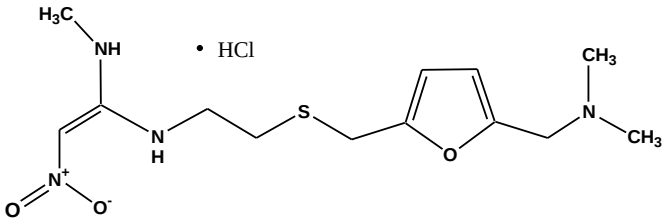
Certificate of Analysis

ISO GUIDE 34
ACLASS Cert# AR-1470

ISO/IEC 17025
ACLASS Cert# AT-1467

RANITIDINE HYDROCHLORIDE

CERTIFIED REFERENCE MATERIAL



CERTIFIED PURITY: 99.4%, U_{crm} = ±0.1% k = 2
(Mass Balance/ basis)

NOMINAL PACKAGE SIZE: 500mg

CATALOG #: PHR1026 **LOT #:** P500026

CERTIFICATE VERSION: 500026.5 **ISSUE DATE:** 20 September 2013
Note: Certificates may be updated due to Pharmacopeial Lot changes or the availability of new data. Check our website at: www.sigma-aldrich.com *for the most current version.*

CRM EXPIRATION: 12 Months from Receipt (Proper Storage and Handling Required).

RECEIPT DATE: _____
Note: this space is provided for convenience only and its use is not required.

STORAGE: Store at Room Temperature/Protect from Light, keep container tightly closed. Attachment of a 20 mm aluminum crimp seal recommended for unused portions.

CHEMICAL FORMULA: $C_{13}H_{22}N_4O_3S \cdot HCl$ **MW:** 350.86

PHYSICAL DESCRIPTION: White powder in amber vial **CAS #:** 66357-59-3

HAZARDS: Read Safety Data Sheet before using. All chemical reference materials should be considered potentially hazardous and should be used only by qualified laboratory personnel.

INSTRUCTIONS FOR USE: Do not dry, use as is. The internal pressure of the container may be slightly different from the atmospheric pressure at the user's location. Open slowly and carefully to avoid dispersion of the material. This material is intended for R&D use only. Not for drug, household or other uses.

TRACEABILITY ASSAY

Comparative assay demonstrates direct traceability to Pharmacopeial Standards
Specification: 97.5% to 102.0% (USP)

ASSAY vs. USP REFERENCE STANDARD (as is basis)

ASSAY VALUE	vs. USP LOT
99.6%	**H1G103**
	Labeled Content = 0.997mg/mg

ASSAY vs. BP CRS (as is basis)

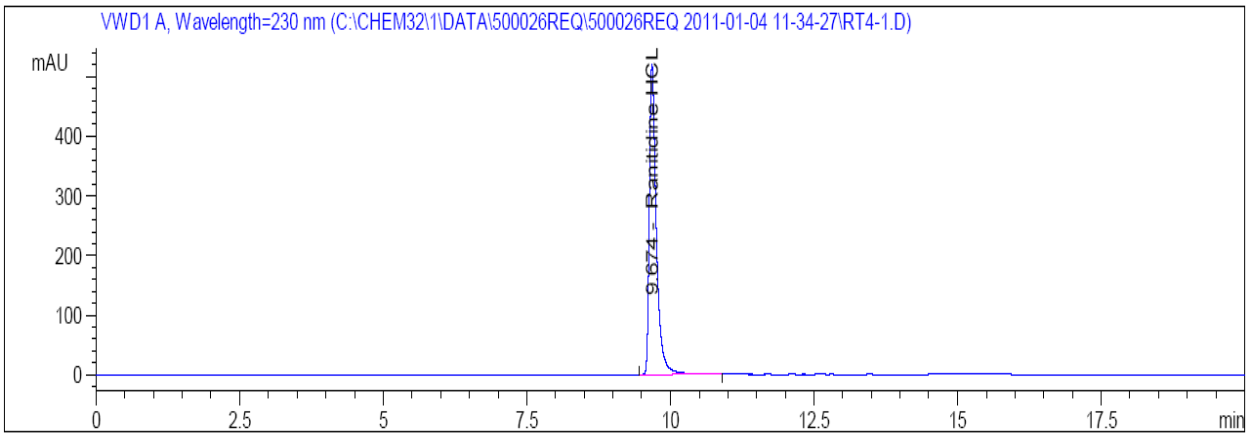
ASSAY VALUE	vs. BP BATCH
99.98% (as HCl)	**2984**
89.6% (as free base)	Labeled Content = 89.4% as free base

METHOD: HPLC (ref.: **Ranitidine Hydrochloride USP33)**
Column: Wakosil 5C18RS 4.6 x 150 mm, 5um
Mobile Phase: Solution A: Phosphate buffer, acetonitrile (98:2)
Solution B: Phosphate buffer, acetonitrile (78:22)
Phosphate buffer: Water, phosphoric acid, NaOH, pH 7.1
Gradient:

Time(minutes)	Solution A %	Solution B %	Elution
0 - 10	100 → 0	0 → 100	Linear gradient
10 - 15	0	100	Isocratic
15 - 16	0 → 100	100 → 0	Linear gradient
16 - 20	100	0	Re-equilibration

Flow: 1.5 mL/min
Column Temperature: 35°C
Injection: 10 µl
Detector: 230 nm

Representative Chromatogram from Lot: P500026 Analysis



ASSAY vs. EP CRS (as is basis)

ASSAY VALUE	vs. EP BATCH
99.5%	**3.0**
	Labeled Content = None
	Assigned Content = 99.9% *

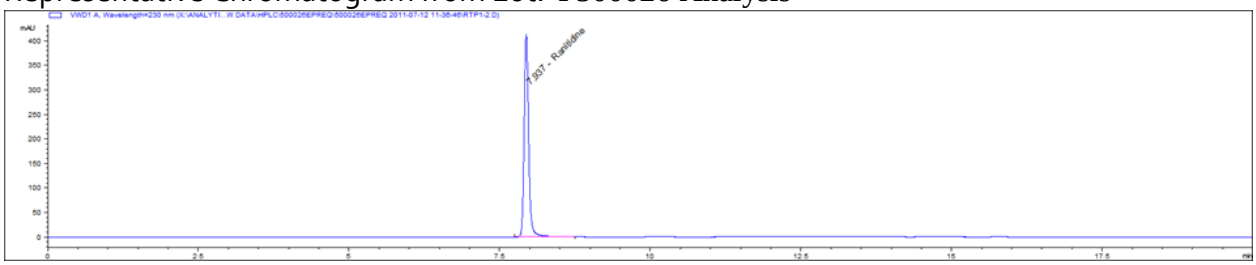
*The assigned content of the EP CRS was determined by assay against the USP Reference Standard

METHOD: HPLC (ref.: **Ranitidine Hydrochloride USP34)**
Column: Ascentis C18 4.6 x 150 mm, 5um
Mobile Phase: Solution A: Phosphate buffer, acetonitrile (98:2)
Solution B: Phosphate buffer, acetonitrile (78:22)
Phosphate buffer: Water, phosphoric acid, NaOH, pH 7.1
Gradient:

Time(minutes)	Solution A %	Solution B %	Elution
0 - 10	100 → 0	0 → 100	Linear gradient
10 - 15	0	100	Isocratic
15 - 16	0 → 100	100 → 0	Linear gradient
16 - 20	100	0	Re-equilibration

Flow: 1.5 mL/min
Column Temperature: 35°C
Injection: 10 µl
Detector: 230 nm

Representative Chromatogram from Lot: P500026 Analysis



PURITY DETERMINATION BY MASS BALANCE

CHROMATOGRAPHIC IMPURITY ANALYSIS

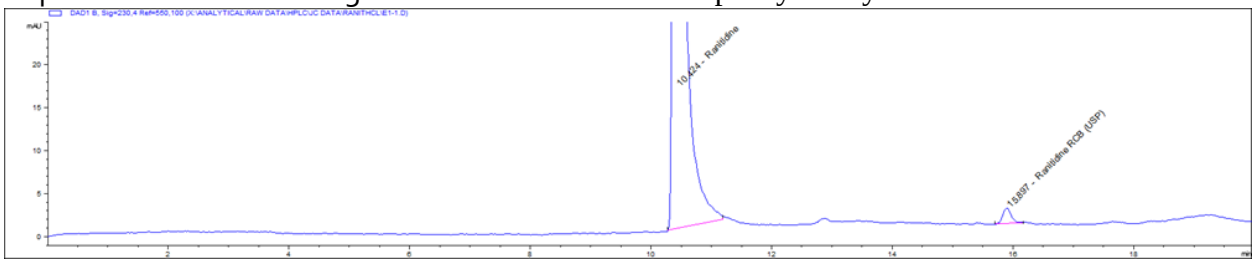
METHOD: HPLC (ref.: **Ranitidine Hydrochloride USP32**)
Column: Wakosil II 5C18, 4.6 x 250mm. 5µm
Mobile Phase: Solution A: Phosphate buffer, acetonitrile (98:2)
Solution B: Phosphate buffer, acetonitrile (78:22)
Phosphate buffer: Water, phosphoric acid, NaOH, pH 7.1
Gradient:

Time(minutes)	Solution A %	Solution B %	Elution
0 - 10	100 → 0	0 → 100	Linear gradient
10 - 15	0	100	Isocratic
15 - 16	0 → 100	100 → 0	Linear gradient
16 - 20	100	0	Re-equilibration

Flow: 2mL/min
Injection: 10 µl
Detector: 230 nm

Impurities Detected
USP Ranitidine Related Compound B (EP Impurity A): **0.5%**

Representative Chromatogram from Lot: P500026 Impurity Analysis



RESIDUAL SOLVENTS

Method: GC-MS Headspace (ref.: Residual Solvents <467>, USP34)
Column: DB-1301
Carrier gas: He
Flow: 1.2mL/min
Split Ratio: 1:5
Injection/Temperature: 1µl/250°C
Temperature Program: 40°C for 20min, 10°C/min to 240°C, hold 20min

Solvents Detected: None

LOSS ON DRYING/VOLATILES

Method: Vacuum at 60° for 3 hours
Mean of three samples, Loss = **0.1%**

RESIDUE ANALYSIS

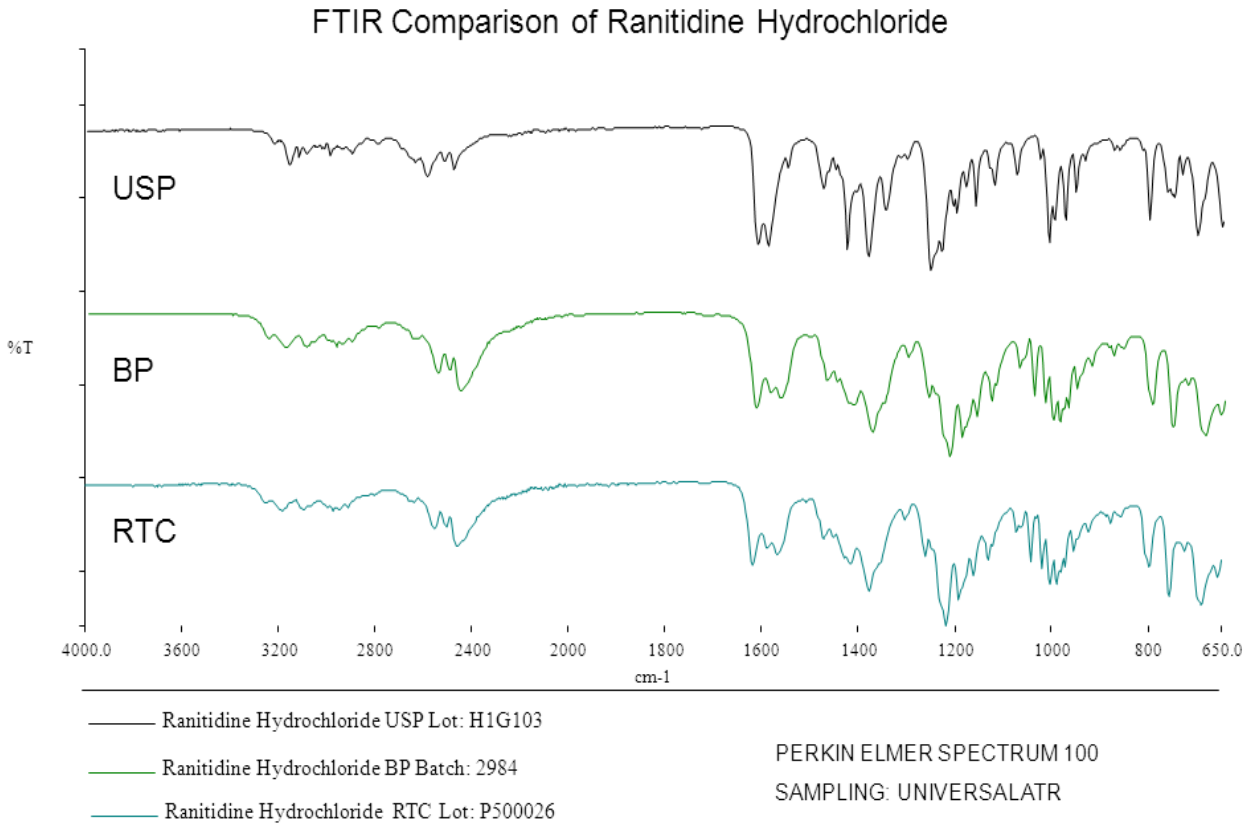
Method: Sulfated Ash
Sample Size: ~1 g
Mean of three determinations, Residue = **0.01%**

CERTIFIED PURITY BY MASS BALANCE [100% - Impurities (normalized)]

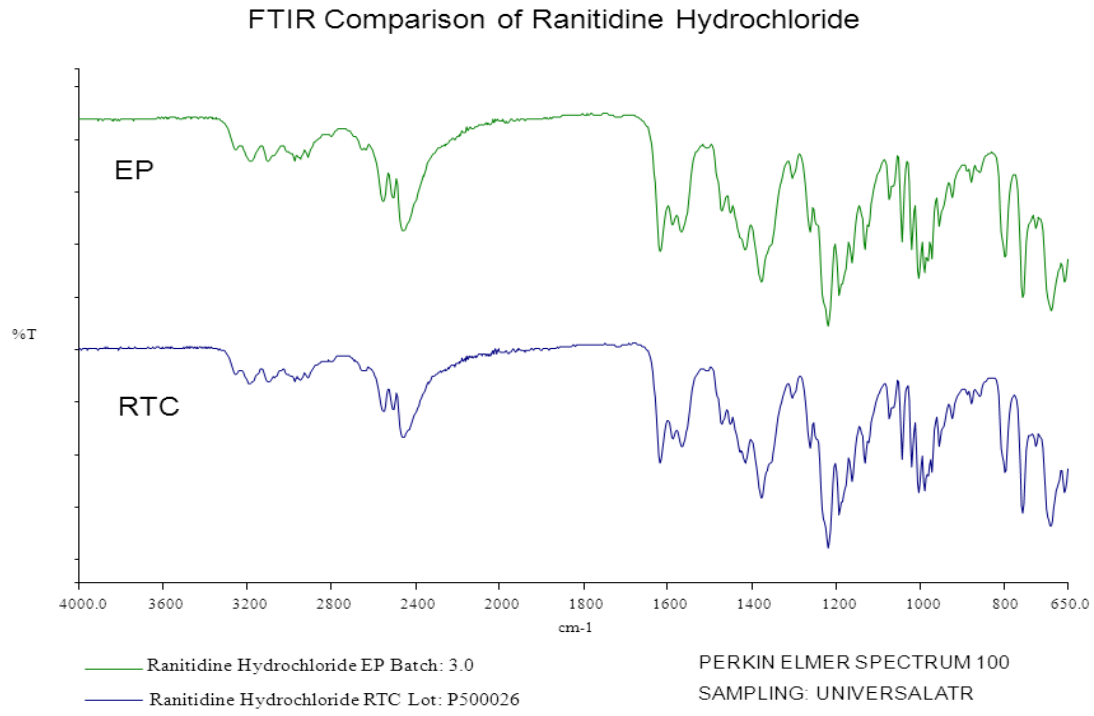
99.4% U_{crm} = ±0.1%, k = 2

IDENTIFICATION TESTS

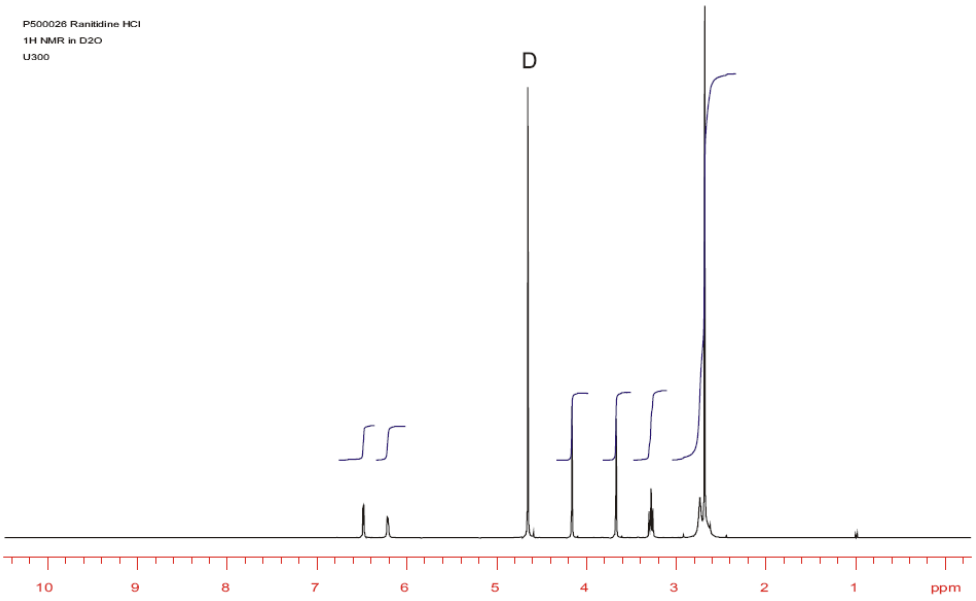
INFRARED SPECTROPHOTOMETRY (Comparative identification analysis demonstrates direct traceability to Pharmacopeial standards)



Ranitidine HCl is known to exist in different polymorphic forms (form I and II). The FTIR spectrum of the RTP sample showed good correlation to the EP and BP samples. However, the USP sample is clearly a different polymorph. Visual comparison of the RTP and USP samples shows good correlation in the position of virtually all peaks. In the RTP, EP, and BP samples, the unique peak at ~1050 cm-1 is indicative that they are form II. In the USP sample, the unique peak at ~1550 cm-1 is indicative that it is form I.



^{1}H NMR (Data provided by an external laboratory; not in scope of accreditation)



Consistent with structure

ELEMENTAL ANALYSIS (Data provided by an external laboratory; not in scope of accreditation)

Exeter Analytical 440 Elemental Analyzer
Combustion method

%	Theoretical	Result 1	Result 2	Mean
C	44.50	44.80	44.77	44.79
H	6.61	6.51	6.55	6.53
N	15.97	16.05	15.89	15.97

ULTRAVIOLET ABSORPTION

Specification: NMT 3.0% difference at 229 nm and 315 nm
Shimadzu UV-2101PC UV-VIS Scanning Spectrophotometer
Path Length: 100 cm

Sample	Conc. ()	Wavelength	Absorptivity	% Difference
USP	10 µg/mL	229 nm	92.80	**0.82 %**
RTP	10 µg/mL	229 nm	93.56	
USP	10 µg/mL	315 nm	94.70	**0.20 %**
RTP	10 µg/mL	315 nm	94.51	

Formula: $\left| Ab_{USP} - Ab_{RTP} \right| / Ab_{USP} \times 100\% = \%$ Difference

HOMOGENEITY ASSESSMENT

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: ~25mg

UNCERTAINTY STATEMENT

Uncertainty values in this document are expressed as Expanded Uncertainty (U_{crm}) corresponding to the 95% confidence interval. U_{crm} is derived from the combined standard uncertainty multiplied by the coverage factor k, which is obtained from a *t*-distribution and degrees of freedom. The components of combined standard uncertainty include the uncertainties due to characterization, homogeneity, long term stability, and short term stability (transport). The components due to stability are generally considered to be negligible unless otherwise indicated by stability studies.

General Manager, Pharmaceutical Standards Operations

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