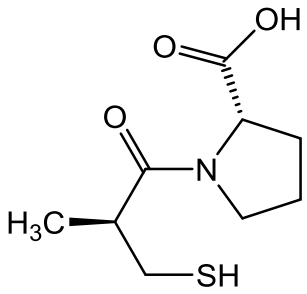
# Certificate of Analysis

ISO 17034
ANAB Cert# AR-1470

ISO/IEC 17025
ANAB Cert# AT-1467

## CAPTOPRIL

### *CERTIFIED REFERENCE MATERIAL*




**CERTIFIED PURITY: 97.8%,** $U_{crm}$ = ±0.2% k = 2
(Mass Balance/as is basis)

**NOMINAL PACKAGE SIZE:** 1g

**CATALOG #:** PHR1307 **LOT #:** LRAA9103

**CERTIFICATE VERSION:** LRAA9103.2 **ISSUE DATE:** 31 January 2019

*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:** 31 December 2020 (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, keep container tightly closed. Attachment of a 20 mm aluminum crimp seal recommended for unused portions.

**CHEMICAL FORMULA:** $C_9H_{15}NO_3S$ **MW:** 217.3

**PHYSICAL DESCRIPTION:** White powder in amber ampule **CAS #:** 62571-86-2

**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 on the as is basis. 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 Laboratory Use only. Not for drug, household or other uses.

## TRACEABILITY ASSAY

Comparative assay demonstrates direct traceability to Pharmacopeial Standards

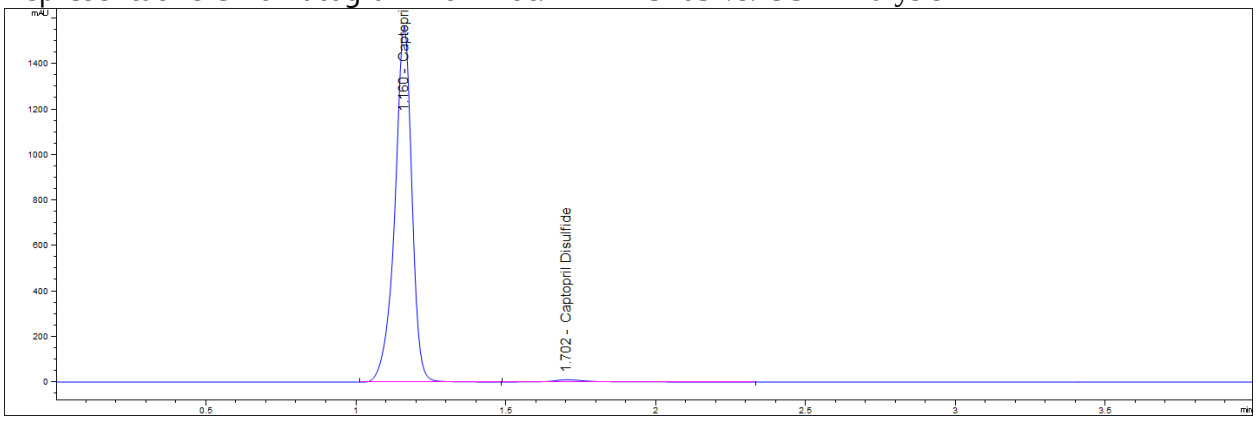
**METHOD: HPLC (ref.: Captopril Tablets, Current Compendial Monographs)**

### *ASSAY vs. USP REFERENCE STANDARD (as is basis)*

| ASSAY VALUE | vs. USP LOT |
|---|---|
| **98.8%** | **R069U0** |
| | Labeled Content = 0.998 mg/mg |

Column: Ascentis Express C18, 4.6 x 100mm, 5µm
Mobile Phase: 0.5 ml/L $H_3PO_4$ in Water, Methanol (45:55)
Flow Rate: 1.0 mL/min
Column Temperature: 30 ºC
Injection: 10 µL
Detector: 220 nm

Representative Chromatogram from Lot: LRAA9103 vs. USP Analysis




### *ASSAY vs. EP CRS (as is basis)*

| ASSAY VALUE | vs. EP BATCH |
|---|---|
| **98.4%** | **2.1** |
| | Labeled Content = None |
| | Assigned Content = 99.7%* |

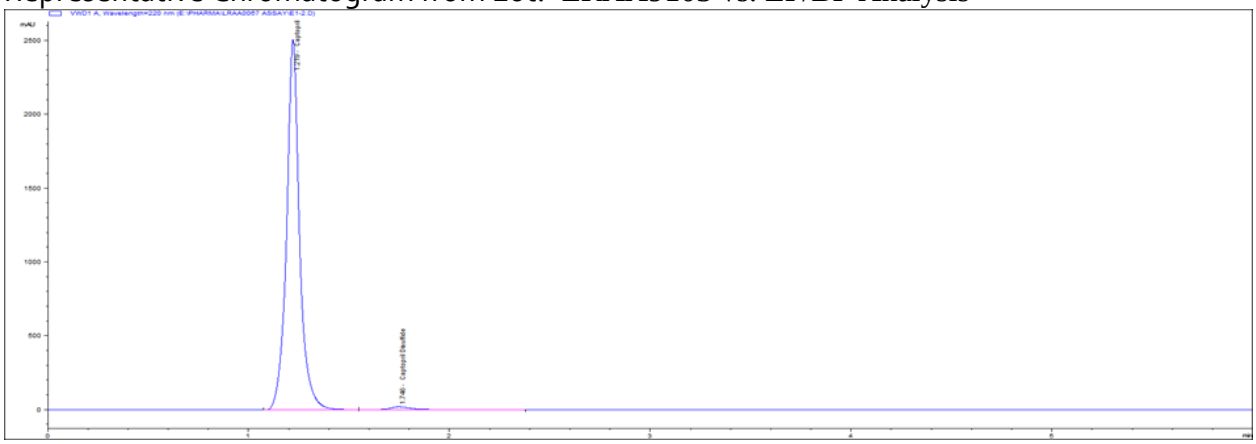
## *ASSAY vs. BP CRS (as is basis)*

| ASSAY VALUE | vs. BP BATCH |
|---|---|
| **98.0%** | **3073** |
| | Labeled Content = 99.7% |

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

Column: Ascentis Express C18, 4.6 x 100mm, 5µm
Mobile Phase: 0.5ml/L $H_3PO_4$ in Water, Methanol (45:55)
Flow Rate: 1mL/min
Column Temperature: 30ºC
Injection: 20µL
Detector: 220nm

Representative Chromatogram from Lot: LRAA9103 vs. EP/BP Analysis



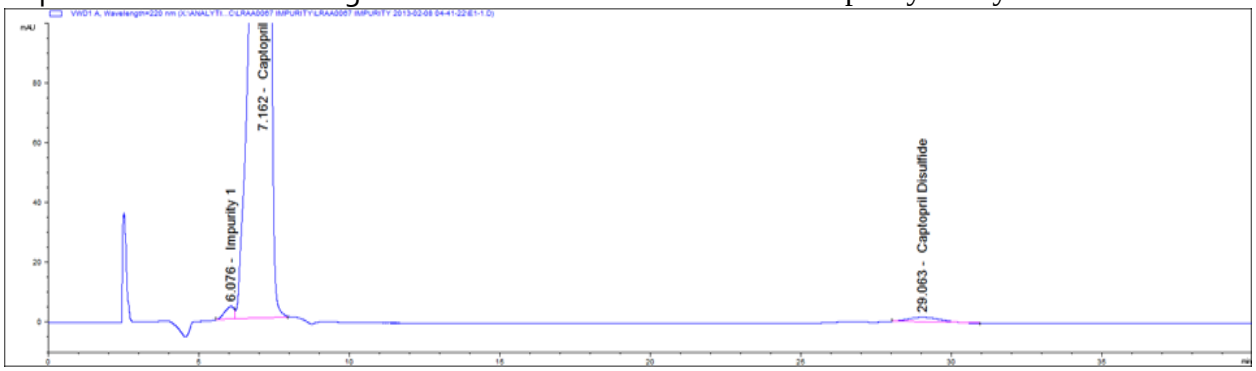
## PURITY DETERMINATION BY MASS BALANCE

**CHROMATOGRAPHIC IMPURITY ANALYSIS**
**METHOD: HPLC (ref.: Captopril, USP35)**
Column: Ascentis Express C18, 4.6 x 100mm, 5µm
Mobile Phase A: 0.5mL/L H3PO4 in Water
Mobile Phase B: Tetrahydrofuran, Methanol (9:91)
Mobile Phase: A, B (67:33)
Flow Rate: 1mL/min
Column Temperature: 30ºC
Injection: 20µL
Detector: 220nm

Impurities Detected:

Unknown Imp 1: 0.4%
Captoril Disulfide: 0.8%

Representative Chromatogram from Lot: LRAA9103 HPLC Impurity Analysis



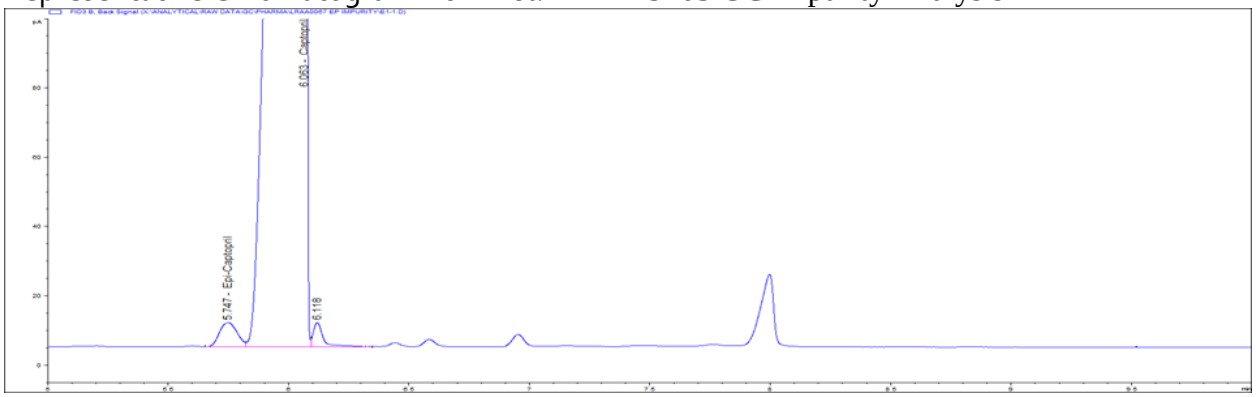

**METHOD: GC (ref.: Captopril, EP7)**
Column: HP-5, 30m x 0.32mm x 0.25µm
Carrier Gas: $H_2$
Flow: 1.2mL/min
Temperature Program: 0-10min 200ºC, 10-14min 200-240ºC, hold 240ºC for 20min
Injection: 1µL, 270ºC
Split Ratio: 40:1
Detector: FID, 300ºC
Internal Standard:

Impurities Detected:

Epi-Captopril: 0.8%

Total Impurities: **2.0%**

Representative Chromatogram from Lot: LRAA9103 GC Impurity Analysis



## RESIDUAL SOLVENTS

Method: GC-MS Headspace (ref.: Residual Solvents USP <467>)
Column: SPB-624
Carrier gas: He
Flow: 1.2 mL/min
Split Ratio: 1:5
Injection/Temperature: 1µL/250°C
Temperature Program: 40°C for 5min, 8°C/min to 200°C, hold 5min

Solvents Detected: None

## LOSS ON DRYING/VOLATILES

Method: Oven at 105°C (ref.: Current Compendial Monographs)
Mean of three measurements, Loss = **0.02%**

## RESIDUE ANALYSIS

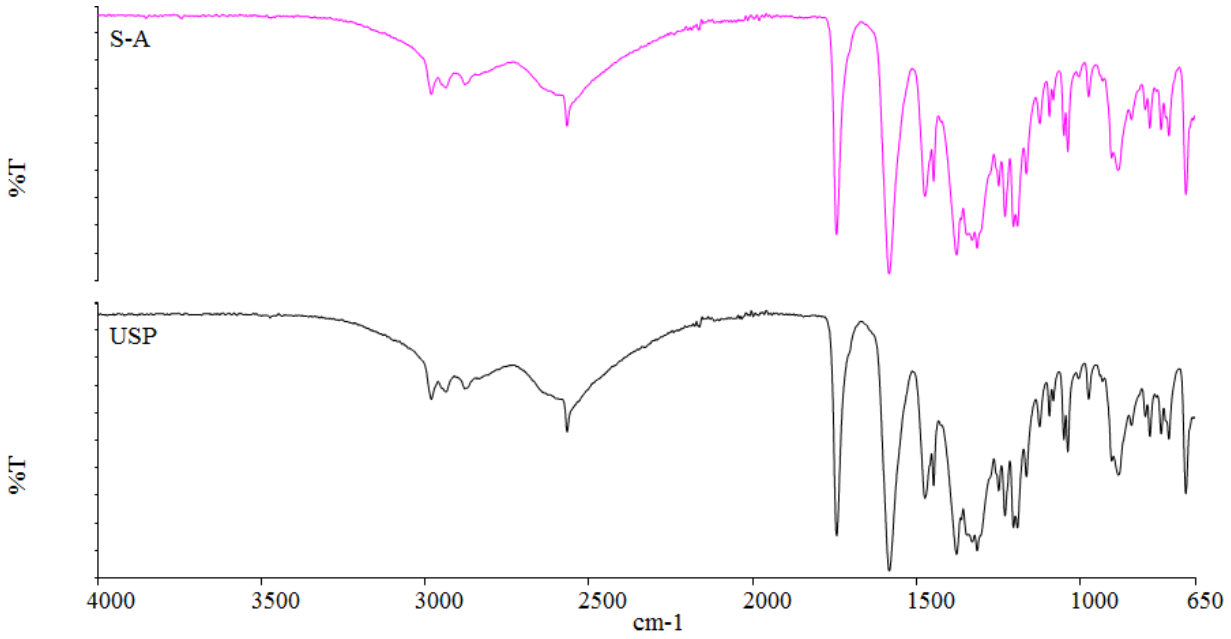
Method: Sulfated Ash (ref.: Current Compendial Monographs)
Sample Size: ~1g
Mean of three measurements, Residue = **0.1%**

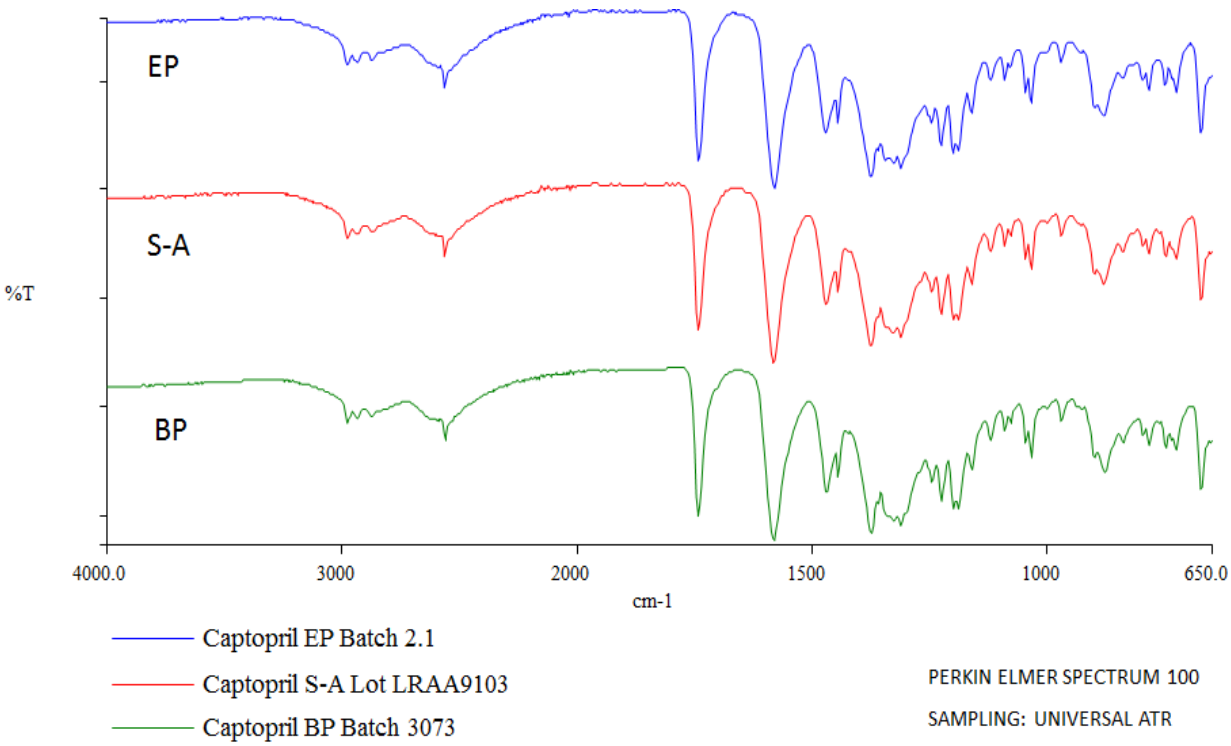
## CERTIFIED PURITY BY MASS BALANCE [100% - Impurities (normalized)]

**97.8%** $U_{crm}$ = ±0.2%, k = 2
(as is basis)

## IDENTIFICATION TESTS

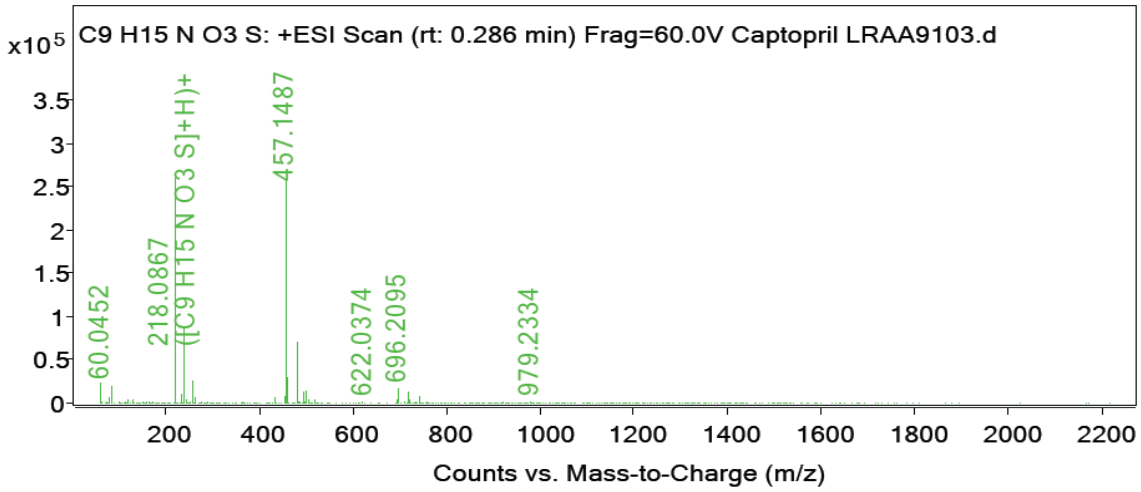
**INFRARED SPECTROPHOTOMETRY** (Comparative identification analysis demonstrates direct traceability to Pharmacopeial standards)



## MASS SPECTRUM

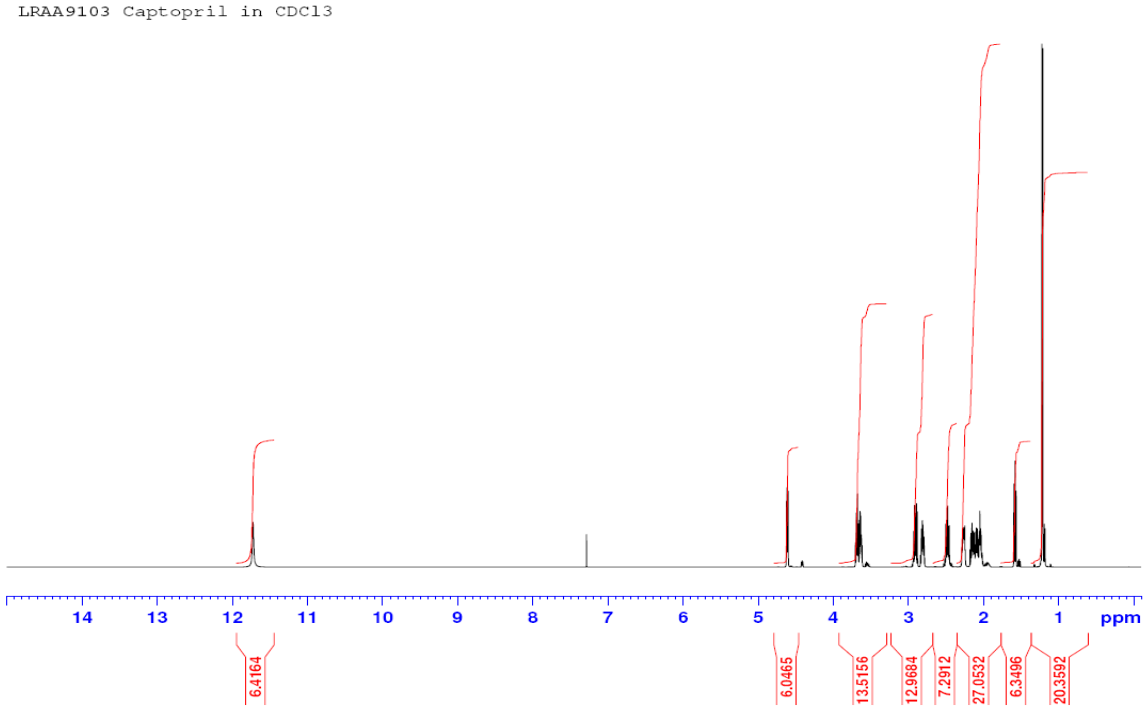
Method: HR-QTOF; 4.0 kV ESI+; temperature: 325 °C




Theoretical value: 218.0851 m/z

The signal of the MS spectrum is consistent with the theoretical value and its interpretation is consistent with the structural formula.

## $^{1}$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 | 49.75 | 49.63 | 50.00 | 49.81 |
| H | 6.96 | 6.78 | 6.65 | 6.72 |
| N | 6.45 | 6.54 | 6.59 | 6.57 |

## OPTICAL ROTATION

Specification: -125º to -134º
Perkin Elmer Polarimeter 343
Wavelength: 589nm
Concentration: ~1g/100mL
Cell Path: 100mm
Mean of three Measurements = **-128.2º**

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: ~ 100 mg

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.

STABILITY ASSESSMENT

Significance of the stability assessment will be demonstrated if the analytical result of the study and the range of values represented by the Expanded Uncertainty do not overlap the result of the original assay and the range of its values represented by the Expanded Uncertainty. The method employed will usually be the same method used to characterize the assay value in the initial evaluation.

Long Term Stability Evaluation - An assessment, or re-test, versus a Compendial Reference Standard may be scheduled, within the 3 year anniversary date of a release of a Secondary Standard. The re-test interval will be determined on a case-by-case basis.
Short Term Stability Study - It is useful to assess stability under reasonably anticipated, short term transport conditions by simulating exposure of the product to humidity and temperature stress. This type of study is conducted under controlled conditions of elevated temperature and humidity.

QC Manager

Head Quality Assurance

APPENDIX

| | |
|---|---|
| Original Release Date: | 16 September 2015 |
| Stability Test Date: | 31 January 2019 |
| Requalification Test Date: | 31 January 2019 |

Manufactured and certified by Sigma-Aldrich RTC, Inc.
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