Merck KGaA
Darmstadt, Germany

Pharmaceutical Secondary Standards: A COA Built for Strong Lab Foundations

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Advanced Analytical, Life Sciences,
August 5., 2020

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Agenda

1. **Hierarchy of Certified Reference Materials**
2. **Traceability of Secondary Standards as Working Standards**
3. **Pharmaceutical Standard COA and Characterization**
4. **Impurity Portfolios and Complex Mixture CRMs**

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Dr. Ilona Matus

- Current Role: Analytical Sciences Liaison, Darmstadt, Germany
- >14 years with Merck
- >10 years in Pharma R&D
- Master’s degree and promotion in Pharmaceutical Chemistry from the University of Budapest, Hungary

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01

Hierarchy of Certified Reference Materials

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Standards and Reference Materials

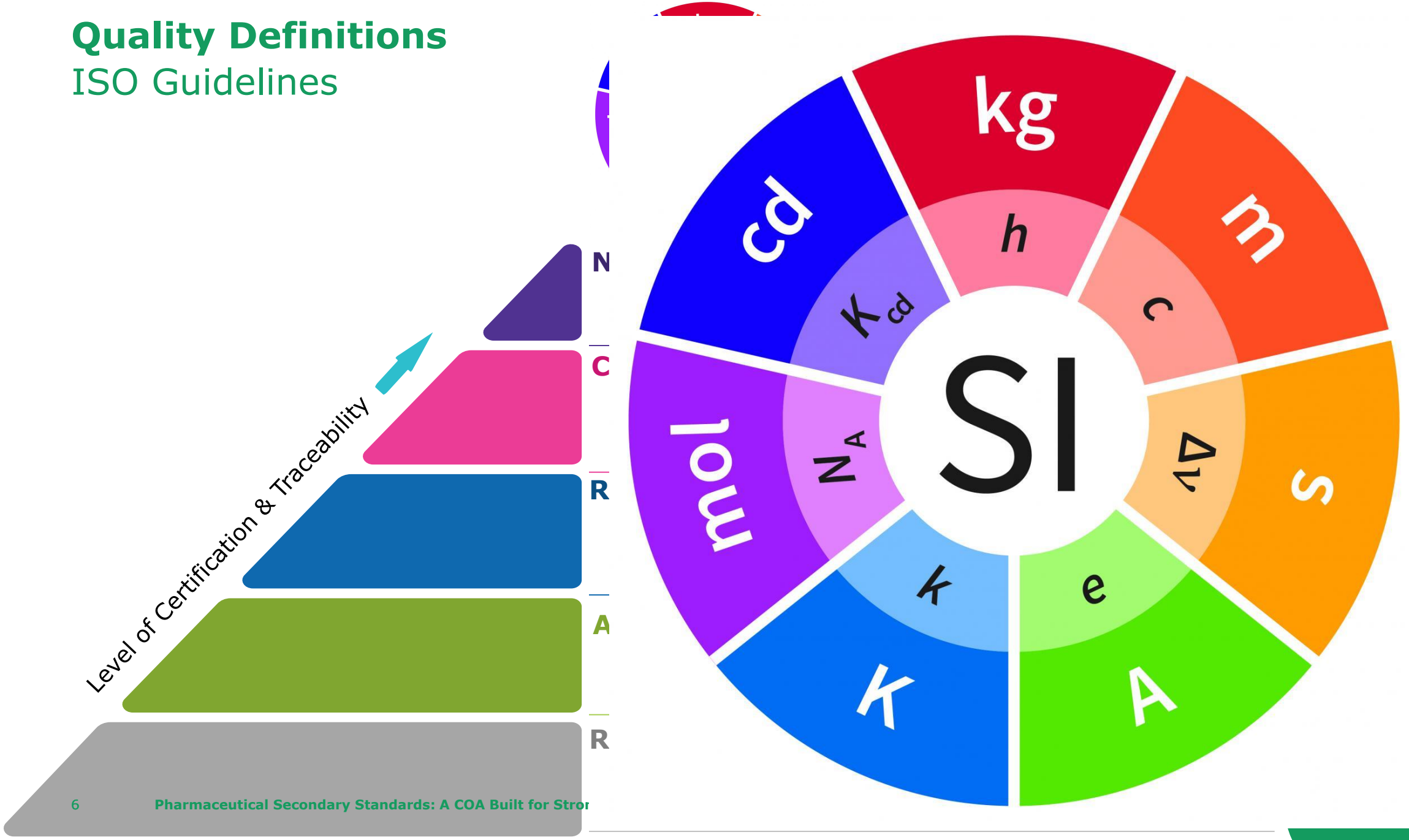
Comparison of a ***sample*** with something **KNOWN** = **Reference Material**

Qualitative
identification
presence or absence
physical properties
-screening, id tests

Quantitative
amount, potency
Cut off
-assays, potency, limit tests

What does testing mean? – Safety, Integrity, Strength, Purity, Quality!

Quality Definitions
ISO Guidelines



USP) Std

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Types of Reference Materials – Authorized Standards

Types of Primary Standards

Primary Measurement Standard

SRM/NMI

A primary standard in metrology is a standard that is designated or widely acknowledged as having the **highest metrological qualities and whose value is accepted without reference to other standards** of the same quantity, within a specified context.*

Certificates provide the Property Value, Associated Uncertainty, and Metrological Traceability

Compendial Primary Standard

USP/EP/BP

In a Pharmaceutical setting, a primary or compendial standard is one having the **highest metrological qualities whose value is accepted without reference (comparison) to another standard**

Certificates proved a content

Quality Definitions
ISO Guidelines

National Metrology (eg. NIST, NRC) or Compendial (eg. USP) Std

- Issued by an authorized body
- Considered to provide the highest level of accuracy and traceability

The validity of using Primary Standards will never be questioned

- Primary Standards are the authority, their value is accepted without reference to other standards
- Immediately recognized by auditors
- Can be used to qualify other standards

Primary Standards are designed to be used with the monograph

- Perform exactly as expected since they were designed according to the monograph
- Can be used in any analytical or laboratory use as specified by compendia

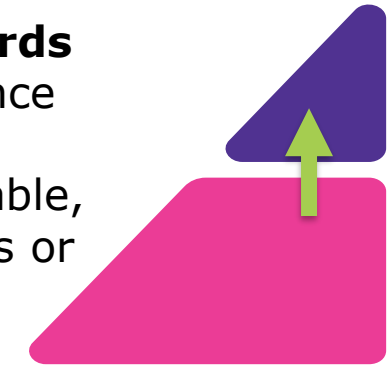
Primary Standards may be what is required for your specific application

- Use of primary standards often written into internal SOPs - GMP

Quality Definitions

Traceable Certified Reference Materials

Secondary Standards are Certified Reference Materials that are **traceable**, as available, to primary standards or to the SI.



National Metrology (eg. NIST, NRC) or Compendial (eg. USP) Std

- Issued by an authorized body
- Considered to provide the highest level of accuracy and traceability

Certified Reference Material (CRM) (ISO 17034, 17025)

- Considered to provide the highest level of accuracy, uncertainty, and traceability to an SI unit of measurement
- Manufactured by an accredited Reference Material Producer

Primary or Secondary Standards are for use in analytical or laboratory applications as specified in compendia

These analytical standards can be used for a variety of method verification practices including instrument qualification and calibration, analytical method validation, system suitability testing, assays and quality control checks.

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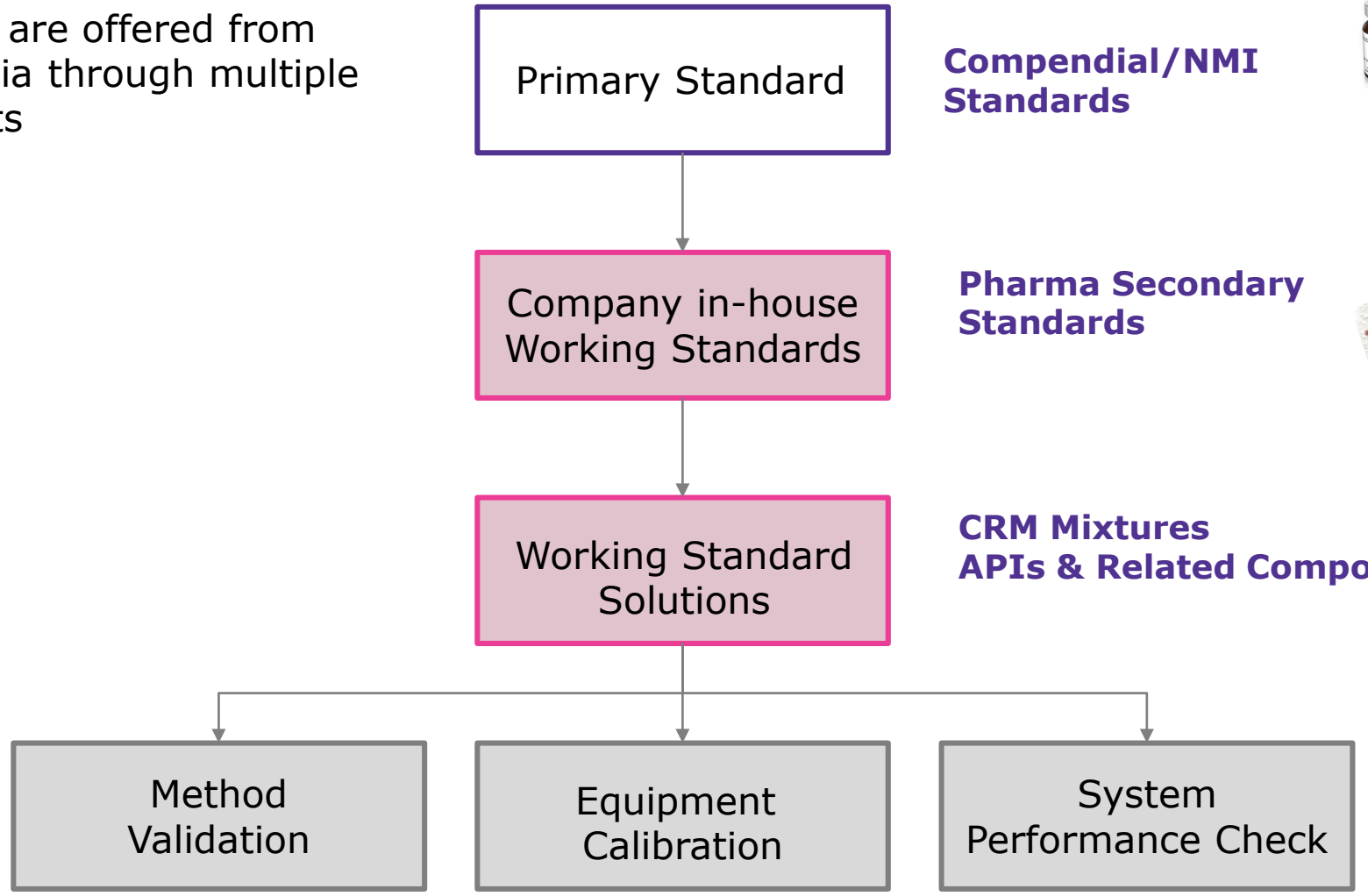
Secondary Standards

Use of Working Standard Solutions

Compendial standards are offered from different Pharmacopoeia through multiple distribution agreements



Compendial/NMI Standards

Pharma Secondary Standards

CRM Mixtures
APIs & Related Compounds

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Secondary Standards
Regulatory Recognition

(US)FDA: Guidance for Industry; Analytical Procedures and Methods Validation, August 2000:

"**A reference standard (i.e., primary standard) may be obtained from the USP/NF** or other official sources (e.g., CBER, 21 CFR 610.0). **A working standard (i.e., in-house or secondary standard)** is a standard that is **qualified against** and used instead of **the reference standard**."

United States Pharmacopeia, General Chapter <1010>:

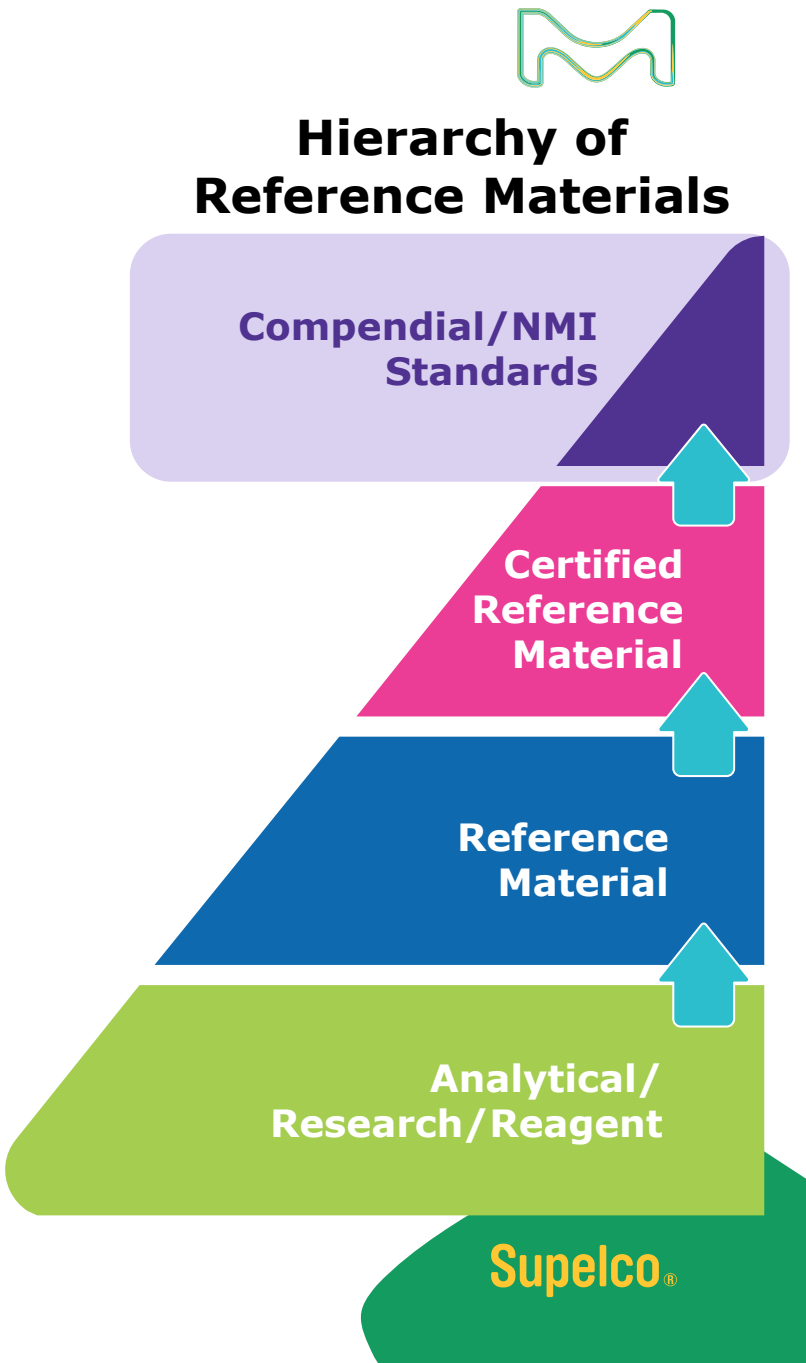
Use of Reference Standards: "Users of *USP* and *NF* apply a range of strategies and practices to assure articles achieve and maintain conformance with compendial requirements, including when and if tested. Such strategies and practices can include the **use of secondary standards traceable to the USP Reference Standard, to supplement or support** any testing undertaken for the purpose of conclusively demonstrating **conformance to applicable compendial standards**."

European Pharmacopoeia, **Chapter 5.12:**

"Secondary standard: **A standard established by comparison with a primary standard**. A secondary standard may be used for routine quality control purposes for any of the uses described above for primary standards provided that it is established **with reference to the primary standard**."

The Hierarchy of Reference Materials – What's the difference?

Parameters	NMI Standard	Compendial Standard	CRM	RM	Analytical/ Research/Reagent
Purity	✓	✓	✓	✓	✓
Identity	✓	✓	✓	✓	✓
Content	✓	✓	✓	✓	maybe
Stability	✓	✓	✓	✓	maybe
Homogeneity	✓	✓	✓	✓	
Uncertainty	✓		✓		
Traceability	✓		✓	✓	
Type	Primary Measurement Standard or Primary Standard (Pharma)		Primary or Secondary Standard		



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Traceability of Secondary Standards as Working Standards

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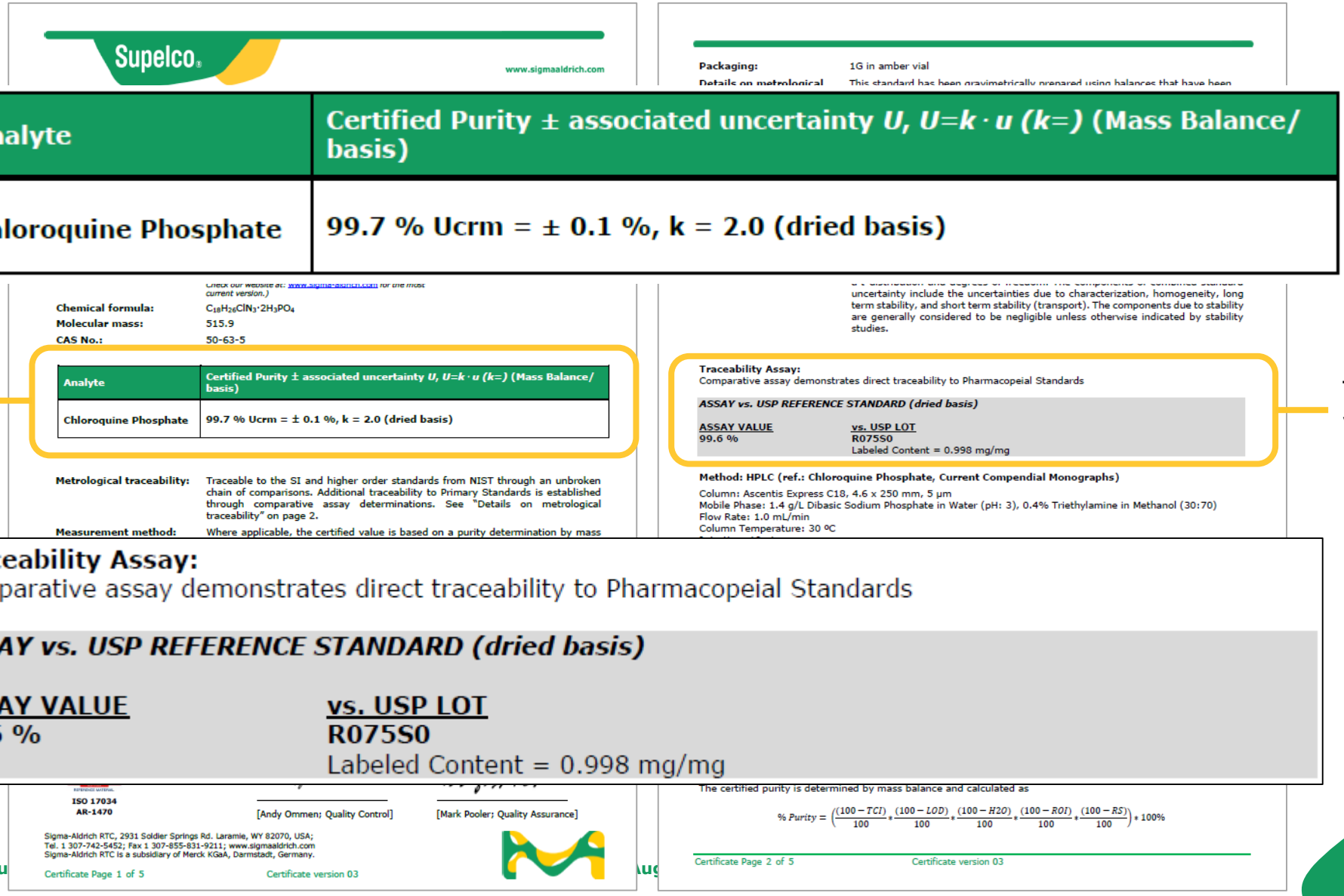
Secondary Pharmaceutical Standards

Comprehensive COA



Analyte	Certified Purity ± associated uncertainty *U*, *U*=*k* · *u* (*k*=) (Mass Balance/ basis)
Chloroquine Phosphate	99.7 % Ucrm = ± 0.1 %, k = 2.0 (dried basis)

Certified Value

Traceable Assay Values

Detailed 5-7 page COA describes analytical parameters us in certified ma balance value and assay valu

Traceability Assay:
Comparative assay demonstrates direct traceability to Pharmacopeial Standards

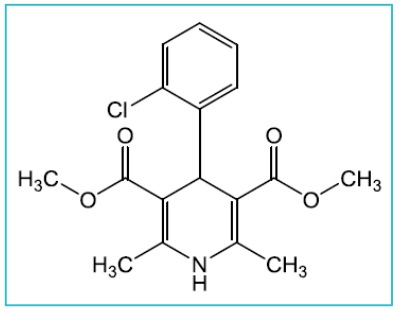
ASSAY vs. USP REFERENCE STANDARD (dried basis)

ASSAY VALUE	vs. USP LOT
99.6 %	R075S0
	Labeled Content = 0.998 mg/mg

Secondary Pharmaceutical Standards

Traceability – Two Ways

Certified Purity
99.0 ± 0.8% (k=2) Mass Balance / as is basis



PHR2052
Amlodipine Related Compound C
(Amlodipine Impurity G)

Traceability Assay
99.4% vs. **USP Lot F012R0** (0.99 mg/mg) as is basis
99.4% vs. **EP CRS Batch 3.0** (*100.2%) as is basis

*The assigned content of the EP CRS was determined by assay against USP Reference Standard, as there was no labeled content on the EP Standard.

USP REFERENCE STANDARD

AMLODIPINE RELATED COMPOUND C 25 mg

(Dimethyl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate)

Name	Amlodipine impurity G CRS
Catalogue code	Y0001070
Batch number*	3
Assigned value	n/a

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03

Pharmaceutical Standard COA and Characterization

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Secondary Pharmaceutical Standards

Qualification of Standards

Secondary Standards

Secondary Standard Qualification

- Compendial monographs are followed – analyses called out in monograph are performed
- If no compendial monograph is available, then methods may be developed from API monograph and validated

IDENTITY	
• **NMR** • **FTIR**	• **GCMS, LCMS** • **Additional Techniques** (Optical Rotation, Melting/Boiling Point, Density, Refractive Index)
PURITY / POTENCY	

• **Mass Balance**
  • Uses multiple techniques for chromatographic purity and residuals
• **Titrations**
  • Assignment of contact through primary standard
	• **Assays – Chromatographic**
	  • Traceable to compendial/primary standard
	  • Sometimes availability of primary reference materials are limited

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Secondary Pharmaceutical Standards

Mass Balance

The certified purity is determined by mass balance and calculated as:

$$\%\ \boldsymbol{Purity} = (\mathbf{100} - \boldsymbol{ROI} - \boldsymbol{LOD} - \boldsymbol{H_2O} - \boldsymbol{RS}) * (\frac{\mathbf{100} - \boldsymbol{TCI}}{\mathbf{100}})$$

Contributions from:

ROI = Residue on Ignition

LOD = Loss on Drying

H_2O = Water content determined by Karl Fischer

RS = Residual Solvents

TCI = Total Chromatographic Impurities

Secondary Pharmaceutical Standards
Mass Balance - Residue

$$\%\ \boldsymbol{Purity} = (\mathbf{100 - ROI - LOD - H_2O - RS}) * (\frac{\mathbf{100 - \mathit{TCI}}}{\mathbf{100}})$$

Certified Purity

99.8 ± 0.2% (k=2)
Mass Balance / as is basis

Excerpt from PHR2478 Adrenalone HCl

RESIDUE ANALYSIS

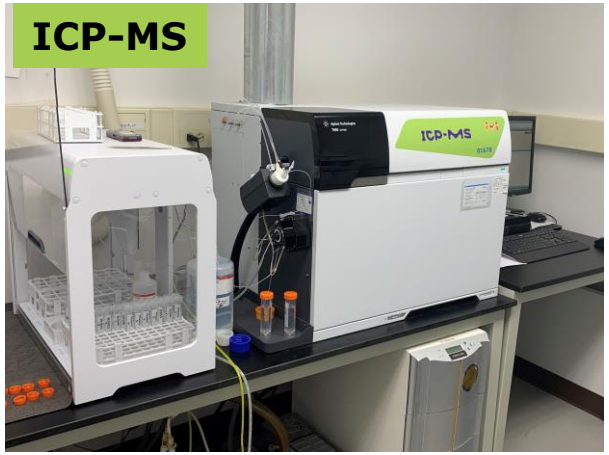
Method: Sulfated Ash
Sample Size: ~ 40 mg

Mean of three measurements, Residue = **0.046%**

ROI contribution = 0.046%

Residue on Ignition

ICP-MS



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Secondary Pharmaceutical Standards
Mass Balance - Water

$$\%\ \boldsymbol{Purity} = (\mathbf{100 - ROI - LOD - H_2O - RS}) * (\frac{\mathbf{100 - \mathit{TCI}}}{\mathbf{100}})$$

Excerpt from PHR2478 Adrenalone HCl

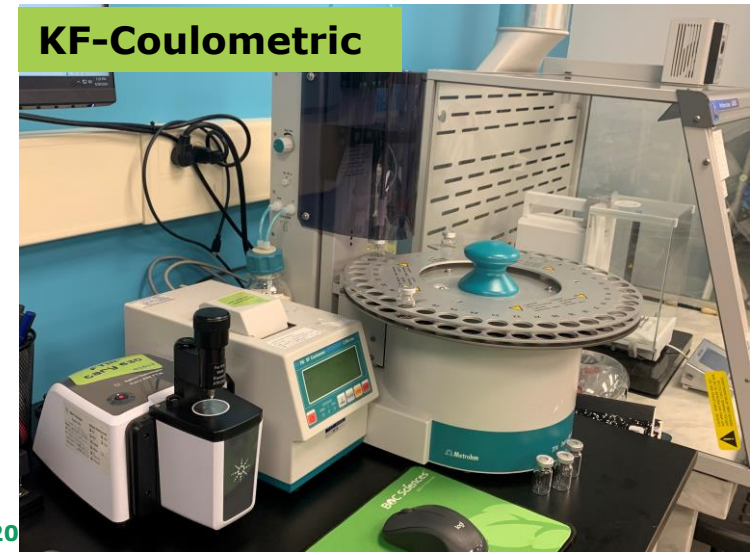
WATER DETERMINATION

Method: Karl Fischer

Mean of three measurements, Water Content = **0.0097%**

Certified Purity
99.8 ± 0.2% (k=2) Mass Balance / as is basis

H_2O contribution = 0.0097%



Secondary Pharmaceutical Standards
Mass Balance – Residual Solvent

$$\%\ \boldsymbol{Purity} = (\mathbf{100} - \mathbf{ROI} - \mathbf{LOD} - \mathbf{H_2O} - \mathbf{RS}) * (\frac{\mathbf{100} - \boldsymbol{TCI}}{\mathbf{100}})$$

Certified Purity
99.8 ± 0.2% (k=2) Mass Balance / as is basis

Excerpt from PHR2478 Adrenalone HCl

RESIDUAL SOLVENTS
Method: GC-MS Headspace (ref.: Adapted from Residual Solvents USP <467>)
Column: SPB-624
Carrier gas: He
Flow: 1.2 mL/min
Split Ratio: 1:5
Injection/Temperature: 1 mL/220 °C
Temperature Program: 40 °C for 5 min, 8 °C/min to 200 °C, hold 5 min

Solvents Detected: **None**

Residual Solvent contribution = 0%

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Secondary Pharmaceutical Standards
Mass Balance – Chromatographic Impurity

$$\%\ \boldsymbol{Purity} = (\mathbf{100 - ROI - LOD - H_2O - RS}) * (\frac{\mathbf{100 - \mathit{TCI}}}{\mathbf{100}})$$

Certified Purity
99.8 ± 0.2% (k=2) Mass Balance / as is basis

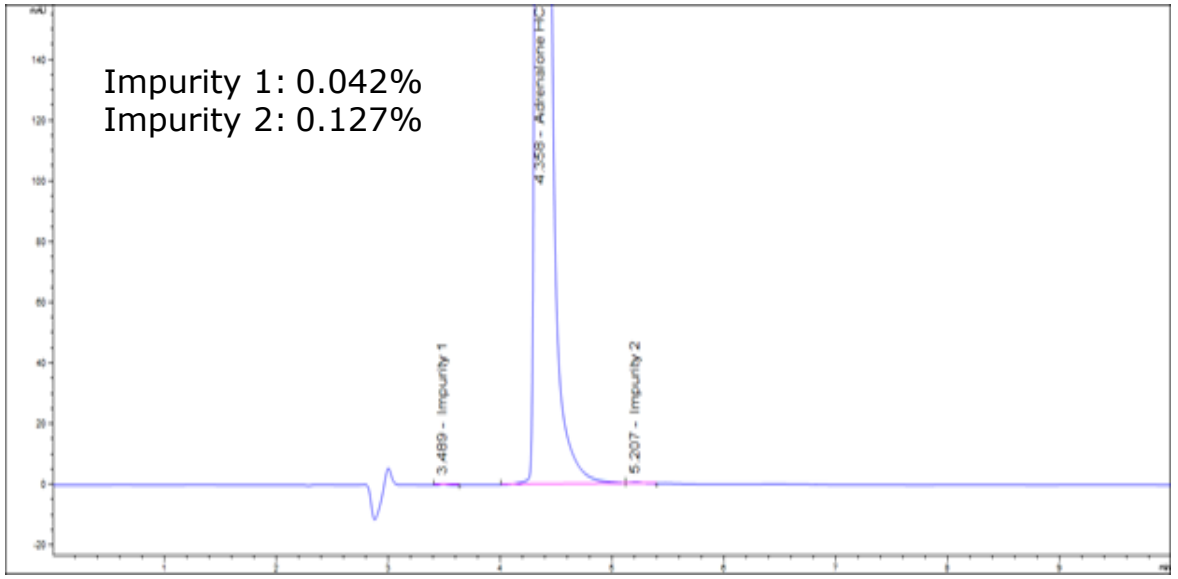
Excerpt from PHR2478 Adrenalone HCl

TCI contribution = 0.169%

TOTAL CHROMATOGRAPHIC IMPURITIES

Method: HPLC
Column: Ascentis Express C18, 150 mm x 4.6mm, 5µm particle size
Mobile Phase A: 0.1% TFA in Water
Mobile Phase B: 0.1% TFA in Acetonitrile
Mobile Phase Ratio: 97:3 (A:B)
Flow Rate: 0.5 mL/min
Column Temperature: 35 °C
Injection Volume: 5 µL
Detector: UV/DAD/VWD, Wavelength: 230 nm

Total Chromatographic Impurities: **0.169%**



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Secondary Pharmaceutical Standards
Purity Assignment

$$\%\ \boldsymbol{Purity} = (\mathbf{100} - \mathbf{ROI} - \mathbf{LOD} - \mathbf{H_2O} - \mathbf{RS}) * (\frac{\mathbf{100} - \boldsymbol{TCI}}{\mathbf{100}})$$

Contributions for PHR2478 Adrenalone HCl

ROI contribution = 0.046%
LOD contribution = 0%
H_2O contribution = 0.0097%
RS contribution = 0%
TCI contribution = 0.169%

$$\%\ \boldsymbol{Purity} = (\mathbf{100} - \mathbf{0.046} - \mathbf{0} - \mathbf{0.0097} - \mathbf{0}) * (\frac{\mathbf{100} - \mathbf{0.169}}{\mathbf{100}})$$

$$\%\ \boldsymbol{Purity} = \mathbf{99.8\%}$$

Certified Purity
99.8 ± 0.2% (k=2) Mass Balance / as is basis

Purity or Potency Value

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Secondary Pharmaceutical Standards
Expanded Uncertainty

Uncertainty Calculation takes into consideration the following sources of uncertainty:

$$u_{CRM} = [u_{char}^2 + u_{bb}^2 + u_{lts}^2 + u_{sts}^2]^{1/2}$$

$$u_{char} = \sqrt{\sum u_i(x_i)^2}$$

$$u_{bb} = \sqrt{MS_w / replicates} * \sqrt[4]{2 / Degrees\ of\ Freedom\ within\ groups} / k,\ k = 2$$

Certified Purity

99.8 ± 0.2% (k=2)
Mass Balance / as is basis

Expa
expa
ed with

Expanded Uncertainty

Excerpt from COA

Homogeneity was assessed in accordance with ISO Guide 35. Completed units were sampled using a random stratified sampling protocol. The results of chemical analysis were then compared by Single Factor Analysis of Variance (ANOVA). The uncertainty due to homogeneity was derived from the ANOVA. Heterogeneity was not detected under the conditions of the ANOVA.

Analytical method: HPLC

Sample size: 50 mg

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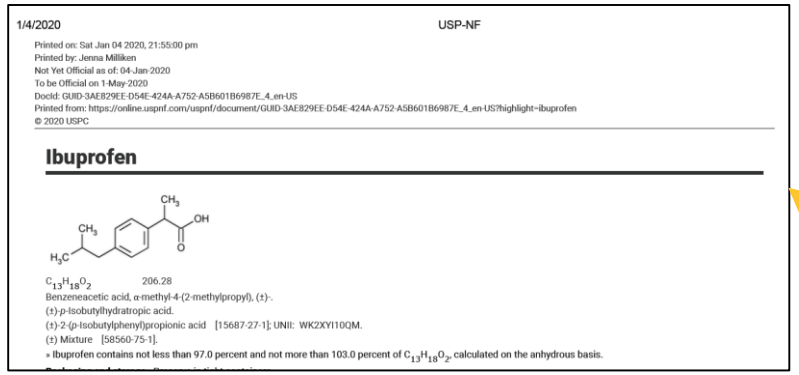
Secondary Pharmaceutical Standards

Traceablity to the Pharmacopoeia



1/4/2020 USP-NF

Printed on: Sat Jan 04 2020, 21:55:00 pm
Printed by: Jenna Milliken
Not Yet Official as of: 04-Jan-2020
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Ibuprofen

$C_{13}H_{18}O_2$ 206.28

Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-.
(±)-*p*-Isobutylhydratropic acid.
(±)-2-(*p*-Isobutylphenyl)propionic acid [15687-27-1]; UNII: WK2XY110QM.
(±) Mixture [58560-75-1].
» Ibuprofen contains not less than 97.0 percent and not more than 103.0 percent of $C_{13}H_{18}O_2$, calculated on the anhydrous basis.

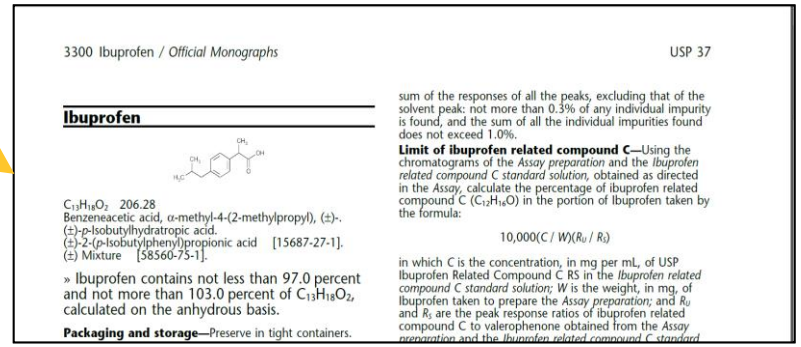
USP Monograph

USP Standards

Secondary Pharma Standards

EP Standards

BP Standards



3300 Ibuprofen / *Official Monographs* USP 37

Ibuprofen

$C_{13}H_{18}O_2$ 206.28
Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-.
(±)-*p*-Isobutylhydratropic acid.
(±)-2-(*p*-Isobutylphenyl)propionic acid [15687-27-1].
(±) Mixture [58560-75-1].

» Ibuprofen contains not less than 97.0 percent and not more than 103.0 percent of $C_{13}H_{18}O_2$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers.

sum of the responses of all the peaks, excluding that of the solvent peak: not more than 0.3% of any individual impurity is found, and the sum of all the individual impurities found does not exceed 1.0%.

Limit of ibuprofen related compound C—Using the chromatograms of the *Assay preparation* and the *Ibuprofen related compound C standard solution*, obtained as directed in the *Assay*, calculate the percentage of ibuprofen related compound C ($C_{12}H_{16}O$) in the portion of Ibuprofen taken by the formula:

$$10{,}000(C / W)(R_U / R_S)$$

in which *C* is the concentration, in mg per mL, of USP Ibuprofen Related Compound C RS in the *Ibuprofen related compound C standard solution*; *W* is the weight, in mg, of Ibuprofen taken to prepare the *Assay preparation*; and R_U and R_S are the peak response ratios of ibuprofen related compound C to valerophenone obtained from the *Assay*

EP Monograph

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Secondary Pharmaceutical Standards
Traceable

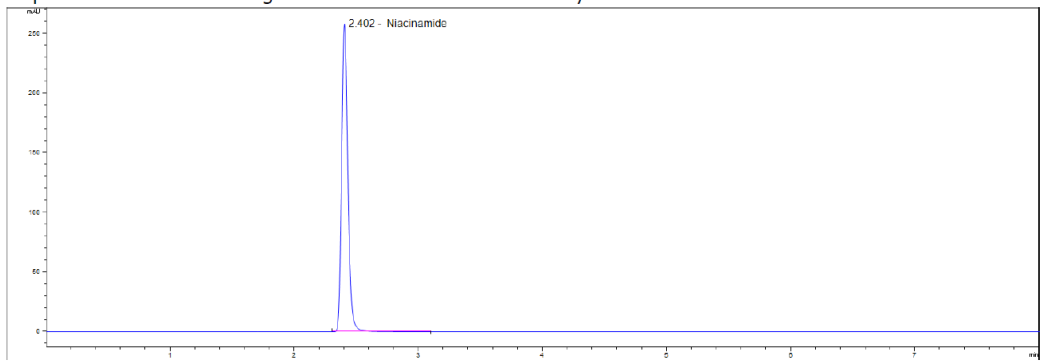
- Methods are referenced to the compendial monograph and analytical conditions are used
- Pharmacopeial lots and content of Primary Standards are provided
- When new lots are released by the pharmacopeia, Secondary Standards are recertified against the new Primary Standard, and the updated COA is available online.

Traceability Assay
99.4% vs. **USP Lot O0L486** (0.999 mg/mg) as is basis
99.6% vs. **EP CRS Batch 1.7** (*99.6%) as is basis
99.8% vs. **BP CRS Batch 2719** (99.8%) as is basis

*The assigned content of the EP CRS was determined by assay against USP and BP Reference Standard, as there was no labeled content on the EP Standard.

Excerpt from PHR1033 Niacinamide COA

Representative Chromatogram from Lot: LRAC1697 Analysis



Method: HPLC (ref.: Niacinamide, Current Compendial Monographs)

Column: Ascentis Express C18, 4.6 x 250 mm, 5 µm

Mobile Phase: 1 g/L Sodium 1-Heptanesulfonic acid in Water: Methanol; (70:30)

Flow: 1.0 mL/min

Column Temperature: 40 °C

Injection: 5 µL

Detector: 254 nm

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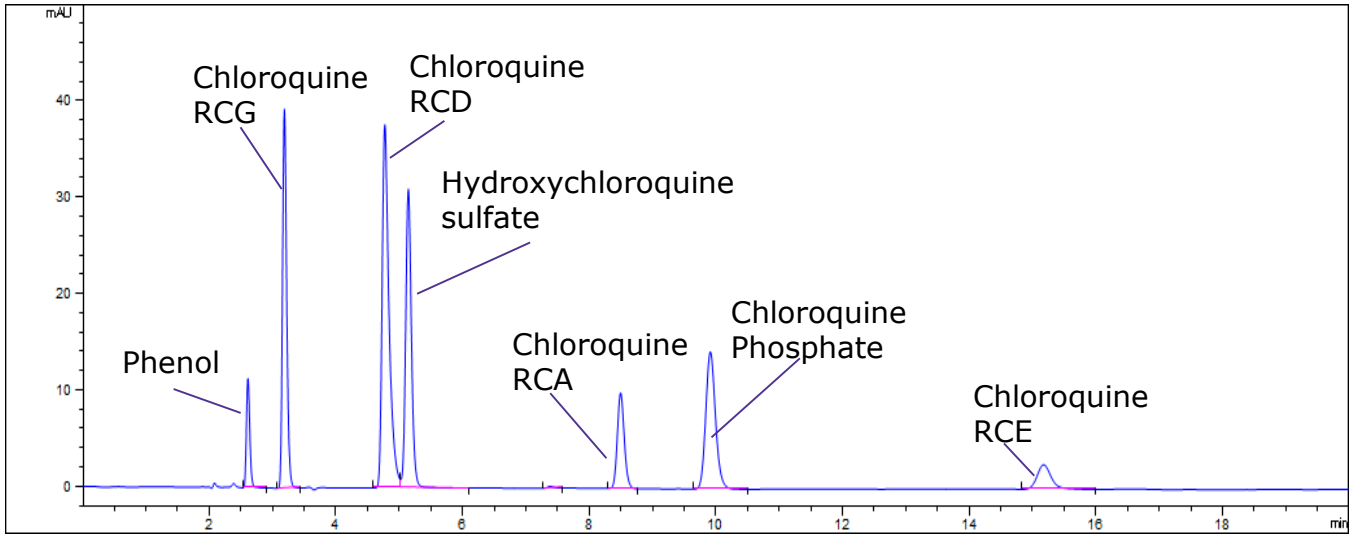
Secondary Pharmaceutical Standards

Assignment of Compendial Standards by Current Compendial Monograph

Chloroquine Phosphate, PHR1258, System Suitability, per USP monograph



When monographs are available, pharma secondary standards are qualified using the compendial monograph methods and held to the requirements of that method.

Excerpts from USP current compendial monograph
Chloroquine Phosphate

System suitability solution: 2.0 µg/mL each of USP Chloroquine Phosphate RS, USP Phenol RS, USP Hydroxychloroquine Sulfate RS, USP Chloroquine Related Compound A RS, USP Chloroquine Related Compound D RS, USP Chloroquine Related Compound E RS, and USP Chloroquine Related Compound G RS in *Mobile phase*

System suitability

Sample: *System suitability solution*

[NOTE— See *Table 1* for the corresponding relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between chloroquine and chloroquine related compound A and NLT 2 between adjacent impurities

Tailing factor: NMT 2.0 for peaks corresponding to chloroquine phosphate, phenol, hydroxychloroquine sulfate, chloroquine related compound A, chloroquine related compound D, chloroquine related compound E, and chloroquine related compound G

Relative standard deviation: NMT 5.0% for chloroquine phosphate, phenol, hydroxychloroquine sulfate, chloroquine related compound A, chloroquine related compound D, chloroquine related compound E, and chloroquine related compound G

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Secondary Pharmaceutical Standards
Additional Compendial Assignments

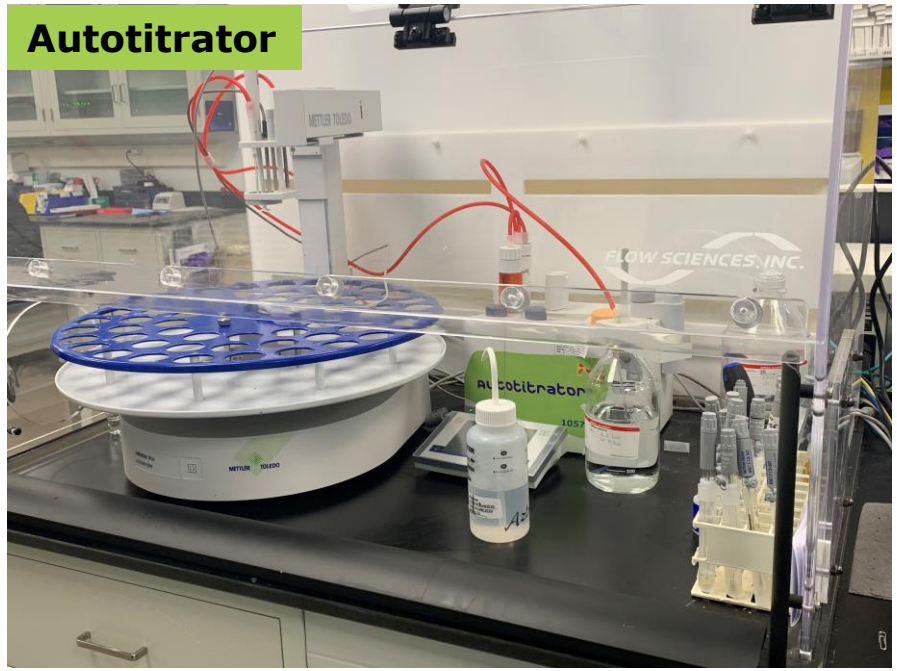
Content can be assigned by Titration

Excerpt from PHR2618 Sodium Acetate Trihydrate COA

ASSAY BY TITRATION

Method: Titrated by 0.1 N Perchloric acid

Mean of nine measurements: **99.6 %** U_{crm} = ± 0.6 %, k = 2.0



Content can be assigned by UV-Vis

Excerpt from PHR1196 Nitrofurazone COA

METHOD: UV (ref.: Nitrofurazone, Current Compendial Monographs)

Solvent: Dimethylformamide, Water
Cell Path length: 1cm
Wavelength: 375nm

100.1% vs. **USP Lot R085G0** (Labeled Content 0.999 mg/mg)
99.95% vs. **EP Lot 2.0** (Labeled Content 0.999 mg/mg)

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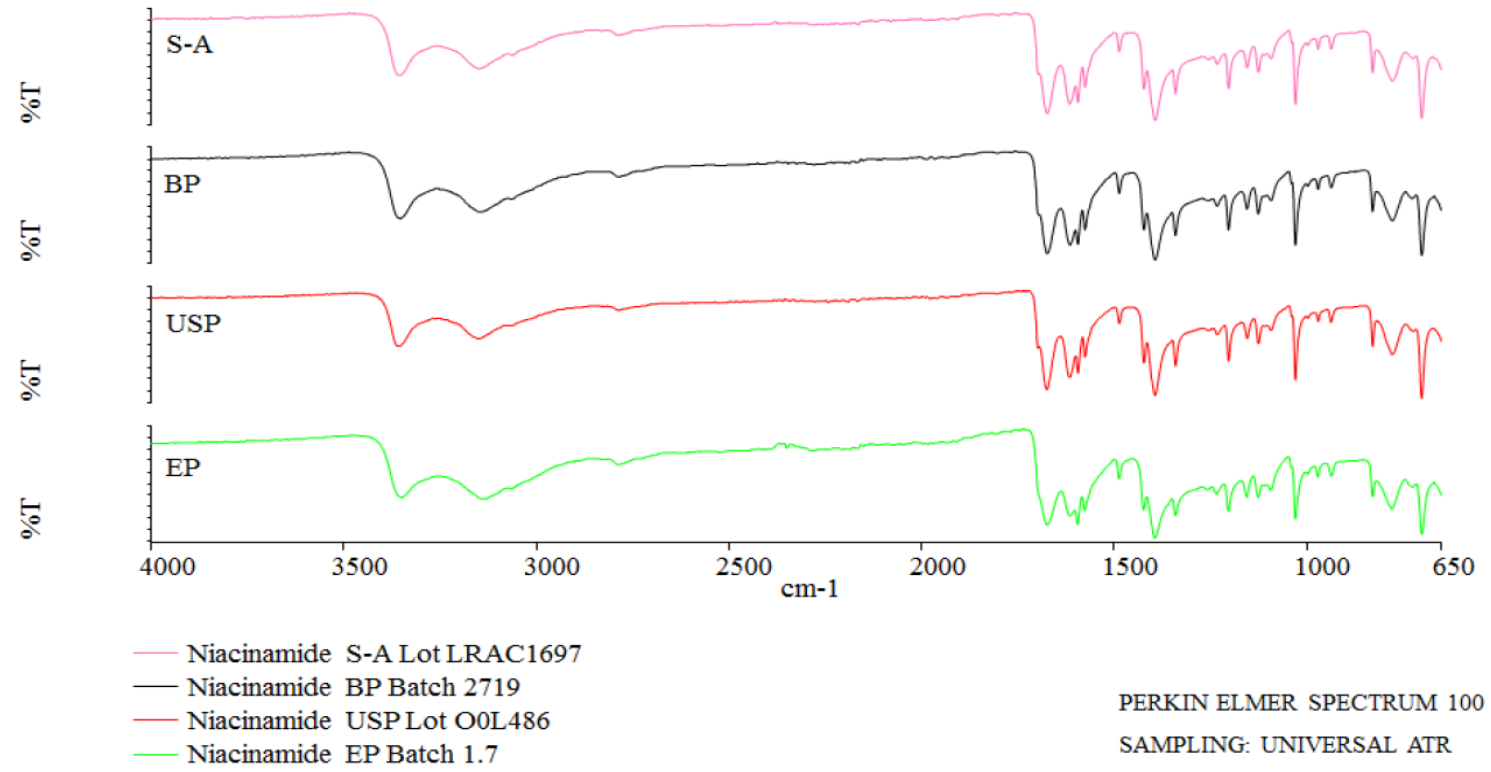
Secondary Pharmaceutical Standards
FTIR Traceability

FTIR comparison shows identification traceability to Primary Pharmacopeial Standards

Excerpt from PHR1033 Niacinamide COA



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Secondary Pharmaceutical Standards

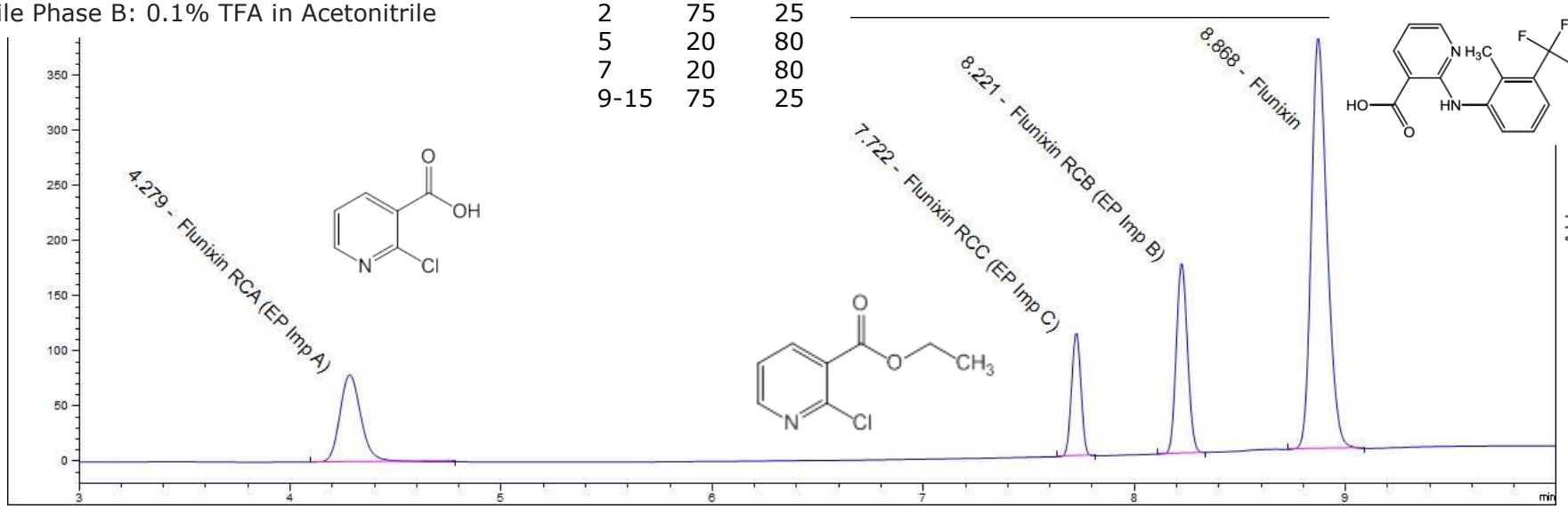
Assignment of Compendial Standards without Monographs

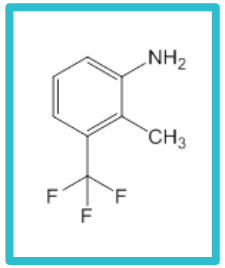
- Related Compounds and Impurities may not have dedicated compendial monographs available
- Sometimes API monographs can be used for development, but sometimes newly developed methods are required due to properties of analyte on hand

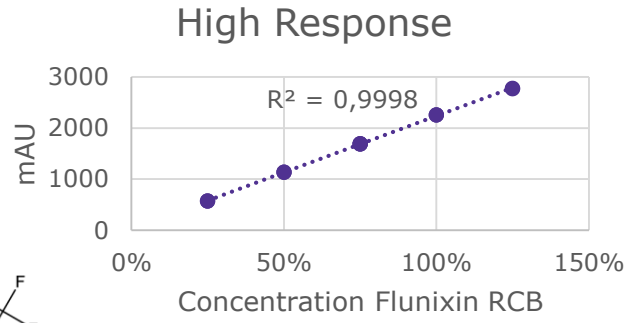
Validation for Resolution of Flunixin Related Compound B, PHR2823

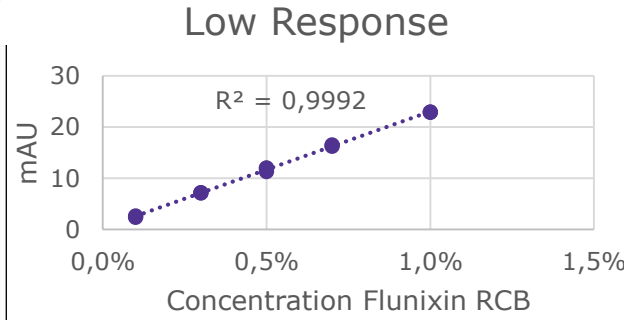
Supelco Discovery HS F5-3, 150mm x 4.6mm, 3µm
Mobile Phase A: 0.1% TFA in Water
Mobile Phase B: 0.1% TFA in Acetonitrile

Time	% A	% B
0	75	25
2	75	25
5	20	80
7	20	80
9-15	75	25









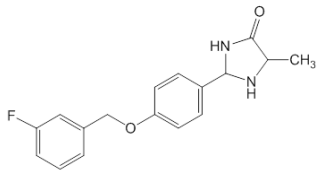
- ✓ **Selectivity**
- ✓ **Peak Shape**
- ✓ **Linearity**
- ✓ **RSD**

Secondary Pharmaceutical Standards

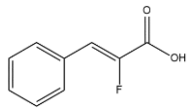
Assignment of Compendial Standards without Monographs References

- New APIs and Impurities may not have official or even pending compendial monographs available
- Mass Balance is performed and methods are validated

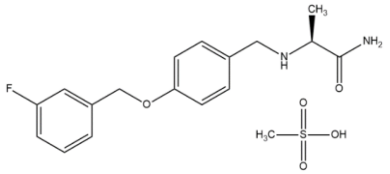
Safinamide Family – Parkinson's Drug



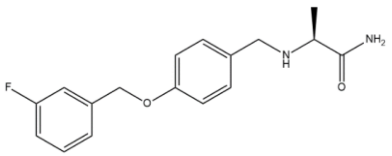
1. Safinamide Imidazolidinone
PHR2382



2. Safinamide Defluor-Derivative
PHR2381



3. Safinamide Mesylate
PHR2379



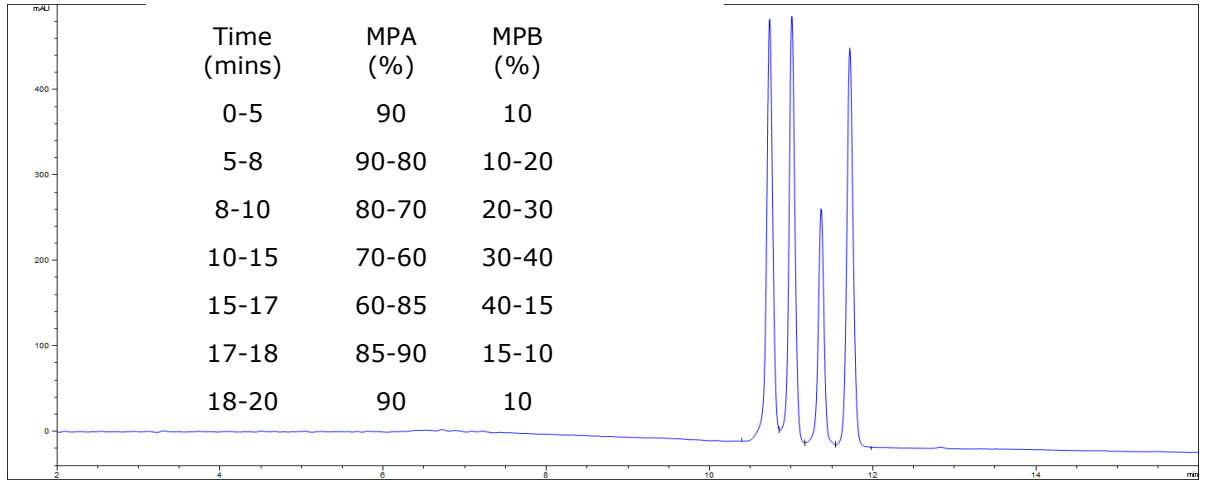
4. Safinamide Free Acid
PHR2380

Ascentis Express C8 (5µm) 150 x 4.6 mm

UV @ 226 nm

MPA: Water with 0.1 % Trifluoroacetic acid
MPB: Acetonitrile

Time (mins)	MPA (%)	MPB (%)
0-5	90	10
5-8	90-80	10-20
8-10	80-70	20-30
10-15	70-60	30-40
15-17	60-85	40-15
17-18	85-90	15-10
18-20	90	10



Peaks	Compound	Resolution	Theoretical plates	Tailing factor
1	Safinamide Imidazolidinone	-	87122	0.927
2	Safinamide Defluor-Derivative	2.11	100843	0.930
3	Safinamide Mesylate	2.87	114974	0.959
4	Safinamide Free Acid	2.69	93783	1.063

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04

Impurity Portfolios and Complex Mixture CRMs

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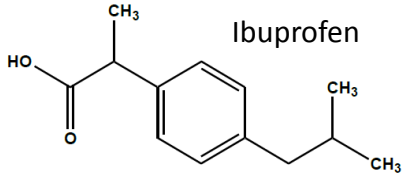
Secondary Pharmaceutical Standards

Ibuprofen Portfolio of Impurities and Related Compounds



Ibuprofen & Related Compounds	PHR Part	CAS	USP	EP	BP
Ibuprofen	PHR1004	15687-27-1	x	x	x
(2RS)-2-[3-(2-methylpropyl)phenyl]propanoic acid, *Ibuprofen Impurity A*	PHR1933	66622-47-7		*ID	
(2RS)-2-(4-butylphenyl)propanoic acid, *Ibuprofen Impurity B*	PHR1934	3585-49-7		x	
4-Isobutylacetophenone, *Ibuprofen Impurity E / Ibuprofen Related Compound C*	PHR1146	38861-78-8	x		x
2-[4-(2-methylpropyl)phenyl]propanoic acid, *Ibuprofen Impurity F / Ibuprofen Related Compound F*	PHR1964	65322-85-2		x	
(1RS,4RS)-7-(2-methylpropyl)-1-[4-(2-methylpropyl)phenyl]-1,2,3,4-tetrahydronaphthalene-1,4-dicarboxylic acid, *Ibuprofen Impurity G*	PHR1965	NA			
(3RS)-1,3-bis[4-(2-methylpropyl)phenyl]butan-1-one, *Ibuprofen Impurity H*	PHR2028	NA			
1-(2-methylpropyl)-4-[(3RS)-3-[4-(2-methylpropyl)phenyl]butyl]benzene, *Ibuprofen Impurity I*	PHR1984	NA			
(2RS)-2-[4-(2-methylpropanoyl)phenyl]propanoic acid, *Ibuprofen Impurity J / Ibuprofen Related Compound J*	PHR1978	65813-55-0	x	*ID	
(2RS)-2-(4-ethylphenyl)propanoic acid, *Ibuprofen Impurity N*	PHR1935	3585-52-2		*ID	
(2RS)-2-[4-(1-methylpropyl)phenyl]propanoic acid, *Ibuprofen Impurity O*	PHR1983	64451-76-9			
1,1'-(ethane-1,1-diyl)-4,4'-(2-methylpropyl)dibenzene, *Ibuprofen Impurity R*	PHR1982	102120-87-6			
4-Isobutyrylacetophenone	PHR2124	103931-20-0			
4-(1-Hydroxy-2-methylpropyl)-acetophenone	PHR2136	1314907-71-5			
2-(4-Isobutylphenyl)prop-2-enoic Acid	PHR2141	6448-14-2			
Ibuprofen 1,3-Butylene Glycol Esters (Mixture of Regio- and Stereoisomers)	PHR2142	NA			
Ibuprofen 2,3-Butylene Glycol Ester	PHR2143	95093-59-7			
Ibuprofen 1,2-Propylene Glycol Esters (Mixture of Regio- and Stereoisomers)	PHR2144	NA			
Ibuprofen 1,2,3-Propanetriol Esters (Mixture of Regio- and Stereoisomers)	PHR2145	NA			
2-(4-Secbutylphenyl)Prop-2-Enoic Acid	PHR2147	NA			

*ID: RT matched through EP Ibuprofen for Peak Identification (ID) CRS

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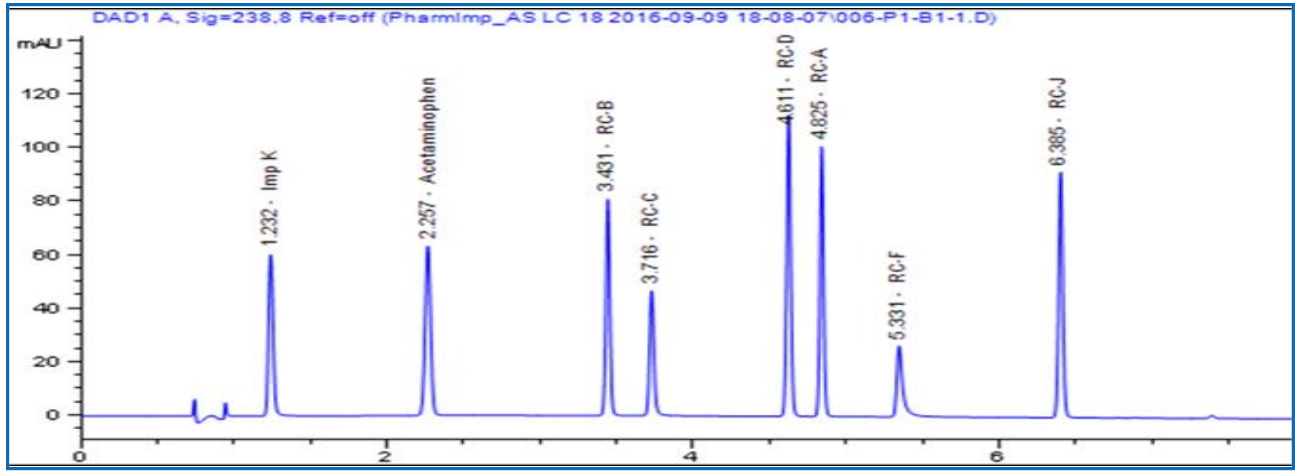
Secondary Standards - Working Solutions for Mixtures

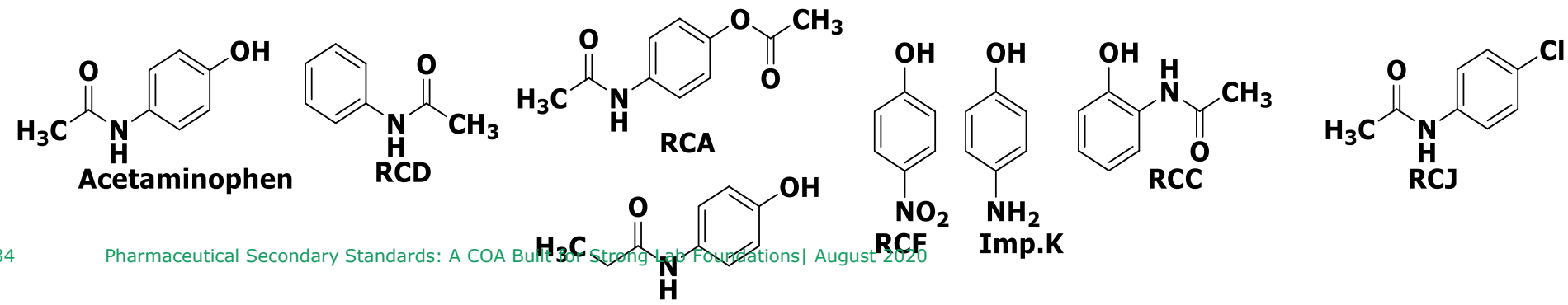
Acetaminophen

Components	USP	EP	RRF
Acetaminophen	-	-	1
4-acetoxyacetanilde	A	H	
N-(4-Hydroxy phenyl)propanamide	B	B	0.91
2- Acetamidophenol	C	A	0.60
Acetanilide	D	D	1.33
4-Nitrophenol	F	F	0.46
4-Chloroacetanilide	J	J	-
4-Aminophenol	-	K	-



USP/EP Impurities

- Secondary Standards certified by mass balance
- Traceable to USP & EP by assay
- Designed solution mixtures for daily working standard use



Wrap Up

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Secondary Pharmaceutical Standards Portfolio
Conclusions

Pharma Secondary standards are CRMs

Secondary Pharmaceutical Standards available with

-Traceability to current primary standards

-Traceability to SI unit through Mass Balance approach

Detailed COA is maintained to current primary lots

Increasing portfolio includes compendial & non-compendial impurities

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