U.S. PHARMACOPEIA
The Standard of Quality℠

PQRI-FDA Workshop on Process Drift
Bethesda, Maryland

Connection Between Quality, Safety, and Efficacy

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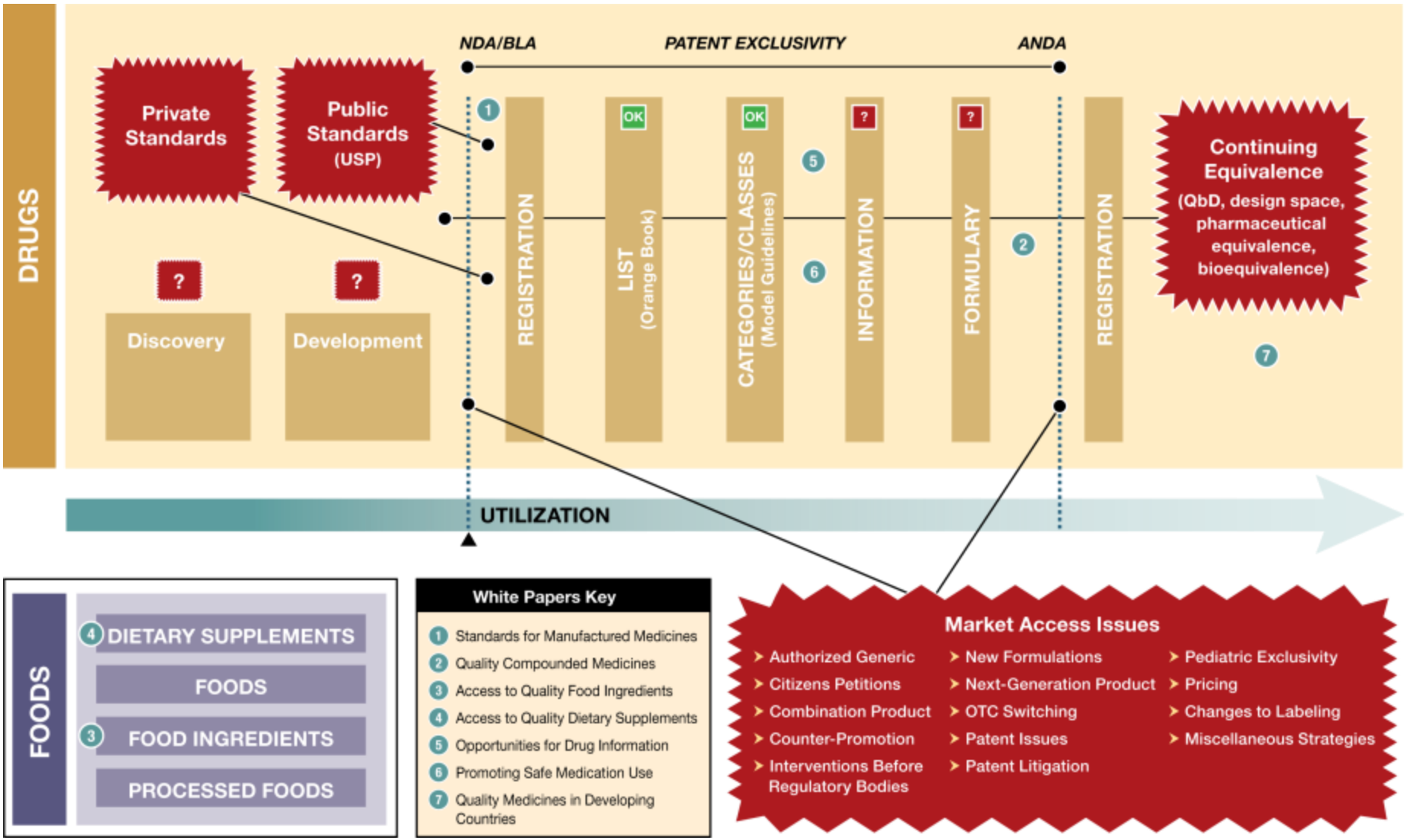
United States Pharmacopeial Convention
December 1–3, 2010

Topics

- **Overview**
- BCS
- The USP Monograph: Pharmaceutical Equivalence and Bioequivalence
- A National/Global RLD

Continuing Equivalence: A Roadmap

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



Federal Food, Drug, and Cosmetic Act
Public Health Service Act

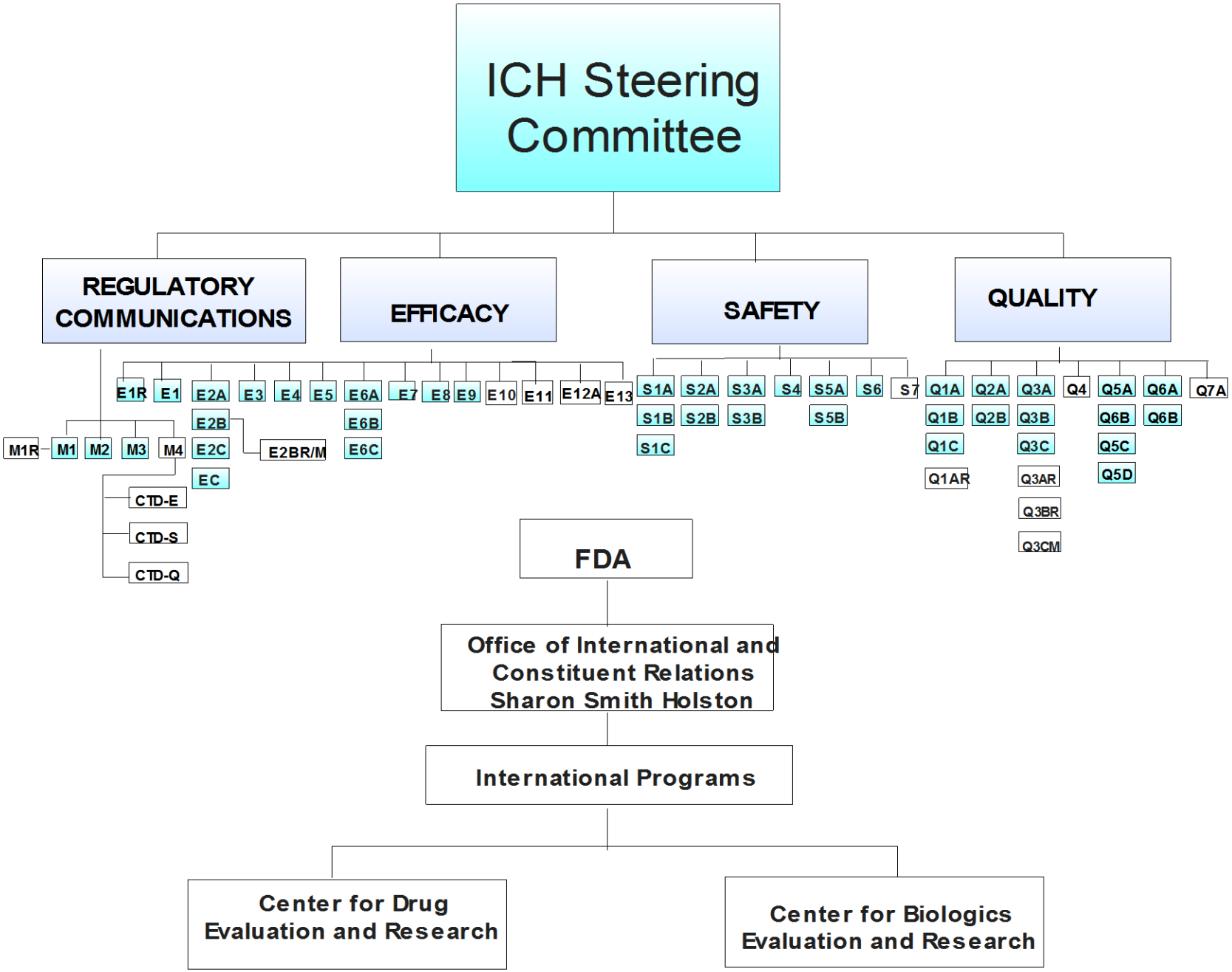
- **FD&C Act**
  - (b)(1)
  - (b)(2)
  - (j)
  - (j)(2)(C)
  - OTC
  - safety/efficacy and identity, strength, quality, purity, potency
  - NDA/ANDA approved
- **PHS Act**
  - PHS: prevention, treatment, or cure of disease
  - safety, purity, potency
  - BLA licensed
- **USP**
  - (Identity), strength, quality, purity
- **ICH**
  - Quality

USP Role Under Federal Law

- **1820** USP—independent, national pharmacopeia
- **1906** Food & Drugs "Wiley" Act
  - Feds can act if adulterated or misbranded
  - USP *strength, quality & purity*
- **1938** Federal Food, Drug, and Cosmetic Act (FD&C Act)
  - FDA application—safety—but **no preapproval**
  - USP *identity* (drug named in official compendium)
    USP *packaging & labeling*
- **1962** FD&C Drug Amendments
  - FDA **pre-market approval authority**; safety & efficacy
  - FDA authority to require manufacturing controls:
    GMPs—assure safety + identity, strength, quality & purity
- **1997** FDA Modernization Act Amendments
  - USP *Positron Emission Tomography (PET) standards*

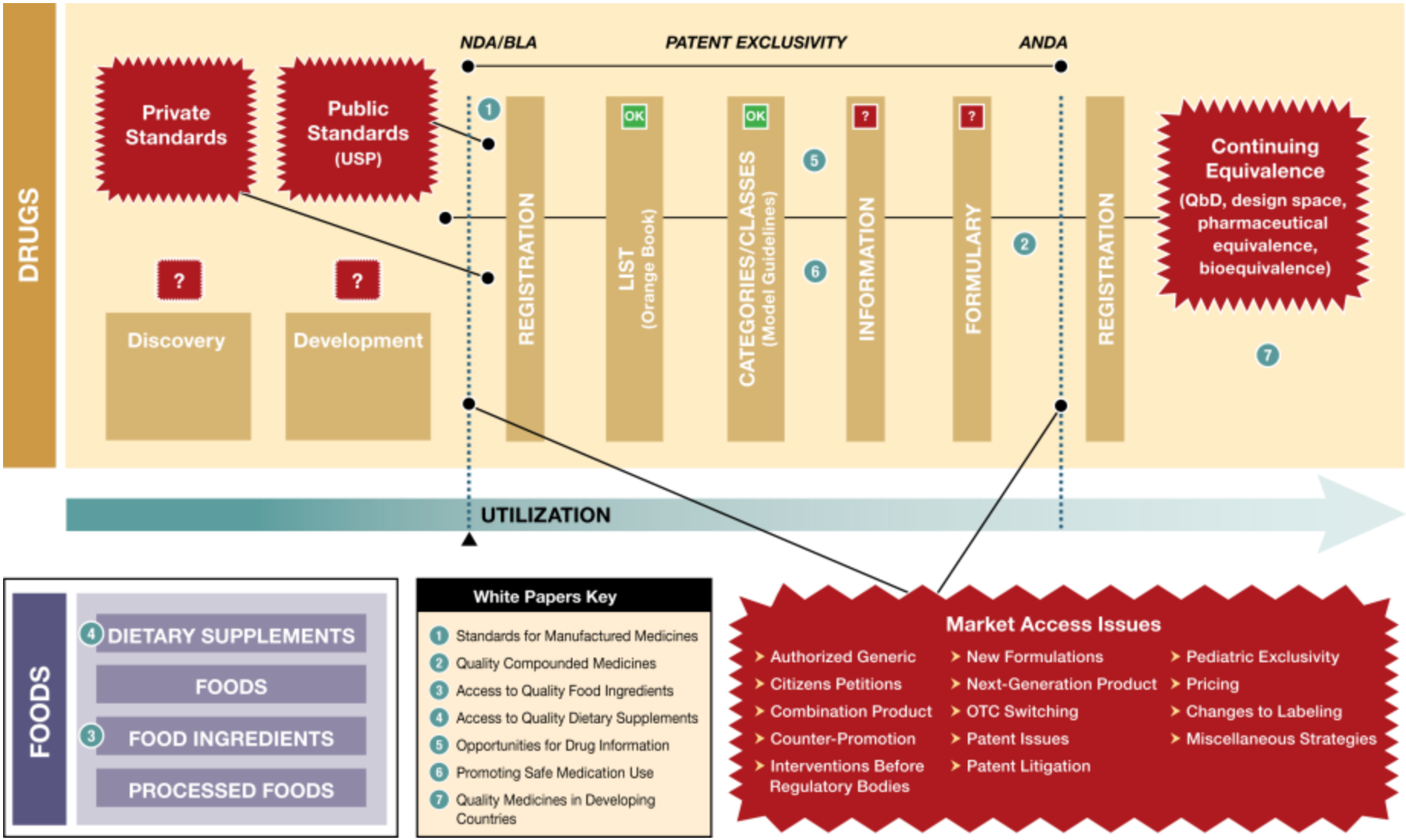
Pharmaceutical Equivalence and Bioequivalence

- Reference Listed Drug (WHO Comparator Pharmaceutical Product) Critical to approach—must be stable via careful post-approval change control
- Pharmaceutical Equivalence
  - Defined at 21 CFR 320
  - BPCI Act: 'similar' statements
- BA/BE—harmonization close and could advance further
- *Continuing equivalence: Is there an end to the story?* RL Williams and Vinod Shah, Journal of Generic Medicines, July 2008

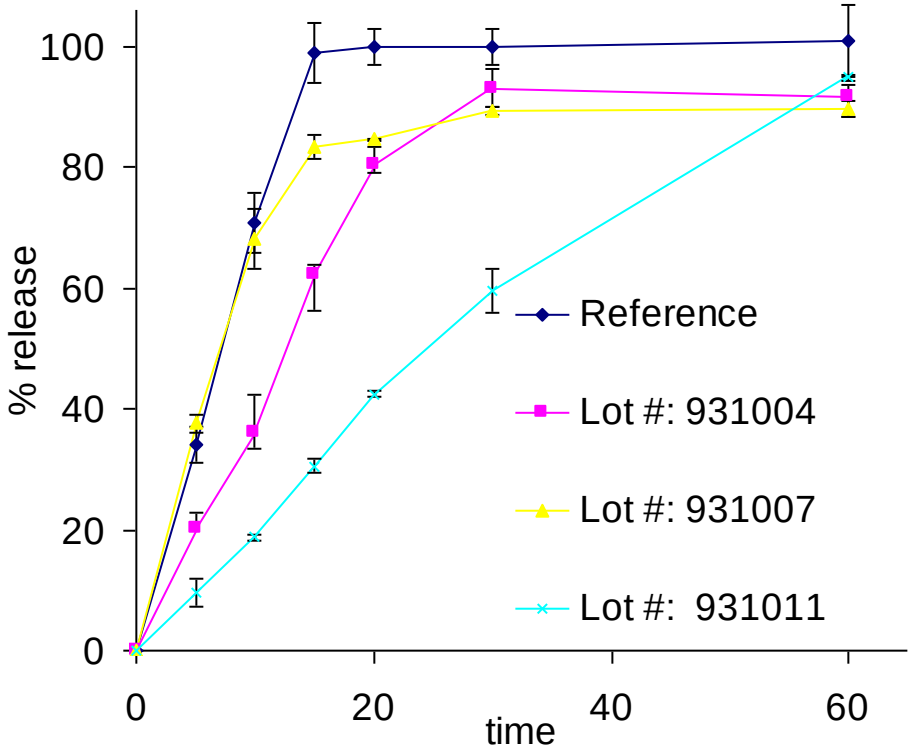

ICH Steering Committee
REGULATORY COMMUNICATIONS
EFFICACY
SAFETY
QUALITY
E1R
E1
E2A
E2B
E2C
EC
E2BR/M
E3
E4
E5
E6A
E6B
E6C
E7
E8
E9
E10
E11
E12A
E13
M1R
M1
M2
M3
M4
CTD-E
CTD-S
CTD-Q
S1A
S1B
S1C
S2A
S2B
S3A
S3B
S4
S5A
S5B
S6
S7
Q1A
Q1B
Q1C
Q1AR
Q2A
Q2B
Q3A
Q3B
Q3C
Q3AR
Q3BR
Q3CM
Q4
Q5A
Q6B
Q5C
Q5D
Q6A
Q6B
Q7A
FDA
Office of International and Constituent Relations Sharon Smith Holston
International Programs
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research

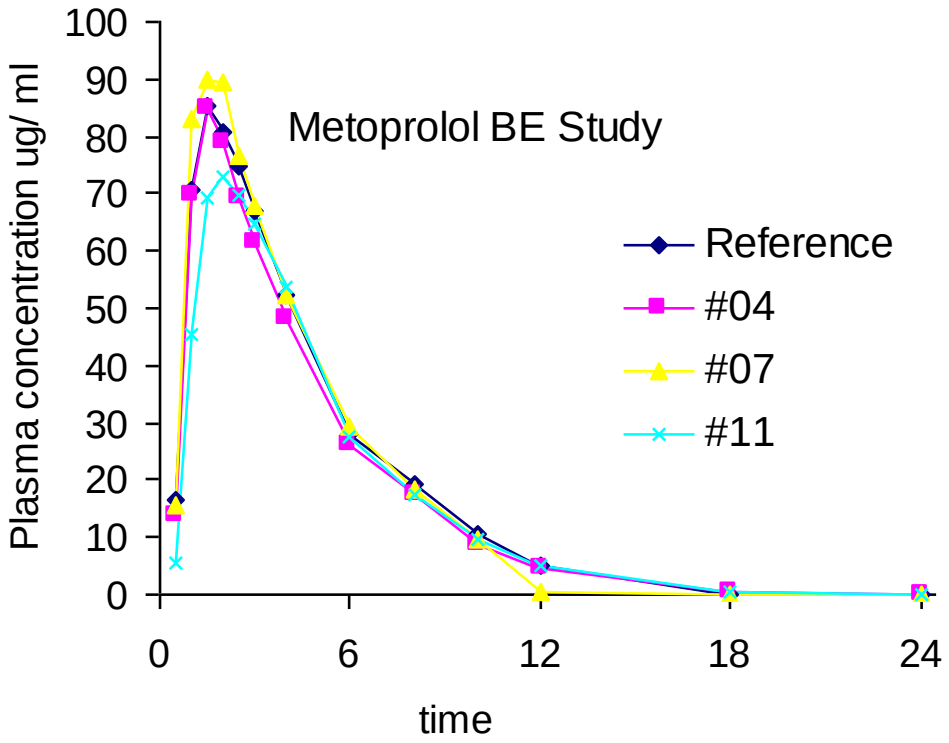
The Food and Drugs Landscape: White Papers

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



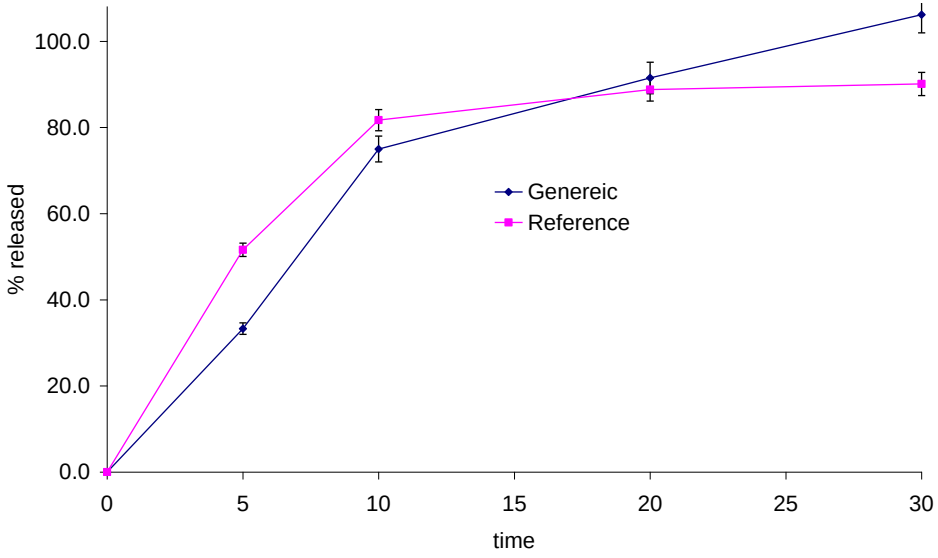
Class I Drug: Over Discriminating



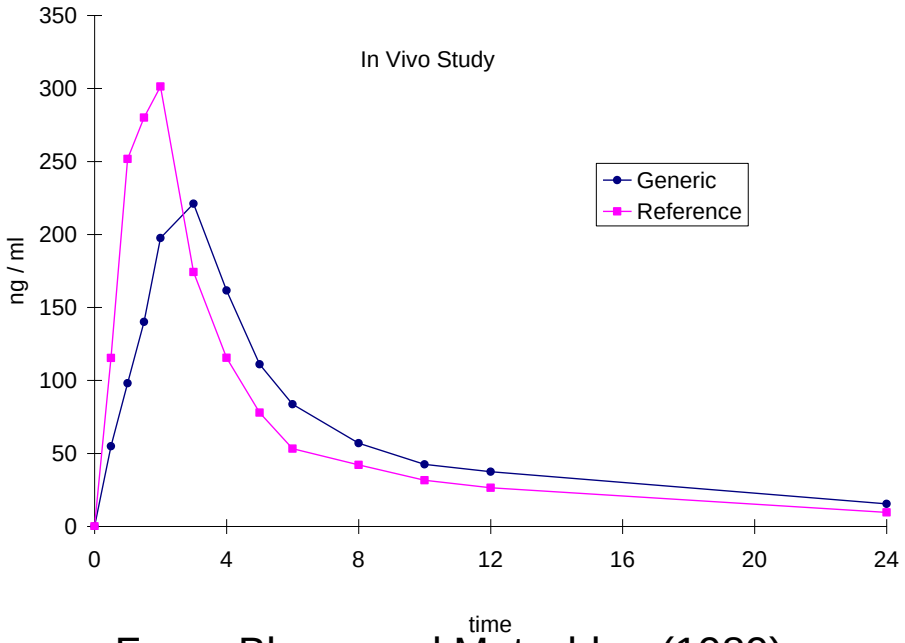


Class II Drug: Under Discriminating

Dissolution Profile of Two Commercial Formations of a Class II Drug in Simulated Intestinal Fluid pH 7.4



From: Lobenberg et al. Pharm Res 2000



From: Blume and Mutschler. (1989) Bioäquivalenz. Govi-Verlag, Eschborn.

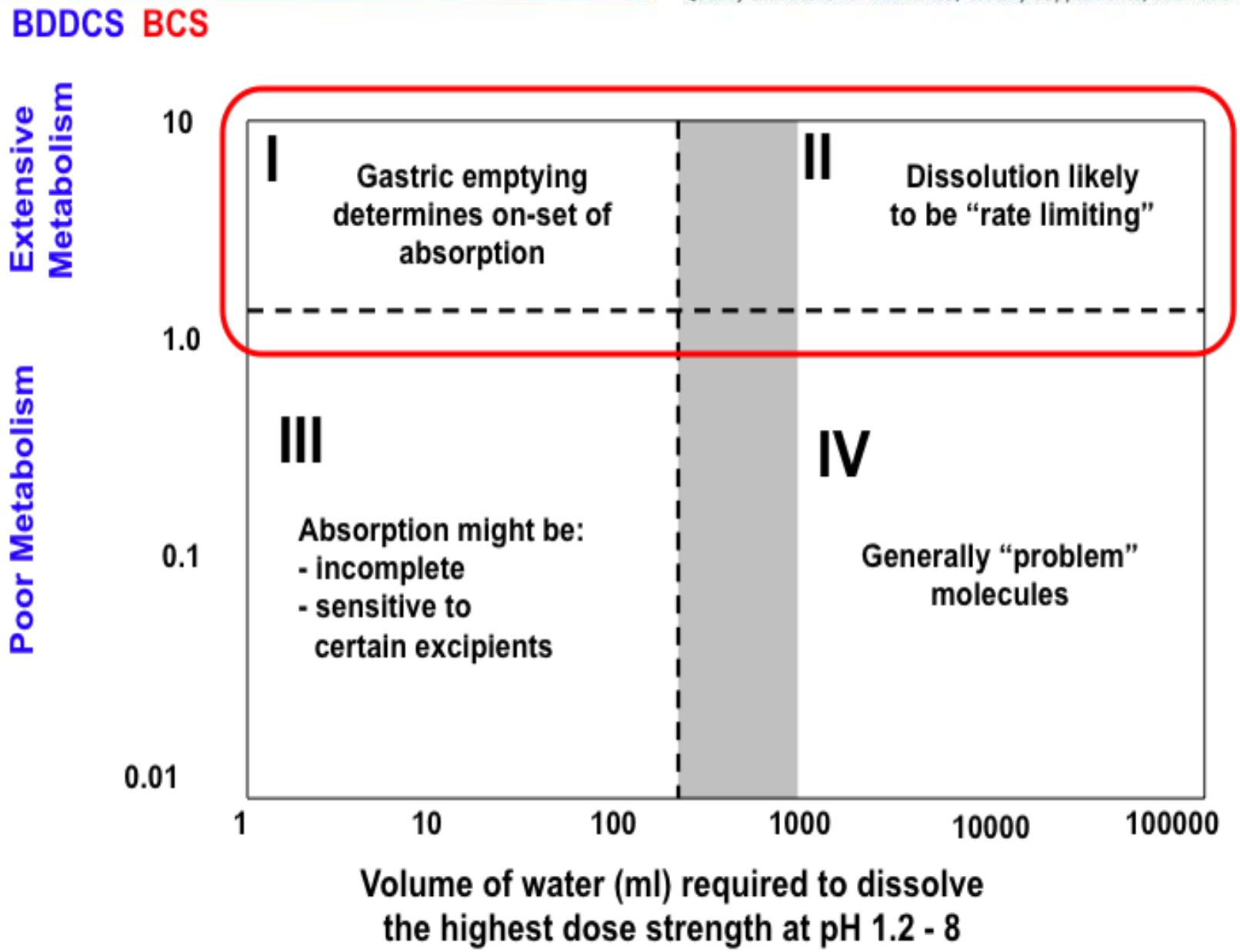
Take Aways

- What Is the question?
  - How to assure continuing equivalence
  - Continuing equivalence for chemical drugs: PE, BE and then TE
  - For biosimilars, it's interchangeability (one-way), not comparability
- The US has a robust system to assure continuing equivalence
- Manufacturers, FDA, USP all play a role
- Process drift is a signal that continuing equivalence may be in jeopardy

Topics

- Overview
- **BCS**
- The USP Monograph: Pharmaceutical Equivalence and Bioequivalence
- A National/Global RLD

Biopharmaceutics Classification System: Update



WHO Essential Drugs

- 325 Medicines
- 260 Drugs
- 123 Oral IR

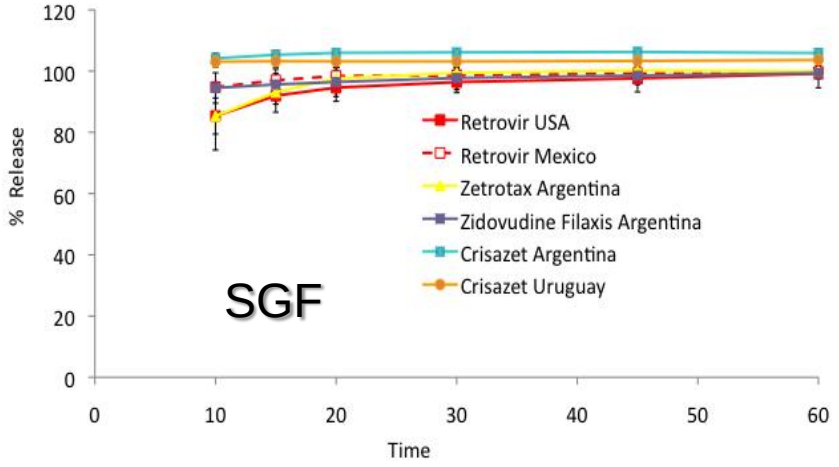
Take Aways

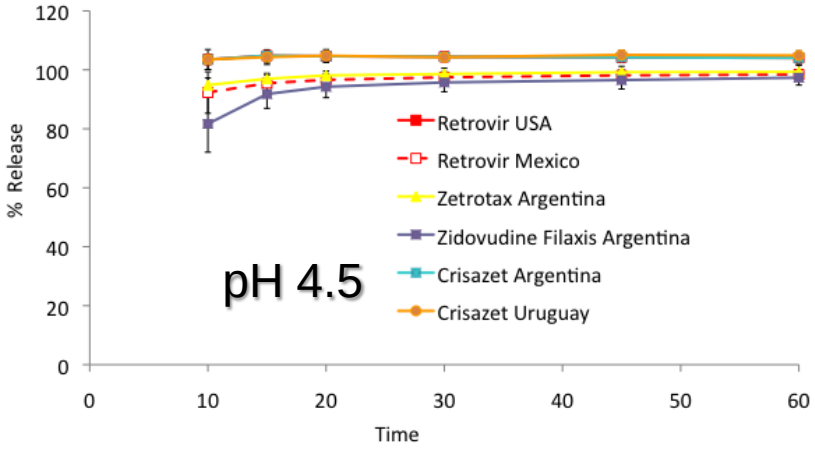
- 67% of WHO IR drugs at High Solubility
- 68% of US Top 200 drugs are HS
- *BCS Approaches* applicable to the majority of drugs—WHO Essential Medicines and US Top 200
- Allows opportunity to assess impact of process drift on BE at low cost

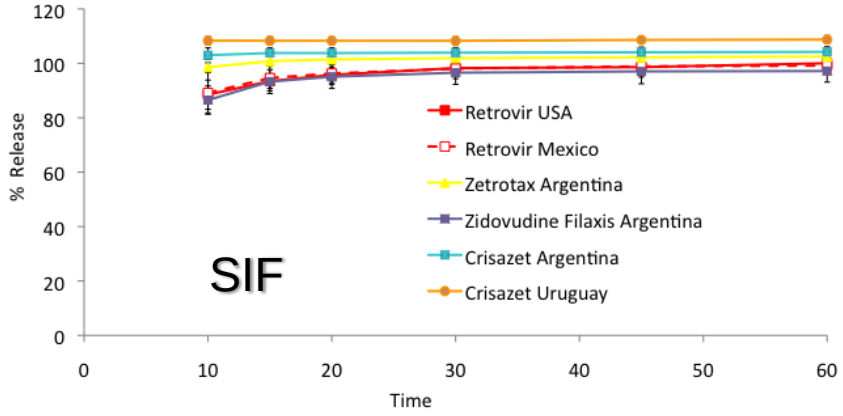
Zidovudine

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

In Vitro Similarity (IVS)

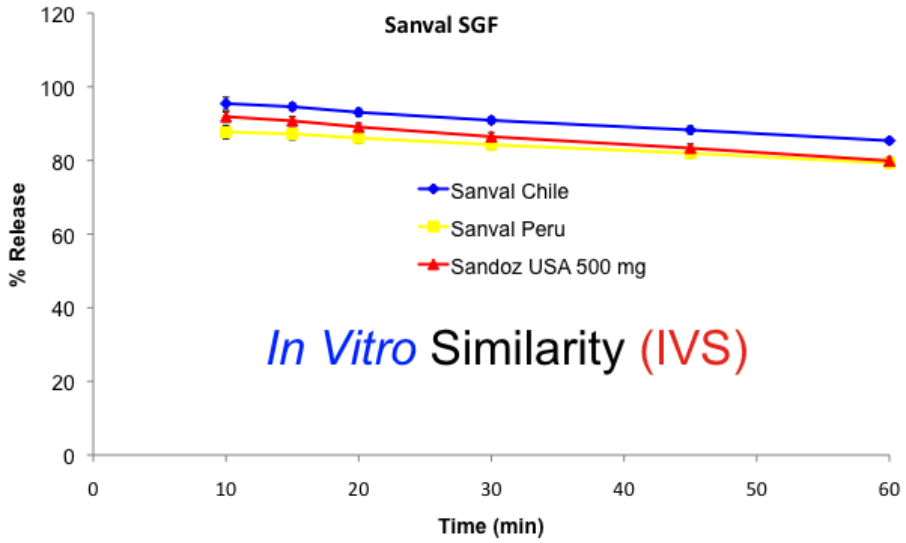


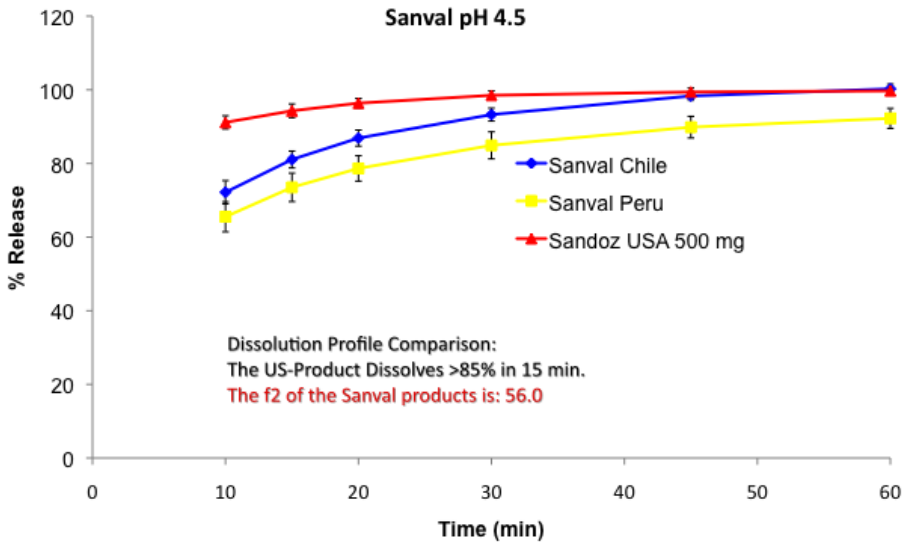


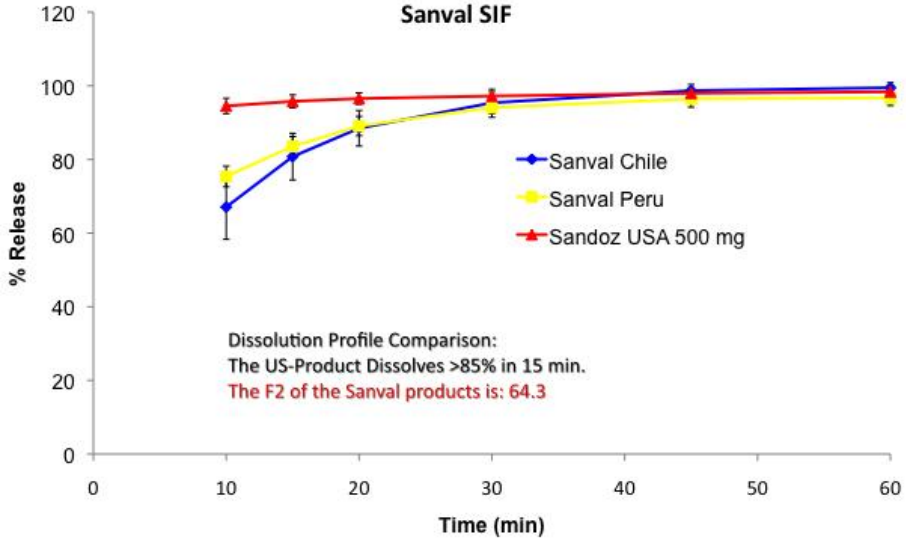


Country	Company	Product	Batch	Exp.	Excipient
USA	GSK USA	Retrovir	7ZP 1642	10/10	Corn Starch, Mg-Stearate, MCC, Sodium Starch Glycolate
Mexico	GSK (England)	Retrovir	X5953	05/10	NA
Argentina	Laboratorios Richmonds	Zetrotax	EMX 4V	04/10	Excipients
	Laboratoris Filaxix	Zidovudina	12119 D1	06/10	Lactose monohydrate, Mg-Stearate, MCC, Cross carmelose Sodium, Silicium Dioxide
	Laboratorio LKM	Crisazet	B853A	04/10	Sodium Starch Glycolate, Lactose Monohydrate, Mg-Stearate
Uruguay	Laboratorio LKM	Crisazet	B853A	04/10	Sodium Starch Glycolate, Lactose Monohydrate, Mg-Stearate

Amoxicillin

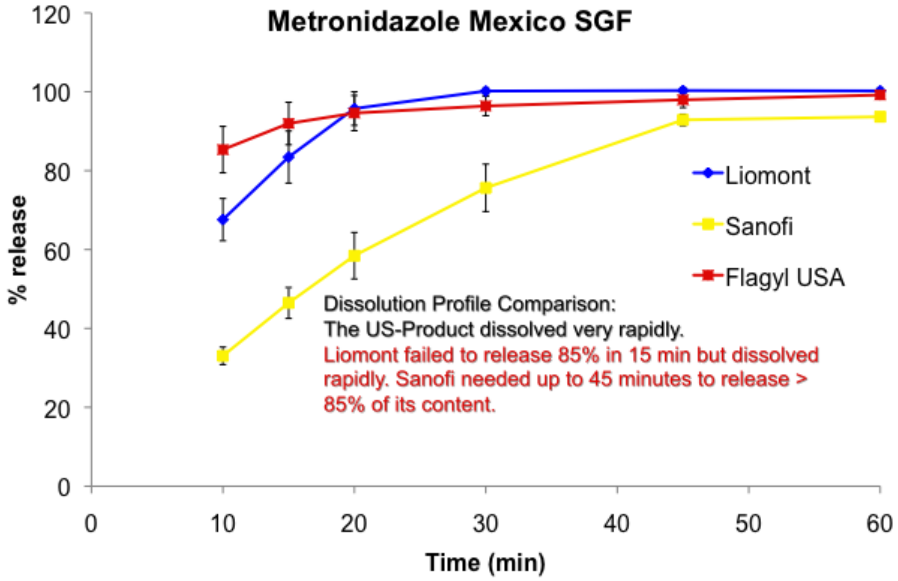


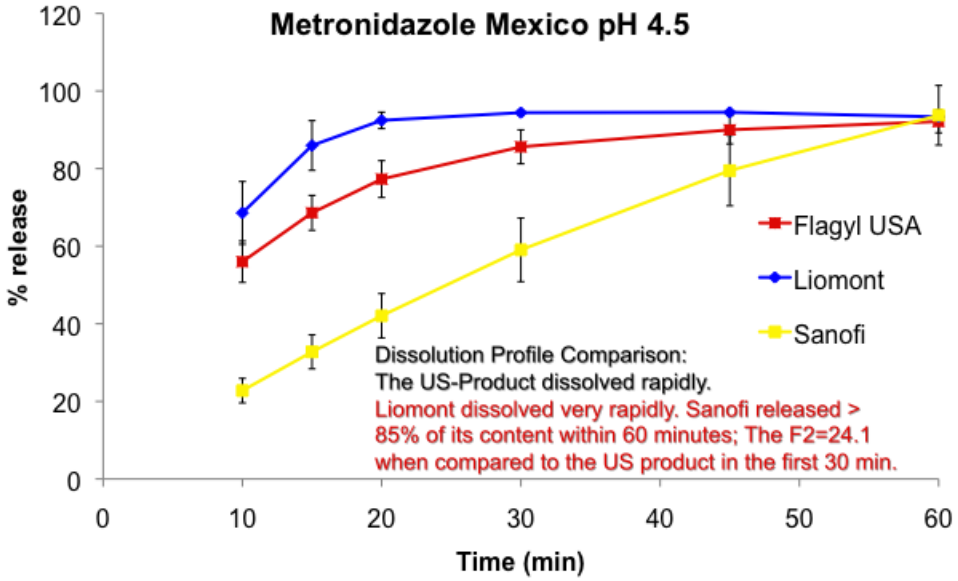


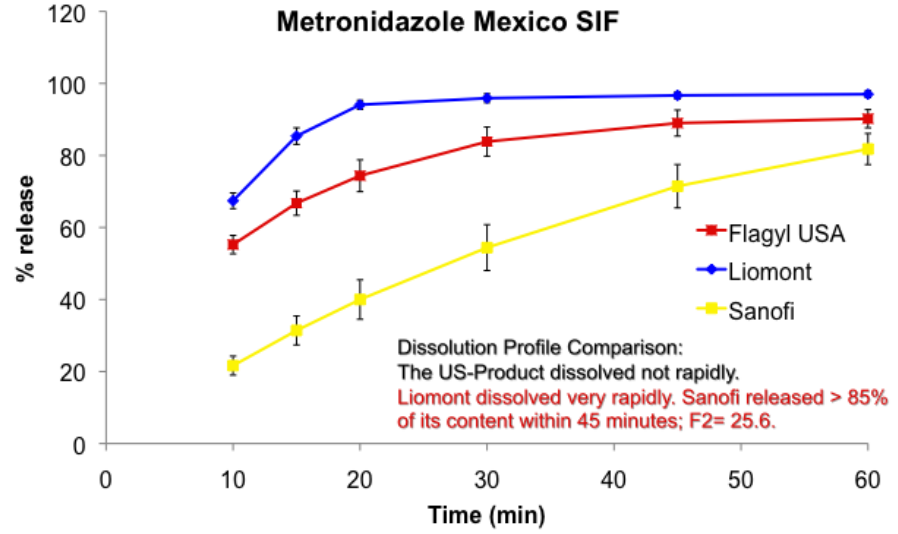


Country	Company	Product	Batch	Exp.	Excipients
USA	Sandoz	Amoxicilin	151645	10/09	Silicon dioxide, crosspovidone, ethylcellulose aqueous dispersion, hypromellose, MG-Stearate, MCC, Sodium Stach glycolate, talc, triethy.citrate, titanium dioxide
Peru	Sanval	Amoval 500 mg	122387	07/12	croscarmellose sodium; micro crystalline cellulose; magnesium stearate; titanium dioxide; polyethylene glycol; hypromellose; *Eicosadioate*
Chile	Sanval	Amoval 500 mg	033608	11/2012	croscarmellose sodium; micro crystalline cellulose; magnesium stearate; titanium dioxide; polyethylene glycol; hypromellose; *Eicosadioate*

Mexico: Metronidazole







Country	Company	Product	Batch	Exp.	Excipient
USA	Searle Pharmacia	Flagyl 500 mg	C061228	03/09	Cellulose, Fd&C Blue,Hydroxypropyl Cellulose, Hypromellose, PEG, Stearic Acid, Titanium Dioxide
Mexico	Sanofi Aventis	500 mg	B8B575	03/11	Excipients
Mexico	Limont	Flagenase	P07009	07/01	Excipients

Metronidazole Summary

Country	Manufacturer	SGF	pH 4.5	SIF
Peru	Genfar	+	-	-
	Hersil	-	+	+
	Alkem	+	-	-
	Sanofi	-	-	-
Mexico	Liomont	-	-	-
	Sanofi	-	-	-
Argentina	Baliarda	-	+	+
	Lazar	+	-	-
	Sanofi	-	-	-
	Austral	-	-	-

Topics

- Overview
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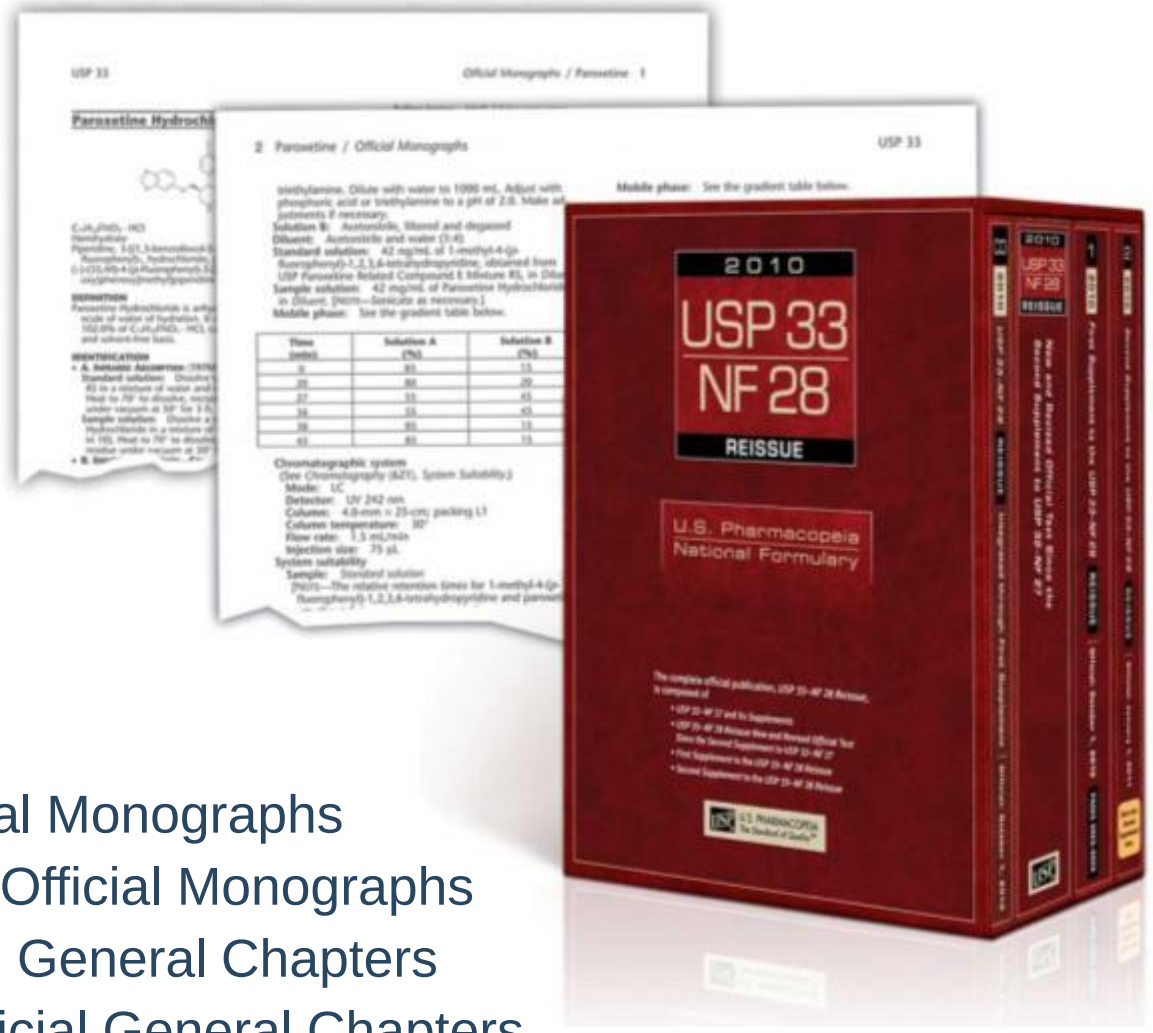
The “Pharmacopeia”: 1) *USP* and 2) *NF*

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



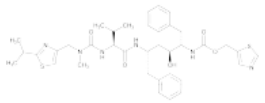
Productivity:

- **370** New Official Monographs
- **1,201** Revised Official Monographs
- **43** New Official General Chapters
- **89** Revised Official General Chapters

Drug Substance Monographs

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Ritonavir



$C_{37}H_{48}N_6O_5S_2$ 720.94

2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-5-thiazolylmethyl ester [5*S*-(5*R**,8*R**,10*R**,11*R**)]-;
5-Thiazolylmethyl [(α*S*)-α-[(1*S*,3*S*)-1-hydroxy-3-[(2*S*)-2-[3-[(2-isopropyl-4-thiazolyl)methyl]-3-methylureido]-3-methylbutyramido]-4-phenylbutyl]phenethyl]carbamate [155213-67-5].

DEFINITION

Ritonavir contains NLT 97.0% and NMT 102.0% of $C_{37}H_{48}N_6O_5S_2$, calculated on the anhydrous basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨197K⟩
- **B.** The retention time of the major peak of the *Sample solution* is within 2% of the retention time of the major peak of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Solution A: 4.1 mg/mL of monobasic potassium phosphate in water
Solution B: Acetonitrile, tetrahydrofuran (inhibitor-free), *n*-butanol, and *Solution A* (18:8:5:69)
Solution C: Acetonitrile, tetrahydrofuran (inhibitor-free), *n*-butanol, and *Solution A* (47:8:5:40)
Mobile phase: See the gradient table below.
[NOTE—Because of the high dependence of retention time and selectivity on the *Mobile phase* composition, the volumes should be accurately measured. Excessive or continued helium sparging must be avoided. Store the *Mobile phase* in a tightly sealed container when not in use.]

Time (min)	Solution B (%)	Solution C (%)
0	100	0
60	100	0
120	0	100
120.1	100	0
155	100	0

Diluent: Acetonitrile and *Solution A* (1:1)
Standard stock solution: 2.0 mg/mL of USP Ritonavir RS in *Diluent*. [NOTE—This solution may be kept for 5 days if refrigerated.]
Standard solution 1: 0.10 mg/mL of USP Ritonavir RS from the *Standard stock solution* diluted with *Diluent*
Standard solution 2: 0.025 mg/mL of USP Ritonavir RS from *Standard solution 1* diluted with *Diluent*
Sample solution: 0.025 mg/mL of Ritonavir in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 240 nm
Column: 4.6-mm × 15-cm; 3-µm packing L26
Column temperature: 60°
Flow rate: 1 mL/min
Injection size: 50 µL
Run time: 40 min
System suitability
Sample: *Standard solution 2*
[NOTE—The retention time for ritonavir is 30–35 min.]
Suitability requirements
Capacity factor, k′: NLT 13
Column efficiency: NLT 5000 theoretical plates
Tailing factor: 0.8–1.2
Relative standard deviation: 2.0%
Analysis
Samples: *Standard solution 2* and *Sample solution*
Calculate the percentage of $C_{37}H_{48}N_6O_5S_2$ in the portion of Ritonavir taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Ritonavir RS in *Standard solution 2* (mg/mL)
C_U = concentration of Ritonavir in the *Sample solution* (mg/mL)

Acceptance criteria: 97.0%–102.0% on the anhydrous basis

IMPURITIES

Inorganic Impurities

- **RESIDUE ON IGNITION** ⟨281⟩: NMT 0.2%, determined on 1.0 g
- **HEAVY METALS**, *Method II* ⟨231⟩: NMT 20 ppm, using 1.0 g of Ritonavir and 2 mL of *Standard Lead Solution* (10 ppm Pb) in the *Standard Preparation*

Organic Impurities

[NOTE—Ritonavir is alkali sensitive. All glassware should be prerinsed with distilled water before use to remove residual detergent contamination.]

- **PROCEDURE**

Solution A, Solution B, Solution C, Mobile phase, Diluent, Standard stock solution, and Standard solution 1: Prepare as directed in the *Assay*.
Identity solution: 1 mg/mL of USP Ritonavir Related Compounds Mixture RS in *Diluent*
Standard solution 2: 5 µg/mL of USP Ritonavir RS, from *Standard solution 1* in *Diluent*. [NOTE—Stable for 48 h.]
Sample solution: 1 mg/mL of Ritonavir in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 240 nm
Column: 4.6-mm × 15-cm; 3-µm packing L26
Column temperature: 60°
Flow rate: 1 mL/min
Injection size: 50 µL
Run time
Standard solution 2: 40 min
System suitability
Samples: *Identity solution* and *Standard solution 2*
[NOTE—The retention time of ritonavir is 30–35 min. See *Impurity Table 1* for relative retention times.]
Suitability requirements
Resolution: NLT 1.0 between Impurity E and Impurity F, *Identity solution*
Peak-to-valley ratio: NLT 1 for ritonavir and Impurity N (regioisomer), *Identity solution*
Capacity factor, k′: NLT 13, *Standard solution 2*
Column efficiency: NLT 5000 theoretical plates, *Standard solution 2*
Tailing factor: 0.8–1.2, *Standard solution 2*
Relative standard deviation NMT 3.0%, *Standard solution 2*

Analysis
Samples: *Diluent*, *Identity solution*, *Standard solution 2*, and *Sample solution*
Calculate the percentage of each Impurity in the portion of Ritonavir taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from *Standard solution 2*
C_S = concentration of *Standard solution 2* (mg/mL)
C_U = nominal concentration of Ritonavir in the *Sample solution* (mg/mL)
F = relative response factor

Acceptance criteria
Individual Impurities: See *Impurity Table 1*.
Total Impurities: NMT 1.0%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Mixture of 2,4-Wing acid and monoacyl valine (A + B)	0.07	1.0	0.1
Monoacylacetamide (C)	0.15	1.0	0.1
5-Wing diacyl (D)	0.24	1.37	0.1
Oxidation impurity (E)	0.36	1.0	0.3
Acid hydrolysis product (F)	0.39	0.73	0.1
Ritonavir hydroperoxide (G)	0.45	1.0	0.1
Acid/base by-product (H)	0.47	0.76	0.1
Ethyl analog (I)	0.64	1.0	0.1
Mixture of Boc-monoacyl and monoacyl isobutyl carbamate (J + K)	0.81	0.74	0.1

Impurity Table 1 *(Continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Base cyclization product (L)	0.87	0.53	0.1
2,4-Wing isobutyl ester (M)	0.94	1.0	0.1
Regioisomer (N)	1.05	1.0	0.1
Isomer #2 (O)	1.11	1.0	0.3
Di-monoacyl urea (P)	1.14	1.0	0.1
Isomer #4 (Q)	1.23	1.0	0.1
Isomer #1 (R)	1.32	1.0	0.1
Di-monoacyl valine urea (S)	1.62	1.0	0.1
2,4-Wing diacyl (T)	2.87	0.73	0.2
Triacyl impurity (U)	3.20	1.0	0.1
Any other individual impurity	—	1.0	0.1

SPECIFIC TESTS

- **WATER DETERMINATION**, *Method I* ⟨921⟩: NMT 0.5%, determined on 0.500 g
- **X-RAY DIFFRACTION** ⟨941⟩: The X-ray diffraction pattern conforms to that of USP Ritonavir RS, if used in a solid dosage form.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store between 5° and 30°.
- **USP REFERENCE STANDARDS** ⟨11⟩
USP Ritonavir RS
USP Ritonavir Related Compounds Mixture RS

Drug Product Monographs and General Chapters

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Metformin Hydrochloride Extended-Release Tablets

DEFINITION

Metformin Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

IDENTIFICATION

- The retention time of the major peak from the *Sample solution* corresponds to that from the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Buffer solution: 0.5 g/L of sodium heptanesulfonate and 0.5 g/L of sodium chloride in water. Prior to final dilution, adjust with 0.06 M phosphoric acid to a pH of 3.85.
Mobile phase: Acetonitrile and *Buffer solution* (1:9).
[NOTE—To improve the separation, the composition of acetonitrile and *Buffer solution* may be changed to 1:19, if necessary.]
Diluent: 1.25% solution of acetonitrile in water
Standard solution: (*L*/4000) mg/mL of USP Metformin Hydrochloride RS in *Diluent*, where *L* is the labeled quantity, in mg, of metformin hydrochloride in each Tablet
System suitability stock solution: 12.5 µg/mL of each of USP Metformin Related Compound B RS and USP Metformin Related Compound C RS in *Diluent*
System suitability solution: Dilute 0.5 mL of the *System suitability stock solution* with the *Standard solution* to 50 mL.
Sample stock solution: Finely powder NLT 10 Tablets. Transfer powder, equivalent to the average Tablet weight, to a homogenization vessel, and accurately add 500 mL of 10% acetonitrile solution. Alternately, homogenize and allow to soak until the sample is fully homogenized. [NOTE—A suggested homogenization sequence is as follows. Homogenize the sample using five pulses, each of 5 s, at about 20,000 rpm, and allow to soak for 2 min. Repeat these steps two additional times.]
Sample solution: Pass a portion of the *Sample stock solution* through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of filtrate. Transfer 25 mL of the filtrate to a 200-mL volumetric flask, and dilute with water to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 218 nm
Column: 3.9-mm × 30-cm; 10-µm packing L1
Temperature: 30°
Flow rate: 1 mL/min
Injection size: 10 µL
Run time: Until after the elution locus of metformin related compound C
System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times for metformin related compound B, metformin, and metformin related compound C are 0.86, 1.0, and 2.1–2.3. Metformin related compound C can have a variable retention time. The composition of the *Mobile phase* may be changed to 1:19, if it elutes at a relative retention time of less than 2.1.]
Suitability requirements
Resolution: NLT 1.5 between peaks due to metformin related compound B and metformin
Tailing factor: NLT 0.8 and NMT 2.0 for the metformin peak
Relative standard deviation: NMT 1.5% for the metformin peak and NMT 10% for each of the peaks due to metformin related compound B and metformin related compound C
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of $C_4H_{11}N_5 \cdot HCl$ in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Metformin Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of metformin hydrochloride in the *Sample solution*
Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

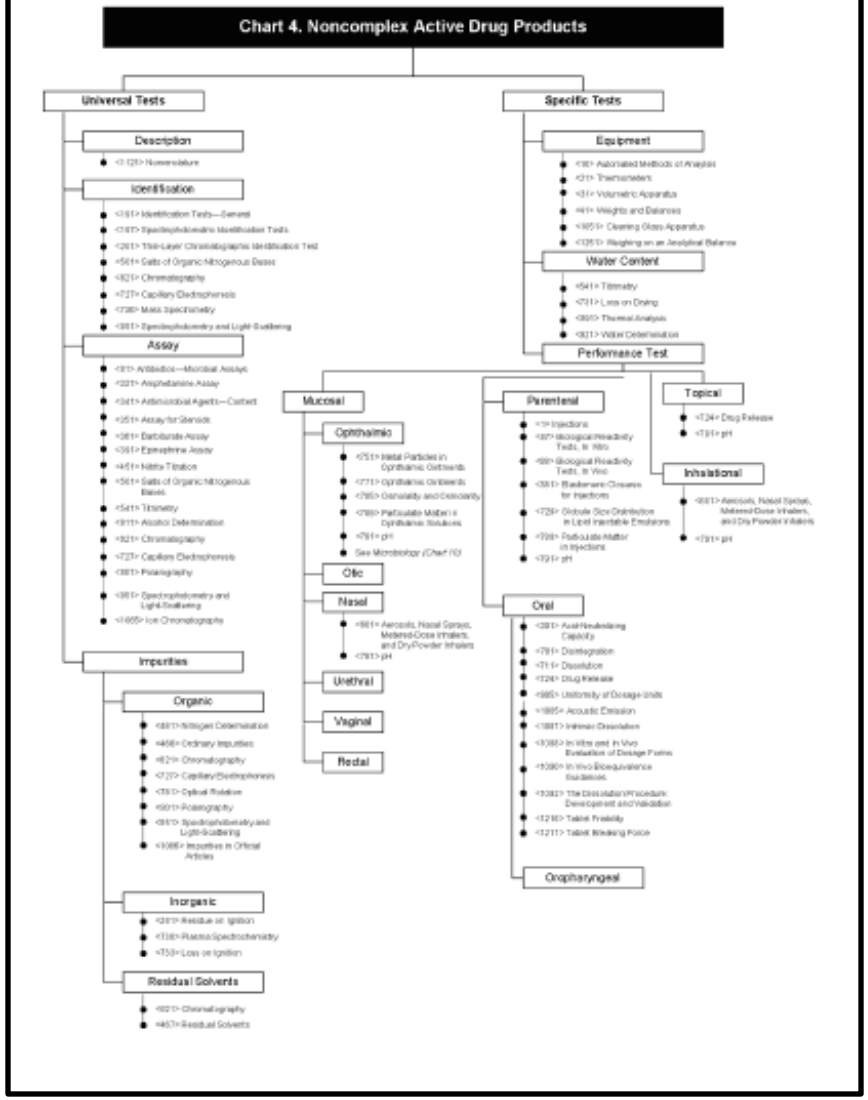
Test 1
Medium: pH 6.8 phosphate buffer (6.8 g of monobasic potassium phosphate in 1000 mL of water; adjust with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.1); 1000 mL.
Apparatus 1: 100 rpm for Tablets labeled to contain 750 mg
Apparatus 2: 100 rpm for Tablets labeled to contain 500 mg
Times: 1, 3, and 10 h
Detector: UV 232 nm
Standard solution: USP Metformin Hydrochloride RS in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable hydrophilic polyethylene filter of 0.45-µm pore size. Dilute, if necessary, with *Medium* to a concentration similar to the *Standard solution*.
Analysis: Calculate the percentage of $C_4H_{11}N_5 \cdot HCl$ released at each time point:

$$\text{Result} = [(A_U/A_S) \times C_S \times (V - V_S) + (C_{60} \times V_S) + (C_{180} \times V_S)] \times 100/L$$

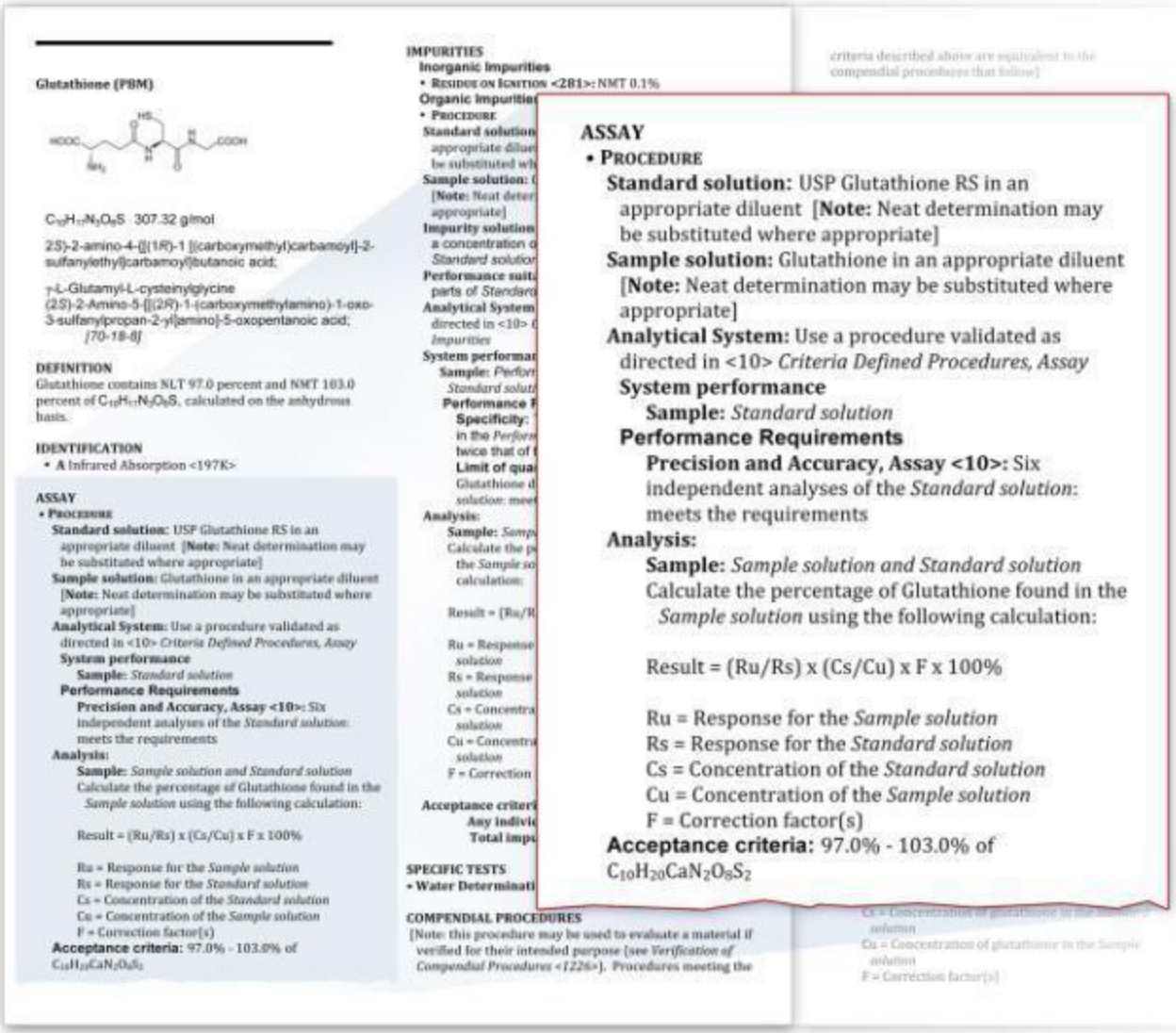
A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
V = initial volume of *Medium* in the vessel (mL)
V_S = volume withdrawn from the vessel for previous samplings (mL)
C_{60} = concentration of metformin hydrochloride in the *Medium* determined at 1 h (mg/mL)
C_{180} = concentration of metformin hydrochloride in the *Medium* determined at 3 h (mg/mL)
L = Tablet label claim (mg)
Tolerances: The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (h)	Amount Dissolved, 500-mg Tablet	Amount Dissolved, 750-mg Tablet
1	20%–40%	27%–47%
3	45%–65%	49%–69%
10	NLT 85%	NLT 85%

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: Prepare as directed for *Test 1*; 1000 mL.
Apparatus 2: 100 rpm
Times: 1, 2, 6, and 10 h
Detector: UV 232 nm
Standard solution: USP Metformin Hydrochloride RS in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable polyethylene filter of 0.45-µm pore size.



Glutathione Example: Assay



Glutathione (PBM)

$C_{10}H_{17}N_3O_6S$ 307.32 g/mol

2*S*)-2-amino-4-{[(1*R*)-1-[(carboxymethyl)carbamoyl]-2-sulfanylethyl]carbamoyl}butanoic acid;

γ-L-Glutamyl-L-cysteinylglycine
(2*S*)-2-Amino-5-{[(2*R*)-1-(carboxymethylamino)-1-oxo-3-sulfanylpropan-2-yl]amino}-5-oxopentanoic acid;
[70-18-8]

DEFINITION
Glutathione contains NLT 97.0 percent and NMT 103.0 percent of $C_{10}H_{17}N_3O_6S$, calculated on the anhydrous basis.

IDENTIFICATION
• **A** Infrared Absorption <197K>

ASSAY
• **Procedure**
Standard solution: USP Glutathione RS in an appropriate diluent [**Note:** Neat determination may be substituted where appropriate]
Sample solution: Glutathione in an appropriate diluent [**Note:** Neat determination may be substituted where appropriate]
Analytical System: Use a procedure validated as directed in <10> *Criteria Defined Procedures, Assay*
System performance
Sample: *Standard solution*
Performance Requirements
Precision and Accuracy, Assay <10>: Six independent analyses of the *Standard solution*: meets the requirements
Analysis:
Sample: *Sample solution and Standard solution*
Calculate the percentage of Glutathione found in the *Sample solution* using the following calculation:

Result = (Ru/Rs) x (Cs/Cu) x F x 100%

Ru = Response for the *Sample solution*
Rs = Response for the *Standard solution*
Cs = Concentration of the *Standard solution*
Cu = Concentration of the *Sample solution*
F = Correction factor(s)
Acceptance criteria: 97.0% - 103.0% of $C_{10}H_{20}CaN_2O_8S_2$

IMPURITIES
Inorganic Impurities
• **Residue on Ignition** <281>: NMT 0.1%
Organic Impurities
• **Procedure**

SPECIFIC TESTS
• **Water Determination**

COMPENDIAL PROCEDURES
[Note: this procedure may be used to evaluate a material if verified for their intended purpose (see *Verification of Compendial Procedures* <1226>). Procedures meeting the

USP Reference Standards

- USP Offers More than 2,500 Reference Standards for Use in the Full Range of *USP–NF* Tests and Procedures
- USP Reference Standards Have Been Rigorously Tested by USP, Industry, and Government Scientists

Productivity:

- 728 New Reference Standards
- 931 Replacement/Continuing Reference Standards

Take Aways

- FDA does BA/BE
- USP does Performance test (with PVT and reference materials)
- Other countries—Performance test may not signal BA/BE (continuing equivalence)
- BA/BE needs GMPs and careful clinical/in vitro studies to establish/document
- In countries without GMPs and BA/BE requirements, USP Performance test signals performance but may not signal BA/BE

Topics

- Overview
- BCS
- The USP Monograph: Pharmaceutical Equivalence and Bioequivalence
- **A National/Global RLD**

US Reference Listed Drug

Most important selection criteria in order of preference:

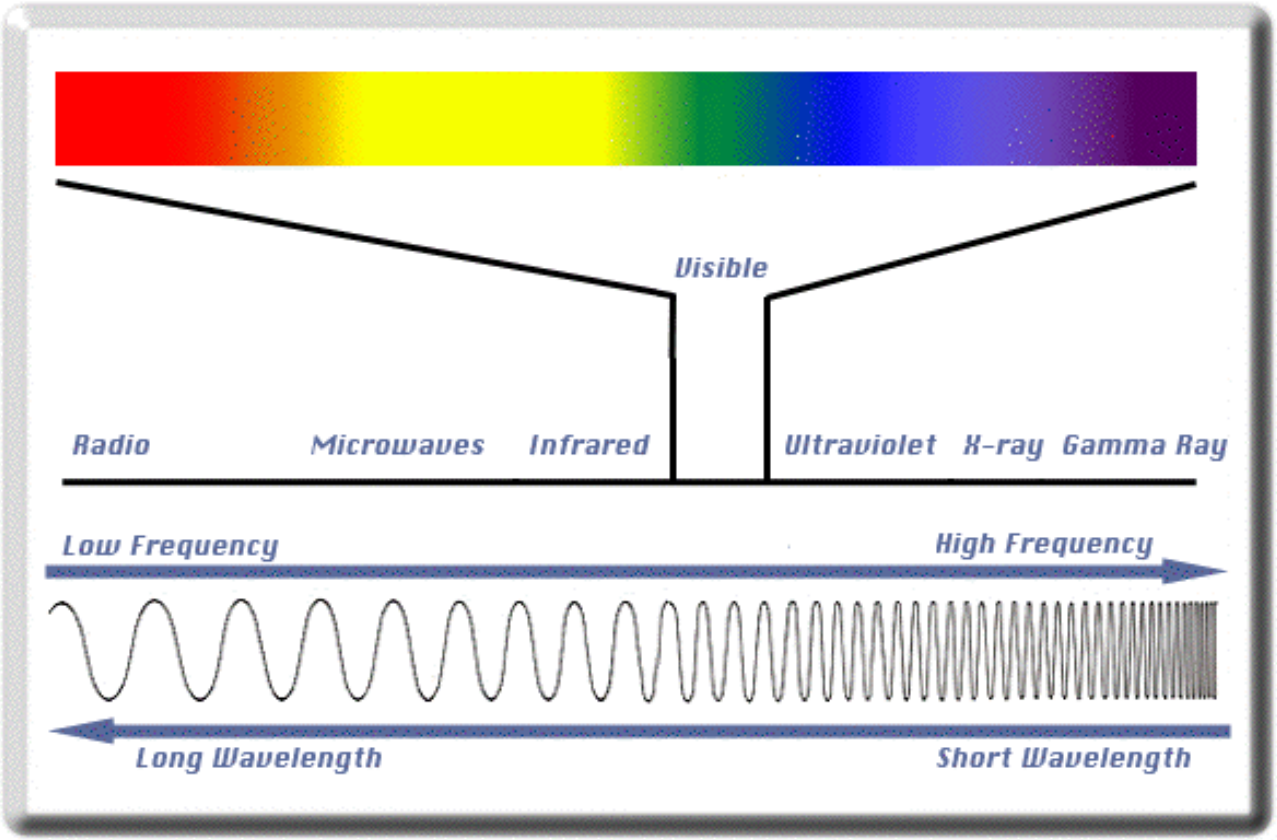
- USP RLD
  - Defined in Orange Book
  - Typically Innovator
- WHO
  - Approval in ICH and associated countries
  - Pre-qualified by WHO
  - Extensive, documented use in clinical trials
  - Reported in peer-reviewed scientific journals
  - Long and unproblematic post-market surveillance.

Would/Could USP Do This?

- Obtain from US market
- Five years in advance of patent expiry
- Study in USP laboratories—characterization and dissolution in three media
- Prepare and release as Certified Drug Product Reference Material—packages for national/international BE studies
- Could lead to only one BE study for many markets
- Pros/Cons: to be considered (e.g., what about non-US national comparator pharmaceutical product)

Additional Payoff to Global “RLD”

Every pharmaceutical ingredient or formulated product, together with its packaging materials, has unique characteristics or **‘fingerprints’** that can be probed using various regions of the electromagnetic spectrum.



USP SPECTRAL LIBRARY
CONCEPT DESIGN
04-07-2010

SMARTCLIENT®

Web Access

ORACLE BASED

Data Historians

Enterprise Systems (SAP, MES, LIMS...)

Analyzer Control systems

Process Control

Visualization

Spectral, Computation, Preprocessing, Analysis (PLS/PCA)

Information Management

DATABASE

- GRAPHICS
- TREND and CHARTS
- EXCEL INTERFACE
- REPORTS

3rd Party

- ERP
- MES
- PLC
- DCS

Raw Data

- Spectra
- Histograms
- Chromatograms
- Calibrations
- etc.

Date can be captured, processed and stored in a regulatory compliant manner

OPC (Open Process Control)

Analyzer Controllers

- X-Ray
- IR/NIR
- RAMAN
- UV/VIS
- MASS SPEC
- HPLC
- PARTICLE SIZE
- IMAGE

Take Aways

- Manufacturers
  - QbD undergirds continuing equivalence
- FDA and USP
  - Create standards that assure continuing equivalence (law, regulations, guidances, compendial monographs)
- Monitoring is key to success
  - Process drift
  - Periodic studies for PE and BE
  - BCS and USP monographs are low cost ways to monitor
  - Change brings in requirement for further study/FDA involvement
- Reference Listing Drug
  - The link to clinical trial material and documentation of safety and efficacy

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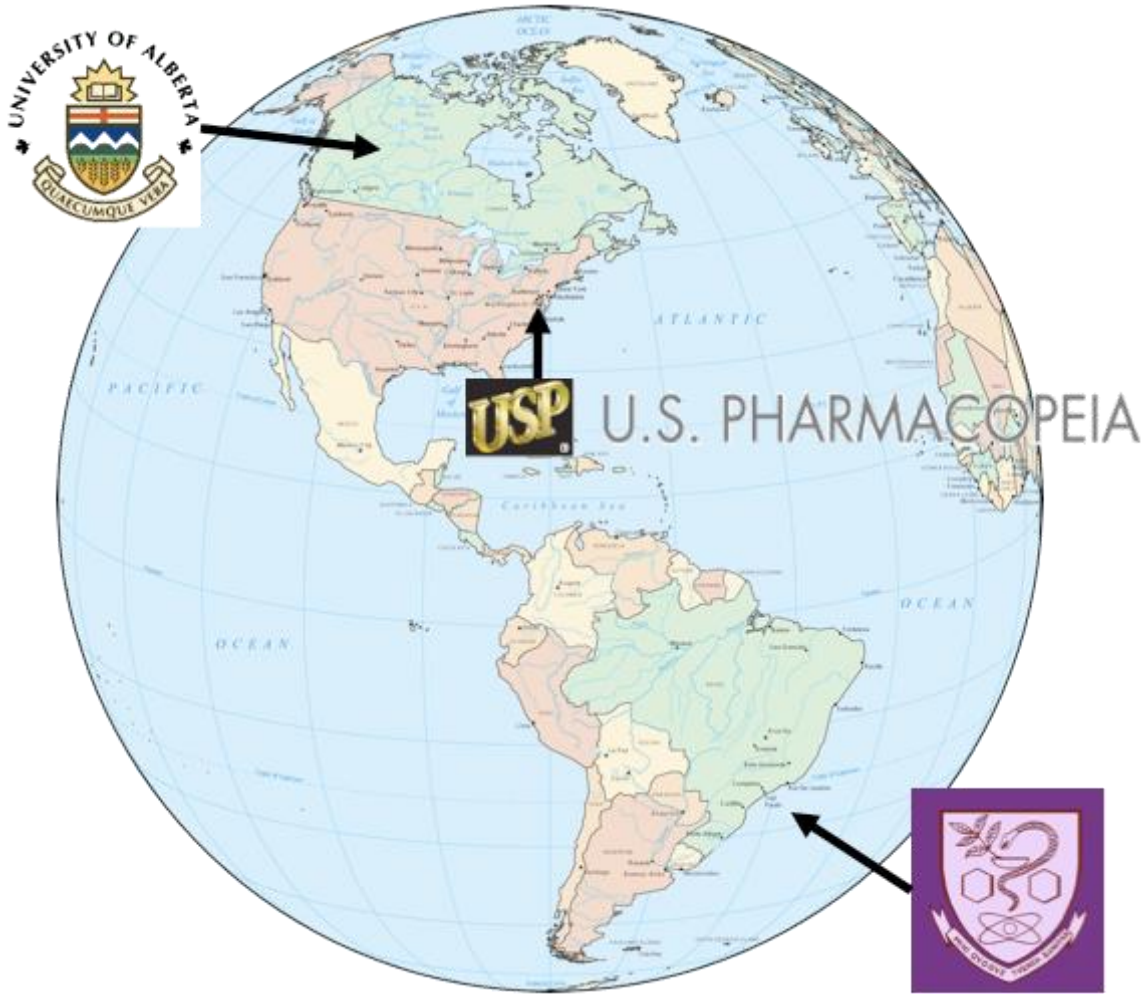

USP Across the Globe

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

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The Standard of Quality℠

Thank You