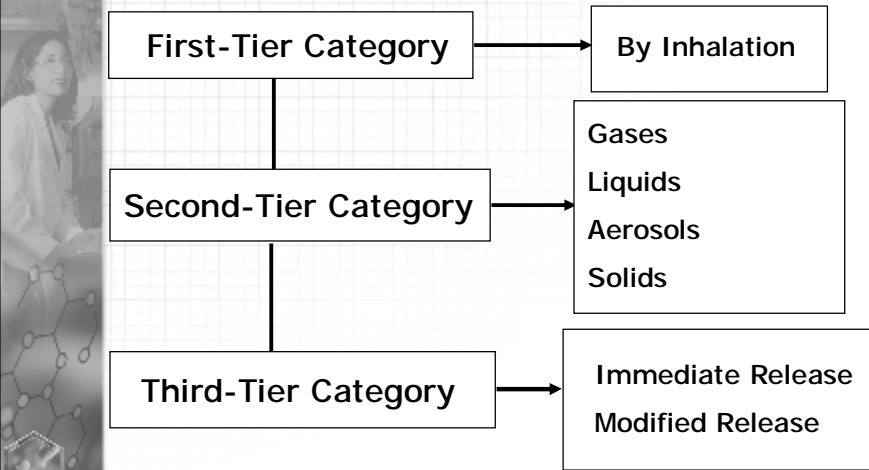
Third-Tier Category
Type of Release (e.g., release pattern of the active)

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Taxonomy- Categories of Dosage Forms

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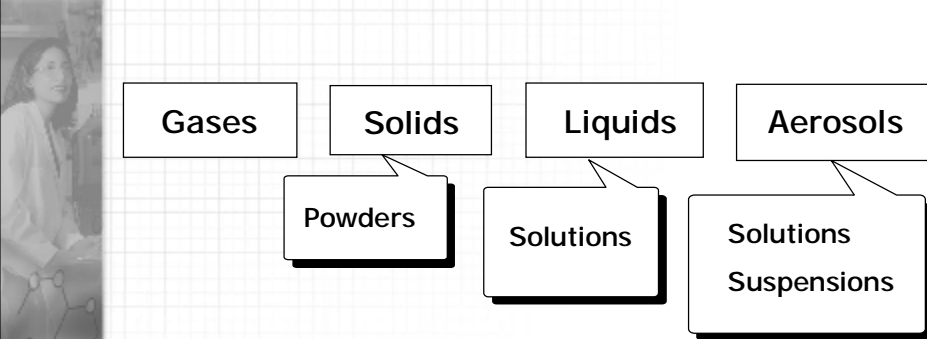


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Second-Tier Category for Inhalation Route

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Also

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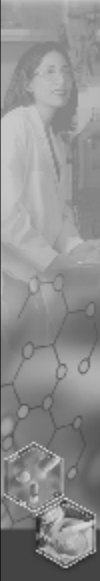
- u Leachables and Extractables
- u Foreign Particulates
- u Aerosol Particulates

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What's Next: What Can We Do Together?

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- u General Chapters
 - 4 Product Development for Aerosols
 - 4 Dosage Form (Inhalanda in EP)
- u Monographs
 - 4 More monographs
 - 4 Partial monographs
- u Performance Verification/Proficiency Testing for Selected Procedures

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Thank You