# 16.1.9.3 BIOANALYTICAL REPORTS

Determination of Nicotine and Cotinine in Human Plasma ($K_2EDTA$) Samples by LC-MS/MS (Study AA99071-02)

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**Determination of Nicotine and Cotinine in Human Plasma ($K_2EDTA$) Samples from "A Randomized, Controlled, Open-label, 3-Arm Parallel Group, Single-Center Study to Demonstrate Reductions in Exposure to Selected Smoke Constituents in Smoking, Healthy Subjects Switching to the Tobacco Heating System 2.2 (THS 2.2) or Smoking Abstinence, Compared to Continuing to Use Conventional Cigarettes, for 5 Days in Confinement" by LC-MS/MS**

Study: AA99071-02

Bioanalytical Final Report

Philip Morris Products S.A.
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Protocol ZRHR-REXC-03-EU

Report Date: 22-Sep-2014

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Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

**APPROVAL SIGNATURES**

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Technical Director, Tobacco Sciences

22-Sep-2014
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## STATEMENT OF COMPLIANCE

The bioanalytical phase of the study was performed according to applicable GLP requirements and in compliance with Standard Operating Procedures (SOPs) in effect in the bioanalytical laboratory of Celerion, Lincoln, Nebraska. The SOPs are written based on the principles and requirements described in United States Food and Drug Administration Title 21 Code of Federal Regulations (CFR) Part 58, the Guidance for Industry – Bioanalytical Method Validation (CDER, May 2001), and Guideline on Bioanalytical Method Validation (European Medicines Agency [EMEA/CHMP/EWP/192217/2009], Effective February 2012).

This production study was conducted in accordance with the guidelines documented in the bioanalytical study plan. To ensure the integrity of the reported data, the bioanalytical laboratory verified all results. The Quality Assurance unit of Celerion, Lincoln, Nebraska, audited the study. A Quality Assurance statement was then issued and is included within this document.

The data summaries, results, and conclusions in this bioanalytical report have been reviewed and were found to be consistent and scientifically rational. All deviations from the protocol and/or significant deviations from SOPs documented in this report have been reviewed and are scientifically valid.

I accept responsibility for the scientific integrity of the data included within this bioanalytical report.

Kirk Newland, B.S.
Technical Director, Tobacco Sciences

22-Sep-2014
Date

## QUALITY ASSURANCE STATEMENT

| Phase Audited | Audit Date(s) | Date Reported to Study Director/ Bioanalytical Principal Investigator | Date Audit Report Signed by Management |
|---|---|---|---|
| Bioanalytical Study Plan | 18-Jun-2013 | 18-Jun-2013 | 24-Jul-2013 |
| Critical Phase | 14, 24, 25-Sep-2013 | 25-Sep-2013 | 26-Sep-2013 |
| Database | 20, 21, 22-Nov-2013 | 22-Nov-2013 | 28-Feb-2014 |
| Bioanalytical Report (Final Draft) | 09, 10-Jul-2014 | 10-Jul-2014 | 04-Sep-2014 |
| Bioanalytical Report (Final) | 22-Sep-2014 | 22-Sep-2014 | 22-Sep-2014 |

Celerion Quality Assurance audited various phases of this study as shown above. This statement confirms that the methods, procedures, and results as presented in this report accurately reflect the raw data of the study.

Amy Sherwood

Amy Sherwood, A.A.S.
Quality Assurance Auditor

22 Sep 2014

Date

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## 1. INTRODUCTION

The purpose of this bioanalytical study (hereafter referred to as study) was to determine the concentration of nicotine and cotinine in human plasma ($K_2EDTA$) samples by a validated LC-MS/MS method [5]. The study samples were collected in the clinical trial ZRHR-REXC-03-EU, entitled, "A Randomized, Controlled, Open-label, 3-Arm Parallel Group, Single-Center Study to Demonstrate Reductions in Exposure to Selected Smoke Constituents in Smoking, Healthy Subjects Switching to the Tobacco Heating System 2.2 (THS 2.2) or Smoking Abstinence, Compared to Continuing to Use Conventional Cigarettes, for 5 Days in Confinement" [3]. Sample analysis was conducted between 15-Sep-2013 and 08-Nov-2013.

This report provides the results and supporting documentation from the analysis of study samples and includes an evaluation of assay performance.

## 2. EXPERIMENTAL

### 2.1. Test Item

The test items are defined in the clinical study protocol [3].

### 2.2. Reference Items and Internal Standards

| | Analyte | Internal Standard (IS) |
|---|---|---|
| ID | Nicotine | $d_4$-Nicotine |
| Source | (b) (4) [redacted] | (b) (4) [redacted] |
| Lot No. | FN092410-01 / AC0105001* | FN083010-01 |
| Purity / Concentration | 99.5% (1.00 mg/mL) / 99.5% (912 µg/mL)* | 98.1% (100 µg/mL) |
| Celerion Assigned Correction Factor | 1.0000 | 1.0000 |
| Expiry Date | 30-Sep-2015 / 04-Jan-2014* | 30-Sep-2015 |
| Storage Conditions | 5 C, protected from light | 5 C, protected from light |

*Recertified with new expiry date of 30-Jun-2014 with purity/concentration of 99.7% (914 µg/mL)

| | Analyte | Internal Standard (IS) |
|---|---|---|
| ID | Cotinine | $d_3$-Cotinine |
| Source | (b) (4) | (b) (4) |
| Lot No. | FN061710-01 | FN102110-02 |
| Purity / Concentration | 99.8% (1.047 mg/mL) | 99.7% (100.0 µg/mL) |
| Celerion Assigned Correction Factor | 1.0000 | 1.0000 |
| Expiry Date | 30-Jun-2015 | 31-Oct-2015 |
| Storage Conditions | Freezer (-20 C), protected from light | Freezer (-20 C), protected from light |

The certificate(s) of analysis for the reference items and internal standards are presented in Attachment 6.

Reference items and internal standards are retained under the conditions that are specified until they become expired. The expired reference materials are denoted as expired within the Labnotes system. They may be stored for the establishment of extended long-term stability.

### 2.3. Biological Matrix

Human plasma, with $K_2EDTA$ as anticoagulant, was collected in-house at Celerion, Lincoln, Nebraska and stored at -20°C. Human plasma ($K_2EDTA$), free of significant interference, was used to prepare quality control (QC) samples. Deionized water was used to prepare calibration standards and used as control matrix.

### 2.4. Test System

#### 2.4.1. Procedure and Instruments

| Procedure and Instrumentation | |
|---|---|
| Extraction Method | Solid-phase extraction |
| Chromatography system | Perkin Elmer Series 200 Micropump HPLC^ |
| MS/MS system | AB SCIEX API 4000™ or API 5000™^ |
| Regression Type | Weighted linear regression curve (1/concentration$^2$) |
| Quantitation Method | Peak area ratio |
| Assay Volume | 0.300 mL |
| Acceptable Level of Hemolysis | 5% |

^ = Qualified systems

### 2.4.2. Computer Application Software

| Software | |
|---|---|
| LC-MS/MS software | Applied Biosystems Analyst® 1.5.1^ |
| LIMS | Thermo Electron Corporation Watson™ 7.3 Bioanalytical LIMS 7.3^ |
| LIMS application | Inspector Version 1.1.1^ |
| Laboratory Documentation System | Labnotes™ Web Client 1.21^ |
| Office applications | Microsoft® Office 2010 Package |

^ = Validated systems

## 2.5. Calibration Standards, Quality Control Samples and Dilution Quality Control Samples

Non-zero calibration standards were prepared fresh daily at the concentration levels of 0.200, 0.400, 0.800, 1.00, 2.50, 5.00, 7.50, 9.00 and 10.0 ng/mL of nicotine and 1.00, 2.00, 4.00, 10.0, 25.0, 50.0, 75.0, 90.0, and 100 ng/mL of cotinine from calibration spiking standards which were prepared in bulk on 12-Aug-2013 and 19-Aug-2013, and stored at -20°C for a period of time up to 323 days.

Quality control (QC) samples at the concentration levels of 0.600, 2.00, 5.00, and 8.00 ng/mL of nicotine and 3.00, 15.0, 50.0, 80.0 ng/mL of cotinine and dilution quality control (DQC) samples at the concentration levels of 20.0 ng/mL of nicotine and of 200 ng/mL of cotinine were prepared in bulk on 22-Aug-2013, 03-Sep-2013, 15-Oct-2013, aliquoted and stored at -20°C. Quality control samples were stored with the clinical samples after receipt at the bioanalytical laboratory. The QC samples were stored for a period less than 1041 days prior to use for analysis. The dilution quality control samples were diluted with deionized water at the time of use.

Standard calibrators and quality control samples were prepared from separate stock solutions.

## 2.6. Study Samples

### 2.6.1. Sample Source and Date of Receipt

Study samples were collected between 12-Jul-2013 and 19-Sep-2013 and were received frozen on dry ice between 22-Jul-2013 and 18-Oct-2013 from Covance CLS, Meyrin, Switzerland and Covance Central Laboratories, Indianapolis, Indiana.

### 2.6.2. Sample Identification

Study samples were identified based on the subject screening number and time point documented on the sample label.

### 2.6.3. Sample Storage and Stability

Study samples were stored from sample collection to the end of sample analysis at a nominal temperature of -20°C for a duration not exceeding 120 days.

Study samples were analyzed without exceeding long-term, short-term, freeze-thaw, or post-preparative stability. The following evaluations have been conducted:

| Stability Summary [5] | Nicotine |
|---|---|
| Long-term stability | 1041 days in polypropylene tubes at -20 C |
| Short-term stability | 27 hours in polypropylene tubes at ambient temperature under white light |
| Freeze-thaw stability | 6 freeze (-20 C)-thaw (ambient temperature) cycles in polypropylene tubes under white light |
| Post-preparative stability | 73 hours in a polypropylene 96 well plate at 5 C |
| Processed sample integrity | 139 hours in a polypropylene 96 well plate at 5 C |
| Sample shipping stability | 19 days in polypropylene tubes at -80 C |

| Stability Summary [5] | Cotinine |
|---|---|
| Long-term stability | 194 days in polypropylene tubes at -20 C |
| Short-term stability | 27 hours in polypropylene tubes at ambient temperature under white light |
| Freeze-thaw stability | 6 freeze (-20 C)-thaw (ambient temperature) cycles in polypropylene tubes under white light |
| Post-preparative stability | 73 hours in a polypropylene 96 well plate at 5 C |
| Processed sample integrity | 139 hours in a polypropylene 96 well plate at 5 C |
| Sample shipping stability | 19 days in polypropylene tubes at -80 C |

### 2.6.4. Sample Summary

The Sponsor's protocol specifies that clinical samples will be collected from 40 subjects with 7 sampling times for the group randomized to SA [3]. In study AA99071, one subject discontinued during the clinical phase. The subject, 0083, was not randomized to SA; therefore, there was no impact on AA99071-02.

| | No. of Samples |
|---|---|
| Specified in protocol/received | 280/276 |
| Not completing study (e.g., dropouts) | 0 |
| Failed analysis/ investigation (SVD, Not Reportable) | 4 for Nicotine<br>1 for Cotinine |
| Duplicates received | 276 |

| | |
|---|---|
| Sample from subject who discontinued before randomization | 3 |
| Total number of study samples analyzed | 269 for Nicotine<br>272 for Cotinine |

Following analysis, the study samples were kept frozen at -20°C. After submission of the final bioanalytical report the study samples will be further stored under the same conditions for up to 1 month on-site. Then, upon agreement with the Sponsor, the study samples will be destroyed after the completion of the clinical study report and Sponsor notification.

## 3. SAMPLE ANALYSIS

### 3.1. Analytical Method

The determination of nicotine and cotinine in human plasma ($K_2EDTA$) samples was carried out over a calibration range of 0.200 ng/mL to 10.0 ng/mL (nicotine), and 1.00 ng/mL to 100 ng/mL (cotinine). The analytical procedure was performed at Celerion, Lincoln, Nebraska and is documented in the Method Validation Report for Celerion Study AA33664-06 [5]. The analytical method is documented in BAM SOP AA33664-06 [6]. See Attachment 7.

An aliquot of human plasma (EDTA) containing the analyte and internal standard was extracted using a solid phase extraction procedure. The extracted samples were analyzed by an HPLC equipped with an AB SCIEX API 4000™ or API 5000™ triple quadrupole mass spectrometer using an ESI source. Positive ions were monitored in the multiple reaction monitoring (MRM) mode. Quantitation was determined using a weighted linear regression analysis ($1/concentration^2$) of peak area ratios of the analyte and internal standard.

Though listed as a standard, the control blank sample with internal standard (Standard A) was not used to plot the calibration curve.

### 3.2. Acceptance Criteria

#### 3.2.1. Analytical Run Acceptance Criteria

An analytical run is acceptable if all of the following criteria are met:

- at least 75% of the non-zero calibration standards were within ±15.0% (±20.0% for the lower limit of quantification (LLOQ) calibration standard) of their nominal concentration,
- at least two-thirds of the QC samples and at least 50% at each concentration level were within ±15.0% of their nominal concentration,
- at least 50% of the standard zero samples are free of interference at the retention time of the analyte(s) of interest,
- at least 50% of the blank samples are free of interference both at the retention time of the analyte(s) of interest and at the retention time of the IS,

- at least two-thirds of all blank and standard zero samples fulfilled the above described interference criteria.

Interference at the retention time of the analyte of interest is defined as a response greater than 20% of the mean analyte response of the LLOQ calibration standard(s).

Interference at the retention time of the IS is defined as a response greater than 5% of the mean IS response of the LLOQ calibration standard(s).

Individual data of QC samples (including DQCs) that were out of their acceptance criteria are flagged appropriately in the study file and in the bioanalytical report. QCs will be excluded from statistics only for analytical reasons (see Attachment 5).

### 3.2.2. Acceptance Criteria for System Suitability Testing

The system suitability testing performed with each analytical run is designed to assess the sensitivity, reproducibility of response (absence of response drift based on interpolated concentrations), and carry-over.

- Sensitivity assessed at the start and end of each analytical run is performed by evaluating the signal-to-noise ratio (SNR) of extracted system suitability samples spiked at the lower limit of quantitation. The SNR must be greater than 5:1 unless otherwise specified in the method.
- System stability (reproducibility of response) is performed by replicate injections at the start (5) and the end (2) of the analytical run with pooled high concentration system suitability samples. The percent coefficient of variation (% CV) of the calculated concentration must be less than or equal to 6%. The mean of the calculated concentration of the last 2 replicates or middle replicates (if applicable) of high concentration system suitability samples must be within 15% difference of the mean of the calculated concentration of the first 5 high concentration system suitability samples.
- The carryover percentage is assessed at the beginning and end of each analytical run. This test is performed by injecting a blank (reconstitution solution) sample immediately after a high concentration system suitability sample. The area counts of the analyte in the blank injection are divided by the analyte area counts in the high concentration system suitability sample and the result is multiplied by 100. Carryover acceptance criteria is specified in the bioanalytical method for each assay.

$$\%\ \text{carryover} = \left(\frac{\text{area (blank sample)}}{\text{area (high sys suit)}}\right) * 100$$

### 3.2.3. Acceptance Criteria for Sample Dilution

The accuracy of study sample dilution is verified by the DQC samples. At least 50% of the DQC samples must be within ±15.0% of their nominal concentration for the respective dilution factor to be accepted.

### 3.2.4. Acceptance Criteria for ISR

The % difference was calculated for each pair of original and repeat analyses as follows:

$$\%\,\text{difference} = 100 * \frac{|(\text{repeat value} - \text{original value})|}{(\text{repeat value} + \text{original value})/2}$$

If the %difference was less than or equal to 20%, a pair of results was considered a passing match. Any pair with a %difference of more than 67% (indicating that the repeat value is either less than half or more than twice the original concentration) was considered an event and was investigated. The analytical method will be considered reproducible if at least 67% of the result pairs match. If less than 67% of the pairs match, an event investigation was initiated.

## 4. RESULTS

Due to rounding procedures, recalculations using the results presented in this report may differ slightly from the reported statistics.

A summary of analytical runs performed is presented in Table 1.

### 4.1. Quality Control and Dilution Quality Control Sample Performance

Between-analytical run precision and accuracy results for QC samples prepared at 0.600, 2.00, and 5.00 ng/mL for nicotine and at 3.00, 15.0, and 50.0 ng/mL for cotinine are summarized in Table 2 and Table 3 for nicotine and cotinine, respectively. The accuracy of sample dilution was verified by the performance of dilution QC samples. Results for dilution QC samples are summarized in Table 2 and Table 3 for nicotine and cotinine, respectively.

### 4.2. Calibration Standard Performance

Back-calculated calibration curve standard concentrations are provided in Table 4 and Table 5 for nicotine and cotinine, respectively.

### 4.3. Standard Curve Parameters

Standard curve parameters from 5 successful analytical runs are provided in Table 6 and Table 7 for nicotine and cotinine, respectively. A representative calibration curve is illustrated in Figure 1 and Figure 2 for nicotine and cotinine, respectively.

### 4.4. Study Sample Concentrations

Study sample concentrations are provided in Table 8 and Table 9 for nicotine and cotinine, respectively. The column "Split" refers to the "for analysis" or "back-up" sample collected.

Study samples, if any, with no significant peak at the mass transition and retention time of nicotine and cotinine, respectively, or with peak area ratios below that of the LLOQ standard, are reported as being below the limit of quantitation (BLQ).

### 4.5. Reassays

#### 4.5.1. Reassays for Analytical Reasons

Study samples needing re-analysis according to section 3.2.1 for nicotine and cotinine are identified in Table 10 and Table 11, respectively. Reassay descriptions are provided in Attachment 5.

#### 4.5.2. Reassays for Non-analytical Reasons (Value Requiring Confirmation, VRC)

There were no study samples that were reassayed due to non-analytical reasons. The procedure for VRC reassays and reporting of reassay results is provided in Attachment 3.

#### 4.5.3. Sponsor Selected Reassays

There were no Sponsor selected reassays. The procedure for SSR reassays and reporting of reassay results is provided in Attachment 3.

#### 4.5.4. Incurred Sample Reproducibility

The method for the determination of nicotine and cotinine was considered reproducible, 100% out of 40 repeat analyses for nicotine and 97.5% out of 40 repeat analyses for cotinine met acceptance criteria as defined in section 3.2.4. Results are presented in Table 12 and Table 13.

## 5. CHROMATOGRAMS

Representative chromatograms are provided in Attachment 8.

## 6. DEVIATIONS

**6.1.** Deviation DEV-LNK-13–0459 was initiated as two QC levels were incorrectly described in the Bioanalytical Study Plan (BSP). The lower QC level 2.00/10.0 ng/mL (Nicotine/Cotinine) should have been described as 2.00/15.0 ng/mL and the mid-QC level 7.50/75.0 ng/mL (Nicotine/Cotinine) should have been described as 8.00/80.0 ng/mL. The QC levels used in the clinical sample analysis were correct and appropriate thus there was no impact on the study.

**6.2.** Deviation DEV-LNK-14–0021 from BAM SOP, Section 5.5, was initiated when working standards were not sub-aliquoted before being stored and were left in bulk for use on all analytical runs in the study. There was no impact, as the working standards demonstrated consistent performance throughout the study. The sub-aliquoting step in the method was implemented to avoid the possibility of contaminating the standards from a possible inadequately washed pipette tip. No issues of standard contamination were observed throughout the study.

## 7. EVENTS

**7.1.** Event Observation EO-LNK-AA99071-02-13–0481 was initiated as it was observed that a single sample appeared to be a PK outlier during the selection of ISR samples. For Subject 0028, a significant spike in measured nicotine and cotinine concentration occurred on Day 4 after the subject had been clearly randomized to the smoking abstinence group. The single day concentration measured for Subject 0028 had been initially assayed on Analytical Run 1. The sample results were above the analytical range. The extrapolated results were 32.4 ng/mL for nicotine and 412 ng/mL for cotinine. The clinical sample for Subject 0028, Day 4 was reassayed with dilution (DF = 10) and the results confirmed the original measurements (30.5 ng/mL for nicotine and 414 ng/mL for cotinine).

Because the results had been confirmed analytically, further investigation into the sample order and sample identity was performed. The sample order was confirmed with the samples that remained within the original racks for Analytical Run 4. The clinical sample label was verified by the accession number both in comparison to the Celerion Watson label and the shipping manifest.

The concentrations of the Day 4 sample were so high that it seemed likely that any possible sample switch would not have come from the smoking abstinence group. A review of Group 1 results (AA99071-01) where the high concentration linear range was used to measure samples from subjects randomized to conventional cigarettes and the test product was performed. The results for Subject 0008, Day 4, stood out as another possible PK outlier. The concentrations of nicotine and cotinine for Subject 0008, Day 4 appeared to match the profile for Subject 0028.

For this reason, it was hypothesized that these two samples were inadvertently switched during sample collection or processing. The central laboratory was notified of the issue. The investigation resulted in no analytical impact for the study.
It is suspected that the Day 4 samples for Subjects 0008 and 0028 were inadvertently switched during sample collection or sample processing resulting in the observed PK outliers. The investigation of the sample from Subject 0028 could not be confirmed with the back-up sample due to limited sample volume. The sample was coded, therefore, as "not reportable." The results from Subject 0008 were confirmed; therefore, the original result was reported.

## 8. ANALYTICAL NOTES

**8.1.** Based on results from Analytical Runs 1 and 2, samples taken at Day 0 were diluted 5-fold prior to assay due to expected concentrations above the upper limit of quantitation.

**8.2.** The following analytical run was not included in the data set.

| Run ID | Analyte | Reason for Non-inclusion |
|---|---|---|
| 3 | Nicotine / Cotinine | Analytical Run 3 was reassayed as Analytical Run 5 due to an extraction error. |

**8.3.** The following analytical run was not included in the data set due to instrumentation issues. The issues were resolved, and the analytical run was reinjected.

| Run ID | Analyte | Reason for Non-inclusion |
|---|---|---|
| 2 | Nicotine | Analytical Run 2 was reinjected as Analytical Run 4 due to the test injections not confirming the original data after an observed QC bias suspected to be caused by ion competition in the mass spectrometer ESI source. |

**8.4.** The following samples could not be reassayed successfully for nicotine and cotinine as the sample volume for both the analysis and back-up sample were depleted.

| Subject | Analyte | Period | Time Point | Sample Number |
|---|---|---|---|---|
| 0017 | Nicotine / Cotinine | 1 | Day 1 0h 0m | 05111460000303 |
| 0062 | Nicotine | 1 | Day 1 0h 0m | 05111460000338 |
| 0169 | Nicotine | 1 | Day 5 0h 0m | 05111460000447 |

**8.5.** Analytical Run 4 consisted of reassays for nicotine only. The analytical run was not regressed for cotinine.

**8.6.** Analytical Runs 9 and 10 were included within the data set as they were part of the event investigation noted above in Section 7.1. The analytical run numbers (29 and 30) were taken from the AA99071-01 where the higher linear range was used. Analytical run summary data was reported under AA99071-01.

**8.7.** When a sample was reassayed for only one compound and the reassay result for the other compound was not needed, the unneeded reassay result was deactivated as "Not Used" and was not reported

## 9. ARCHIVES

At a minimum the following records will be retained:

- Study Plan Bioanalysis (and all amendments, if applicable)
- Raw data
- Study related correspondence
- Bioanalytical report (and all amendments, if applicable)

These documents will be kept in the archives of Celerion for at least ten (10) years, taken from the date of Bioanalytical Principal Investigator's signature on the final bioanalytical report. After this time the Sponsor will be contacted to decide if the records should be retained for a further defined time at Celerion, returned to the Sponsor, or disposed of. Study data and documentation are archived at the Celerion Lincoln facility for 90 days, after which the records may be transferred to:

Iron Mountain
1601 Leavenworth
Omaha, Nebraska 68102

## 10. CONCLUSION

In this bioanalytical study the concentration of nicotine for 269 samples and cotinine for 272 samples was determined in human plasma ($K_2EDTA$) samples collected in the Philip Morris International Research and Development clinical study ZRHR-REXC-03-EU using a validated LC-MS/MS method.

The overall performance of the LC-MS/MS method met acceptance criteria and the results obtained were of the required integrity and quality. These data can be used for further interpretation.

## 11. REFERENCES

[1] Guidance for Industry – Bioanalytical Method Validation: US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM) May 2001

[2] OECD Principles on Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17, OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, No. 1, OECD Publishing, Paris, France (2003).

[3] Protocol ZRHR-REXC-03-EU: "A Randomized, Controlled, Open-label, 3-Arm Parallel Group, Single-Center Study to Demonstrate Reductions in Exposure to Selected Smoke Constituents in Smoking, Healthy Subjects Switching to the Tobacco Heating System 2.2 (THS 2.2) or Smoking Abstinence, Compared to Continuing to Use Conventional Cigarettes, for 5 Days in Confinement"

[4] Study Plan Bioanalysis: Determination of Nicotine and Cotinine in Human Plasma ($K_2EDTA$) Samples from "A Randomized, Controlled, Open-label, 3-Arm Parallel Group, Single-Center Study to Demonstrate Reductions in Exposure to Selected Smoke Constituents in Smoking, Healthy Subjects Switching to the Tobacco Heating System 2.2 (THS 2.2) or Smoking Abstinence, Compared to Continuing to Use Conventional Cigarettes, for 5 Days in Confinement" by LC-MS/MS, Celerion Study AA99071-01 and AA99071-02

[5] Validation of an LC-MS/MS Method for the Determination of Nicotine and Cotinine in Human Plasma (EDTA), Celerion Study AA33664-06

[6] Bioanalytical Method SOP for the Determination of Nicotine and Cotinine in Human Plasma (EDTA), Celerion Study AA33664-06

[7] United States Food and Drug Administration Title 21 Code of Federal Regulations (CFR) Part 58

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

## RESULT TABLES

Table 1 Summary of Analytical Runs Performed

| Analyte Name | Run ID | Regression Status | Extraction Date | Assay Date | Description | Comment |
|---|---|---|---|---|---|---|
| Nicotine | 1 | Accepted | 15-Sep-2013 | 17-Sep-2013 | SEE WORKLIST FOR SUB AND TIMEPOINTS | OK |
| Nicotine | 2 | Rejected | 07-Oct-2013 | 07-Oct-2013 | SUB 0169,0185 PD 1 + REASSAYS | QC's fail |
| Nicotine | 4 | Accepted | 07-Oct-2013 | 08-Oct-2013 | RI of Run-002 (SUB 0169,0185 PD 1 + REASSAYS) | OK |
| Nicotine | 5 | Accepted | 11-Oct-2013 | 12-Oct-2013 | RR FAILED BATCH 3 + REASSAYS | OK |
| Nicotine | 6 | Accepted | 17-Oct-2013 | 17-Oct-2013 | ISRs | OK |
| Nicotine | 7 | Accepted | 21-Oct-2013 | 21-Oct-2013 | SUB 0015 PD 1 + REASSAYS | OK |
| Nicotine | 8 | Accepted | 31-Oct-2013 | 31-Oct-2013 | REASSAYS + ISRs (split 2's) | OK |
| Cotinine | 1 | Accepted | 15-Sep-2013 | 17-Sep-2013 | SEE WORKLIST FOR SUB AND TIMEPOINTS | OK |
| Cotinine | 2 | Accepted | 07-Oct-2013 | 07-Oct-2013 | SUB 0169,0185 PD 1 + REASSAYS | OK |
| Cotinine | 5 | Accepted | 11-Oct-2013 | 12-Oct-2013 | RR FAILED BATCH 3 + REASSAYS | OK |
| Cotinine | 6 | Accepted | 17-Oct-2013 | 17-Oct-2013 | ISRs | OK |
| Cotinine | 7 | Accepted | 21-Oct-2013 | 21-Oct-2013 | SUB 0015 PD 1 + REASSAYS | OK |
| Cotinine | 8 | Accepted | 31-Oct-2013 | 31-Oct-2013 | REASSAYS + ISRs (split 2's) | OK |

"Regression Status" reflects the status of the run with respect to run acceptance criteria.

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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Table 2 Quality Control and Dilution Quality Control Sample Data (Between-Analytical Run Precision and Accuracy) for Nicotine

| Assay Date | Run ID | QC A 0.600 ng/mL | QC E 2.00 ng/mL | QC F 5.00 ng/mL | QC F DF2 5.00 ng/mL | QC G 8.00 ng/mL | QC D DF4 20.0 ng/mL | QC D DF5 20.0 ng/mL | QC D DF10 20.0 ng/mL |
|---|---|---|---|---|---|---|---|---|---|
| 17-Sep-2013 | 1 | 0.572 | 1.89 | 4.41 | | 6.88 | | | |
| | | 0.571 | 1.85 | 4.26 | | 7.12 | | | |
| 08-Oct-2013 | 4 | 0.612 | 1.80 | 4.55 | | 6.97 | | | 17.8 |
| | | 0.612 | 1.72 | 4.39 | | 6.82 | | | 18.8 |
| | | | | | | | | | 19.5 |
| 12-Oct-2013 | 5 | 0.607 | 1.78 | 4.67 | | 7.08 | | 17.0 | |
| | | 0.607 | 1.89 | ~4.15 | | 6.89 | | 17.1 | |
| | | | | | | | | 18.1 | |
| 21-Oct-2013 | 7 | 0.573 | 2.04 | 4.84 | | 7.54 | | | 17.7 |
| | | ~0.749 | 2.04 | 4.96 | | 7.61 | | | 18.1 |
| | | | | | | | | | 17.2 |
| 31-Oct-2013 | 8 | 0.610 | 2.10 | 4.92 | 5.42 | 7.36 | ~16.7 | | |
| | | 0.565 | 2.14 | 5.44 | 5.61 | 8.34 | 17.2 | | |
| | | | | | 5.20 | | 17.8 | | |
| Mean | | 0.608 | 1.93 | 4.66 | 5.41 | 7.26 | 17.2 | 17.4 | 18.2 |
| S.D. | | 0.0534 | 0.145 | 0.390 | 0.205 | 0.470 | 0.551 | 0.608 | 0.833 |
| %CV | | 8.8 | 7.5 | 8.4 | 3.8 | 6.5 | 3.2 | 3.5 | 4.6 |
| %Theoretical | | 101.3 | 96.5 | 93.2 | 108 2 | 90.8 | 86.0 | 87.0 | 91.0 |
| %Bias | | 1.3 | -3.5 | -6.8 | 8.2 | -9.3 | -14.0 | -13.0 | -9.0 |
| n | | 10 | 10 | 10 | 3 | 10 | 3 | 3 | 6 |

~ > 15%Bias

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

Table 3 Quality Control and Dilution Quality Control Sample Data (Between-Analytical Run Precision and Accuracy) for Cotinine

| Assay Date | Run ID | QC A 3.00 ng/mL | QC E 15.0 ng/mL | QC F 50.0 ng/mL | QC F DF2 50.0 ng/mL | QC G 80.0 ng/mL | QC D DF4 200 ng/mL | QC D DF5 200 ng/mL | QC D DF10 200 ng/mL |
|---|---|---|---|---|---|---|---|---|---|
| 17-Sep-2013 | 1 | 3.13 | 15.4 | 47.3 | | 74.9 | | | |
| | | 3.17 | 14.4 | 47.8 | | 73.2 | | | |
| 07-Oct-2013 | 2 | 3.17 | 14.5 | 47.2 | | 75.0 | | | 194 |
| | | 3.13 | 14.2 | 46.6 | | 75.9 | | | 198 |
| | | | | | | | | | 197 |
| 12-Oct-2013 | 5 | 3.14 | 15.0 | 51.4 | | 72.7 | | 183 | |
| | | 3.25 | 14.5 | 47.3 | | 71.3 | | 184 | |
| | | | | | | | | 189 | |
| 21-Oct-2013 | 7 | 3.17 | 14.7 | 47.9 | | 76.3 | | | 191 |
| | | 3.21 | 14.7 | 49.2 | | 71.8 | | | 192 |
| | | | | | | | | | 193 |
| 31-Oct-2013 | 8 | 3.13 | 15.1 | 49.0 | 50.0 | 75.7 | 181 | | |
| | | 3.20 | 15.1 | 47.0 | 49.9 | 72.8 | 190 | | |
| | | | | | 50.5 | | 187 | | |
| Mean | | 3.17 | 14.8 | 48.1 | 50.1 | 74.0 | 186 | 185 | 194 |
| S.D. | | 0.0403 | 0.378 | 1.44 | 0.321 | 1.81 | 4.58 | 3.21 | 2.79 |
| %CV | | 1.3 | 2.6 | 3.0 | 0.6 | 2.4 | 2.5 | 1.7 | 1.4 |
| %Theoretical | | 105.7 | 98.7 | 96.2 | 100.2 | 92.5 | 93.0 | 92.5 | 97.0 |
| %Bias | | 5.7 | -1.3 | -3.8 | 0.2 | -7.5 | -7.0 | -7.5 | -3.0 |
| n | | 10 | 10 | 10 | 3 | 10 | 3 | 3 | 6 |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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Table 4 Back-calculated Calibration Standard Concentrations for Nicotine

| Assay Date | Run ID | STD B 0.200 ng/mL | STD C 0.400 ng/mL | STD D 0.800 ng/mL | STD E 1.00 ng/mL | STD F 2.50 ng/mL | STD G 5.00 ng/mL | STD H 7.50 ng/mL | STD I 9.00 ng/mL | STD J 10.0 ng/mL |
|---|---|---|---|---|---|---|---|---|---|---|
| 17-Sep-2013 | 1 | 0 208 | 0.375 | 0.756 | 1.01 | 2.57 | 5.12 | 7.49 | 9.10 | 10.0 |
| 08-Oct-2013 | 4 | *0 202 | 0.408 | 0.758 | 1.01 | 2.51 | 5.29 | 7.73 | 8.58 | 9.81 |
| 12-Oct-2013 | 5 | 0 198 | 0.415 | 0.787 | 0.977 | 2.43 | 5.13 | 7.55 | 8.94 | 10.1 |
| 21-Oct-2013 | 7 | 0 201 | 0.403 | 0.752 | 1.04 | 2.52 | 4.97 | 7.38 | 9.16 | 10.1 |
| 31-Oct-2013 | 8 | 0 194 | 0.429 | 0.752 | 1.02 | 2.66 | 5.02 | 7.27 | 8.56 | 10.1 |
| Mean | | 0 200 | 0.406 | 0.761 | 1.01 | 2.54 | 5.11 | 7.48 | 8.87 | 10.0 |
| S.D. | | 0.00591 | 0.0199 | 0.0148 | 0.0228 | 0.0847 | 0.123 | 0.174 | 0.284 | 0.126 |
| %CV | | 3.0 | 4.9 | 1.9 | 2.3 | 3.3 | 2.4 | 2.3 | 3.2 | 1.3 |
| %Bias | | 0.0 | 1.5 | -4.9 | 1.0 | 1.6 | 2.2 | -0.3 | -1.4 | 0.0 |
| n | | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Reason Deactivated
* Not Used (Interference)

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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Table 5 Back-calculated Calibration Standard Concentrations for Cotinine

| Assay Date | Run ID | STD B 1.00 ng/mL | STD C 2.00 ng/mL | STD D 4.00 ng/mL | STD E 10.0 ng/mL | STD F 25.0 ng/mL | STD G 50.0 ng/mL | STD H 75.0 ng/mL | STD I 90.0 ng/mL | STD J 100 ng/mL |
|---|---|---|---|---|---|---|---|---|---|---|
| 17-Sep-2013 | 1 | 0 991 | 2.04 | 3.99 | 10.0 | 25.3 | 50.4 | 73.7 | 89.0 | 100 |
| 07-Oct-2013 | 2 | 0 980 | 2.07 | 4.05 | 9.86 | 24.7 | 51.1 | 75.4 | 89.4 | 97.6 |
| 12-Oct-2013 | 5 | 0 973 | 2.09 | 4.07 | 10.0 | 25.5 | 51.2 | 72.7 | 88.9 | 96.4 |
| 21-Oct-2013 | 7 | 0 999 | 2.01 | 3.96 | 9.93 | 25.1 | 50.8 | 75.2 | 91.3 | 97.3 |
| 31-Oct-2013 | 8 | 0 974 | 2.07 | 4.09 | 10.2 | 25.1 | 52.2 | 72.3 | 87.5 | 96.3 |
| Mean | | 0 983 | 2.06 | 4.03 | 10.0 | 25.1 | 51.1 | 73.9 | 89.2 | 97.5 |
| S.D. | | 0.0113 | 0.0313 | 0.0550 | 0.127 | 0.297 | 0.669 | 1.41 | 1.37 | 1.50 |
| %CV | | 1.1 | 1.5 | 1.4 | 1.3 | 1.2 | 1.3 | 1.9 | 1.5 | 1.5 |
| %Bias | | -1.7 | 3.0 | 0.8 | 0.0 | 0.4 | 2.2 | -1.5 | -0.9 | -2.5 |
| n | | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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Table 6 Standard Curve Parameters for Nicotine

| Assay Date | Run ID | Slope | Intercept | R-Squared |
|---|---|---|---|---|
| 17-Sep-2013 | 1 | 1.98324044 | -0.0257441243 | 0.9982 |
| 08-Oct-2013 | 4 | 0.950765806 | -0.0296328097 | 0.9977 |
| 12-Oct-2013 | 5 | 1.30257596 | -0.0410928162 | 0.9993 |
| 21-Oct-2013 | 7 | 0.689847741 | -0.0198566469 | 0.9990 |
| 31-Oct-2013 | 8 | 6.04565140 | -0.264430937 | 0.9968 |
| Mean | | 2.19441627 | -0.0761514668 | 0.9982 |
| S.D. | | 2.20694242 | 0.105537032 | 0.0010 |
| %CV | | 100.6 | -138.6 | 0.1 |
| n | | 5 | 5 | 5 |

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Table 7 Standard Curve Parameters for Cotinine

| Assay Date | Run ID | Slope | Intercept | R-Squared |
|---|---|---|---|---|
| 17-Sep-2013 | 1 | 0.0284840878 | -0.00303013370 | 0.9998 |
| 07-Oct-2013 | 2 | 0.0290046184 | -0.00409440100 | 0.9995 |
| 12-Oct-2013 | 5 | 0.0620225573 | -0.00817218476 | 0.9990 |
| 21-Oct-2013 | 7 | 0.0326449719 | -0.00638351671 | 0.9998 |
| 31-Oct-2013 | 8 | 0.129043508 | -0.0186440129 | 0.9987 |
| Mean | | 0.0562399487 | -0.00806484981 | 0.9994 |
| S.D. | | 0.0430193874 | 0.00624239384 | 0.0005 |
| %CV | | 76.5 | -77.4 | 0.1 |
| n | | 5 | 5 | 5 |

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Table 8 Study Sample Concentrations for Nicotine

| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000001 | 4 | 0010 | 0 | 0 | 0 | 1 | 11.3 | OK | | Nicotine |
| 05111460000002 | 1 | 0010 | 1 | 0 | 0 | 1 | 0.311 | OK | | Nicotine |
| 05111460000003 | 1 | 0010 | 2 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000004 | 1 | 0010 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000005 | 1 | 0010 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000006 | 1 | 0010 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000007 | 1 | 0010 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000008 | 4 | 0013 | 0 | 0 | 0 | 1 | 19.2 | OK | | Nicotine |
| 05111460000009 | 1 | 0013 | 1 | 0 | 0 | 1 | 0.420 | OK | | Nicotine |
| 05111460000010 | 1 | 0013 | 2 | 0 | 0 | 1 | 0.301 | OK | | Nicotine |
| 05111460000011 | 1 | 0013 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000012 | 1 | 0013 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000013 | 1 | 0013 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000014 | 1 | 0013 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000015 | 4 | 0015 | 0 | 0 | 0 | 1 | 14.5 | OK | | Nicotine |
| 05111460000016 | 1 | 0015 | 1 | 0 | 0 | 1 | 0.252 | OK | | Nicotine |
| 05111460000017 | 1 | 0015 | 2 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000018 | 7 | 0015 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000019 | 1 | 0015 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000020 | 1 | 0015 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000021 | 1 | 0015 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000022 | 4 | 0017 | 0 | 0 | 0 | 1 | 25.3 | OK | | Nicotine |
| 05111460000023 | | 0017 | 1 | 0 | 0 | 1 | . | OK | SVD for Nicotine only | Nicotine |
| 05111460000024 | 1 | 0017 | 2 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000025 | 1 | 0017 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |

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| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000026 | 1 | 0017 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000027 | 1 | 0017 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000028 | 1 | 0017 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000029 | 4 | 0028 | 0 | 0 | 0 | 1 | 13.8 | OK | | Nicotine |
| 05111460000030 | 1 | 0028 | 1 | 0 | 0 | 1 | 0.380 | OK | | Nicotine |
| 05111460000031 | 5 | 0028 | 2 | 0 | 0 | 1 | 0.377 | OK | | Nicotine |
| 05111460000032 | 1 | 0028 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000033 | | 0028 | 4 | 0 | 0 | 1 | . | Other | Not Reportable | Nicotine |
| 05111460000034 | 1 | 0028 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000035 | 1 | 0028 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000036 | 4 | 0049 | 0 | 0 | 0 | 1 | 28.1 | OK | | Nicotine |
| 05111460000037 | 1 | 0049 | 1 | 0 | 0 | 1 | 0.431 | OK | | Nicotine |
| 05111460000038 | 1 | 0049 | 2 | 0 | 0 | 1 | 0.221 | OK | | Nicotine |
| 05111460000039 | 1 | 0049 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000040 | 1 | 0049 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000041 | 1 | 0049 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000042 | 1 | 0049 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000043 | 1 | 0051 | 0 | 0 | 0 | 1 | 9.91 | OK | | Nicotine |
| 05111460000044 | 1 | 0051 | 1 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000045 | 1 | 0051 | 2 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000046 | 1 | 0051 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000047 | 1 | 0051 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000048 | 1 | 0051 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000049 | 1 | 0051 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000050 | 4 | 0052 | 0 | 0 | 0 | 1 | 17.6 | OK | | Nicotine |
| 05111460000051 | 1 | 0052 | 1 | 0 | 0 | 1 | 0.313 | OK | | Nicotine |
| 05111460000052 | 1 | 0052 | 2 | 0 | 0 | 1 | 0.245 | OK | | Nicotine |
| 05111460000053 | 1 | 0052 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000054 | 1 | 0052 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000055 | 1 | 0052 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000056 | 1 | 0052 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000057 | 4 | 0062 | 0 | 0 | 0 | 1 | 19.3 | OK | | Nicotine |
| 05111460000058 | | 0062 | 1 | 0 | 0 | 1 | . | OK | SVD for Nicotine only | Nicotine |
| 05111460000059 | 1 | 0062 | 2 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000060 | 1 | 0062 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000061 | 5 | 0062 | 4 | 0 | 0 | 1 | 0.219 | OK | | Nicotine |
| 05111460000062 | 1 | 0062 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000063 | 1 | 0062 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000064 | 4 | 0063 | 0 | 0 | 0 | 1 | 13.9 | OK | | Nicotine |
| 05111460000065 | 1 | 0063 | 1 | 0 | 0 | 1 | 0.247 | OK | | Nicotine |
| 05111460000066 | 1 | 0063 | 2 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000067 | 1 | 0063 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000068 | 1 | 0063 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000069 | 1 | 0063 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000070 | 1 | 0063 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000071 | 4 | 0071 | 0 | 0 | 0 | 1 | 24.0 | OK | | Nicotine |
| 05111460000072 | 1 | 0071 | 1 | 0 | 0 | 1 | 0.660 | OK | | Nicotine |
| 05111460000073 | 1 | 0071 | 2 | 0 | 0 | 1 | 0.537 | OK | | Nicotine |
| 05111460000074 | 1 | 0071 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000075 | 1 | 0071 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000076 | 1 | 0071 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000077 | 1 | 0071 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000078 | 4 | 0076 | 0 | 0 | 0 | 1 | 14.5 | OK | | Nicotine |
| 05111460000079 | 1 | 0076 | 1 | 0 | 0 | 1 | 0.722 | OK | | Nicotine |
| 05111460000080 | 1 | 0076 | 2 | 0 | 0 | 1 | 0.210 | OK | | Nicotine |
| 05111460000081 | 1 | 0076 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000082 | 1 | 0076 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000083 | 1 | 0076 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000084 | 1 | 0076 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000085 | 1 | 0086 | 0 | 0 | 0 | 1 | 9.95 | OK | | Nicotine |
| 05111460000086 | 1 | 0086 | 1 | 0 | 0 | 1 | 0.994 | OK | | Nicotine |
| 05111460000087 | 1 | 0086 | 2 | 0 | 0 | 1 | 0.253 | OK | | Nicotine |
| 05111460000088 | 1 | 0086 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000089 | 1 | 0086 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000090 | 1 | 0086 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000091 | 1 | 0086 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000092 | 1 | 0104 | 0 | 0 | 0 | 1 | 8.72 | OK | | Nicotine |
| 05111460000093 | 1 | 0104 | 1 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000094 | 1 | 0104 | 2 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000095 | 1 | 0104 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000096 | 1 | 0104 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000097 | 1 | 0104 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000098 | 1 | 0104 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000099 | 4 | 0114 | 0 | 0 | 0 | 1 | 15.1 | OK | | Nicotine |
| 05111460000100 | 1 | 0114 | 1 | 0 | 0 | 1 | 0.250 | OK | | Nicotine |
| 05111460000101 | 1 | 0114 | 2 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000102 | 1 | 0114 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000103 | 1 | 0114 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000104 | 1 | 0114 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000105 | 1 | 0114 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000106 | 4 | 0123 | 0 | 0 | 0 | 1 | 16.5 | OK | | Nicotine |
| 05111460000107 | 1 | 0123 | 1 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000108 | 1 | 0123 | 2 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000109 | 1 | 0123 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000110 | 1 | 0123 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000111 | 1 | 0123 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000112 | 1 | 0123 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000120 | 1 | 0127 | 0 | 0 | 0 | 1 | 9.48 | OK | | Nicotine |
| 05111460000121 | 1 | 0127 | 1 | 0 | 0 | 1 | 0.414 | OK | | Nicotine |
| 05111460000122 | 1 | 0127 | 2 | 0 | 0 | 1 | 0.204 | OK | | Nicotine |
| 05111460000123 | 1 | 0127 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000124 | 1 | 0127 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000125 | 1 | 0127 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000126 | 1 | 0127 | 6 | 0 | 0 | 1 | 0.232 | OK | | Nicotine |
| 05111460000127 | 4 | 0128 | 0 | 0 | 0 | 1 | 13.6 | OK | | Nicotine |
| 05111460000128 | 1 | 0128 | 1 | 0 | 0 | 1 | 0.534 | OK | | Nicotine |
| 05111460000129 | 1 | 0128 | 2 | 0 | 0 | 1 | 0.220 | OK | | Nicotine |
| 05111460000130 | 1 | 0128 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000131 | 1 | 0128 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000132 | 1 | 0128 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000133 | 1 | 0128 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000134 | 4 | 0133 | 0 | 0 | 0 | 1 | 25.6 | OK | | Nicotine |
| 05111460000135 | 1 | 0133 | 1 | 0 | 0 | 1 | 0.403 | OK | | Nicotine |
| 05111460000136 | 1 | 0133 | 2 | 0 | 0 | 1 | 0.267 | OK | | Nicotine |
| 05111460000137 | 1 | 0133 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000138 | 1 | 0133 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000139 | 1 | 0133 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000140 | 1 | 0133 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000141 | 1 | 0137 | 0 | 0 | 0 | 1 | 8.35 | OK | | Nicotine |
| 05111460000142 | 1 | 0137 | 1 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000143 | 1 | 0137 | 2 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000144 | 1 | 0137 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |

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| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000145 | 1 | 0137 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000146 | 1 | 0137 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000147 | 1 | 0137 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000148 | 4 | 0145 | 0 | 0 | 0 | 1 | 10.8 | OK | | Nicotine |
| 05111460000149 | 1 | 0145 | 1 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000150 | 1 | 0145 | 2 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000151 | 1 | 0145 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000152 | 1 | 0145 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000153 | 1 | 0145 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000154 | 1 | 0145 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000155 | 1 | 0150 | 0 | 0 | 0 | 1 | 9.40 | OK | | Nicotine |
| 05111460000156 | 1 | 0150 | 1 | 0 | 0 | 1 | 0.495 | OK | | Nicotine |
| 05111460000157 | 1 | 0150 | 2 | 0 | 0 | 1 | 0.239 | OK | | Nicotine |
| 05111460000158 | 1 | 0150 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000159 | 1 | 0150 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000160 | 1 | 0150 | 5 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000161 | 1 | 0150 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000162 | 4 | 0169 | 0 | 0 | 0 | 1 | 4.88 | OK | | Nicotine |
| 05111460000163 | 5 | 0169 | 1 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000164 | 5 | 0169 | 2 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000165 | 5 | 0169 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000166 | 5 | 0169 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000167 | | 0169 | 5 | 0 | 0 | 1 | . | OK | SVD for Nicotine only | Nicotine |
| 05111460000168 | 5 | 0169 | 6 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000170 | 5 | 0185 | 1 | 0 | 0 | 1 | 0.259 | OK | | Nicotine |
| 05111460000171 | 5 | 0185 | 2 | 0 | 0 | 1 | 0.242 | OK | | Nicotine |
| 05111460000172 | 5 | 0185 | 3 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000173 | 5 | 0185 | 4 | 0 | 0 | 1 | BLQ<(0.200) | OK | | Nicotine |

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| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000174 | 5 | 0185 | 5 | 0 | 0 | 1 | 0.241 | OK | | Nicotine |
| 05111460000175 | 5 | 0185 | 6 | 0 | 0 | 1 | 0.208 | OK | | Nicotine |
| 05111460000236 | 5 | 0266 | 4 | 0 | 0 | 1 | 0.201 | OK | | Nicotine |
| 05111460000243 | 5 | 0273 | 4 | 0 | 0 | 1 | 0.296 | OK | | Nicotine |
| 05111460000245 | 5 | 0273 | 6 | 0 | 0 | 1 | 0.238 | OK | | Nicotine |
| 05111460000250 | 5 | 0289 | 4 | 0 | 0 | 1 | 0.258 | OK | | Nicotine |
| 05111460000257 | 5 | 0292 | 4 | 0 | 0 | 1 | 0.235 | OK | | Nicotine |
| 05111460000264 | 5 | 0306 | 4 | 0 | 0 | 1 | 0.443 | OK | | Nicotine |
| 05111460000271 | 5 | 0317 | 4 | 0 | 0 | 1 | 0.204 | OK | | Nicotine |
| 05111460000272 | 5 | 0317 | 5 | 0 | 0 | 1 | 0.250 | OK | | Nicotine |
| 05111460000273 | 5 | 0317 | 6 | 0 | 0 | 1 | 0.239 | OK | | Nicotine |
| 05111460000278 | 5 | 0325 | 4 | 0 | 0 | 1 | 0.273 | OK | | Nicotine |
| 05111460000303 | | 0017 | 1 | 0 | 0 | 2 | . | OK | SVD for Nicotine only | Nicotine |
| 05111460000313 | | 0028 | 4 | 0 | 0 | 2 | . | Other | Not Reportable | Nicotine |
| 05111460000338 | | 0062 | 1 | 0 | 0 | 2 | . | OK | SVD for Nicotine only | Nicotine |
| 05111460000447 | | 0169 | 5 | 0 | 0 | 2 | . | OK | SVD for Nicotine only | Nicotine |
| 05111460000449 | 5 | 0185 | 0 | 0 | 0 | 2 | 16.1 | OK | | Nicotine |
| 05111460000456 | 5 | 0197 | 0 | 0 | 0 | 2 | 17.8 | OK | | Nicotine |
| 05111460000457 | 5 | 0197 | 1 | 0 | 0 | 2 | 0.394 | OK | | Nicotine |
| 05111460000458 | 5 | 0197 | 2 | 0 | 0 | 2 | 0.269 | OK | | Nicotine |
| 05111460000459 | 5 | 0197 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000460 | 5 | 0197 | 4 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000461 | 5 | 0197 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000462 | 5 | 0197 | 6 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000463 | 5 | 0203 | 0 | 0 | 0 | 2 | 11.8 | OK | | Nicotine |
| 05111460000464 | 5 | 0203 | 1 | 0 | 0 | 2 | 0.249 | OK | | Nicotine |
| 05111460000465 | 5 | 0203 | 2 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000466 | 5 | 0203 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000467 | 5 | 0203 | 4 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000468 | 5 | 0203 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000469 | 5 | 0203 | 6 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000470 | 5 | 0218 | 0 | 0 | 0 | 2 | 15.8 | OK | | Nicotine |
| 05111460000471 | 5 | 0218 | 1 | 0 | 0 | 2 | 0.239 | OK | | Nicotine |
| 05111460000472 | 5 | 0218 | 2 | 0 | 0 | 2 | 0.341 | OK | | Nicotine |
| 05111460000473 | 5 | 0218 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000474 | 5 | 0218 | 4 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000475 | 5 | 0218 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000476 | 5 | 0218 | 6 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000477 | 5 | 0240 | 0 | 0 | 0 | 2 | 15.7 | OK | | Nicotine |
| 05111460000478 | 5 | 0240 | 1 | 0 | 0 | 2 | 0.363 | OK | | Nicotine |
| 05111460000479 | 5 | 0240 | 2 | 0 | 0 | 2 | 0.214 | OK | | Nicotine |
| 05111460000480 | 5 | 0240 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000481 | 5 | 0240 | 4 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000482 | 5 | 0240 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000483 | 5 | 0240 | 6 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000484 | 5 | 0249 | 0 | 0 | 0 | 2 | 27.7 | OK | | Nicotine |
| 05111460000485 | 5 | 0249 | 1 | 0 | 0 | 2 | 0.271 | OK | | Nicotine |
| 05111460000486 | 5 | 0249 | 2 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000487 | 5 | 0249 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000488 | 5 | 0249 | 4 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000489 | 5 | 0249 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000490 | 5 | 0249 | 6 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000491 | 5 | 0251 | 0 | 0 | 0 | 2 | 19.0 | OK | | Nicotine |
| 05111460000492 | 5 | 0251 | 1 | 0 | 0 | 2 | 0.262 | OK | | Nicotine |
| 05111460000493 | 5 | 0251 | 2 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000494 | 5 | 0251 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |

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| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000495 | 5 | 0251 | 4 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000496 | 5 | 0251 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000497 | 5 | 0251 | 6 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000498 | 5 | 0252 | 0 | 0 | 0 | 2 | 12.6 | OK | | Nicotine |
| 05111460000499 | 5 | 0252 | 1 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000500 | 5 | 0252 | 2 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000501 | 5 | 0252 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000502 | 5 | 0252 | 4 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000503 | 5 | 0252 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000504 | 5 | 0252 | 6 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000505 | 5 | 0265 | 0 | 0 | 0 | 2 | 12.8 | OK | | Nicotine |
| 05111460000506 | 5 | 0265 | 1 | 0 | 0 | 2 | 0.495 | OK | | Nicotine |
| 05111460000507 | 5 | 0265 | 2 | 0 | 0 | 2 | 0.235 | OK | | Nicotine |
| 05111460000508 | 5 | 0265 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000509 | 5 | 0265 | 4 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000510 | 5 | 0265 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000511 | 5 | 0265 | 6 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000512 | 5 | 0266 | 0 | 0 | 0 | 2 | 12.6 | OK | | Nicotine |
| 05111460000513 | 5 | 0266 | 1 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000514 | 5 | 0266 | 2 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000515 | 7 | 0266 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000517 | 7 | 0266 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000518 | 7 | 0266 | 6 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000519 | 5 | 0273 | 0 | 0 | 0 | 2 | 13.2 | OK | | Nicotine |
| 05111460000520 | 5 | 0273 | 1 | 0 | 0 | 2 | 0.210 | OK | | Nicotine |
| 05111460000521 | 5 | 0273 | 2 | 0 | 0 | 2 | 0.216 | OK | | Nicotine |
| 05111460000522 | 7 | 0273 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000524 | 7 | 0273 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000526 | 5 | 0289 | 0 | 0 | 0 | 2 | 14.2 | OK | | Nicotine |
| 05111460000527 | 5 | 0289 | 1 | 0 | 0 | 2 | 0.268 | OK | | Nicotine |
| 05111460000528 | 5 | 0289 | 2 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000529 | 7 | 0289 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000531 | 7 | 0289 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000532 | 7 | 0289 | 6 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000533 | 5 | 0292 | 0 | 0 | 0 | 2 | 18.6 | OK | | Nicotine |
| 05111460000534 | 5 | 0292 | 1 | 0 | 0 | 2 | 0.711 | OK | | Nicotine |
| 05111460000535 | 5 | 0292 | 2 | 0 | 0 | 2 | 0.353 | OK | | Nicotine |
| 05111460000536 | 7 | 0292 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000538 | 7 | 0292 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000539 | 7 | 0292 | 6 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000540 | 5 | 0306 | 0 | 0 | 0 | 2 | 28.4 | OK | | Nicotine |
| 05111460000541 | 5 | 0306 | 1 | 0 | 0 | 2 | 1.03 | OK | | Nicotine |
| 05111460000542 | 5 | 0306 | 2 | 0 | 0 | 2 | 0.640 | OK | | Nicotine |
| 05111460000543 | 7 | 0306 | 3 | 0 | 0 | 2 | 0.299 | OK | | Nicotine |
| 05111460000545 | 7 | 0306 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000546 | 7 | 0306 | 6 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000547 | 5 | 0317 | 0 | 0 | 0 | 2 | 6.04 | OK | | Nicotine |
| 05111460000548 | 5 | 0317 | 1 | 0 | 0 | 2 | 0.434 | OK | | Nicotine |
| 05111460000549 | 5 | 0317 | 2 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000550 | 7 | 0317 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000554 | 5 | 0325 | 0 | 0 | 0 | 2 | 18.5 | OK | | Nicotine |
| 05111460000555 | 5 | 0325 | 1 | 0 | 0 | 2 | 0.553 | OK | | Nicotine |
| 05111460000556 | 5 | 0325 | 2 | 0 | 0 | 2 | 0.287 | OK | | Nicotine |
| 05111460000557 | 7 | 0325 | 3 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000559 | 7 | 0325 | 5 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |
| 05111460000560 | 7 | 0325 | 6 | 0 | 0 | 2 | BLQ<(0.200) | OK | | Nicotine |

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| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000561 | | 0242 | 0 | 0 | 0 | 2 | . | Other | Analysis not required. | Nicotine |
| 05111460000568 | | 0242 | 0 | 0 | 0 | 1 | . | Other | Analysis not required. | Nicotine |
| 05111460000575 | | 0245 | 0 | 0 | 0 | 2 | . | Other | Analysis not required. | Nicotine |
| 05111460000582 | | 0245 | 0 | 0 | 0 | 1 | . | Other | Analysis not required. | Nicotine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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Table 9 Study Sample Concentrations for Cotinine

| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000001 | 2 | 0010 | 0 | 0 | 0 | 1 | 182 | OK | | Cotinine |
| 05111460000002 | 1 | 0010 | 1 | 0 | 0 | 1 | 68.0 | OK | | Cotinine |
| 05111460000003 | 1 | 0010 | 2 | 0 | 0 | 1 | 22.9 | OK | | Cotinine |
| 05111460000004 | 1 | 0010 | 3 | 0 | 0 | 1 | 8.40 | OK | | Cotinine |
| 05111460000005 | 1 | 0010 | 4 | 0 | 0 | 1 | 3.22 | OK | | Cotinine |
| 05111460000006 | 1 | 0010 | 5 | 0 | 0 | 1 | 2.25 | OK | | Cotinine |
| 05111460000007 | 1 | 0010 | 6 | 0 | 0 | 1 | 1.23 | OK | | Cotinine |
| 05111460000008 | 2 | 0013 | 0 | 0 | 0 | 1 | 289 | OK | | Cotinine |
| 05111460000009 | 2 | 0013 | 1 | 0 | 0 | 1 | 118 | OK | | Cotinine |
| 05111460000010 | 1 | 0013 | 2 | 0 | 0 | 1 | 44.4 | OK | | Cotinine |
| 05111460000011 | 1 | 0013 | 3 | 0 | 0 | 1 | 19.8 | OK | | Cotinine |
| 05111460000012 | 1 | 0013 | 4 | 0 | 0 | 1 | 6.36 | OK | | Cotinine |
| 05111460000013 | 1 | 0013 | 5 | 0 | 0 | 1 | 2.75 | OK | | Cotinine |
| 05111460000014 | 1 | 0013 | 6 | 0 | 0 | 1 | 2.41 | OK | | Cotinine |
| 05111460000015 | 2 | 0015 | 0 | 0 | 0 | 1 | 241 | OK | | Cotinine |
| 05111460000016 | 1 | 0015 | 1 | 0 | 0 | 1 | 93.0 | OK | | Cotinine |
| 05111460000017 | 1 | 0015 | 2 | 0 | 0 | 1 | 30.8 | OK | | Cotinine |
| 05111460000018 | 7 | 0015 | 3 | 0 | 0 | 1 | 11.1 | OK | | Cotinine |
| 05111460000019 | 1 | 0015 | 4 | 0 | 0 | 1 | 3.65 | OK | | Cotinine |
| 05111460000020 | 1 | 0015 | 5 | 0 | 0 | 1 | 2.37 | OK | | Cotinine |
| 05111460000021 | 1 | 0015 | 6 | 0 | 0 | 1 | 1.19 | OK | | Cotinine |
| 05111460000022 | 2 | 0017 | 0 | 0 | 0 | 1 | 204 | OK | | Cotinine |
| 05111460000023 | 2 | 0017 | 1 | 0 | 0 | 1 | 94.0 | OK | SVD for Nicotine only | Cotinine |
| 05111460000024 | 1 | 0017 | 2 | 0 | 0 | 1 | 29.6 | OK | | Cotinine |
| 05111460000025 | 1 | 0017 | 3 | 0 | 0 | 1 | 10.3 | OK | | Cotinine |
| 05111460000026 | 1 | 0017 | 4 | 0 | 0 | 1 | 4.13 | OK | | Cotinine |

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| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000027 | 1 | 0017 | 5 | 0 | 0 | 1 | 2.88 | OK | | Cotinine |
| 05111460000028 | 1 | 0017 | 6 | 0 | 0 | 1 | 1.54 | OK | | Cotinine |
| 05111460000029 | 2 | 0028 | 0 | 0 | 0 | 1 | 212 | OK | | Cotinine |
| 05111460000030 | 1 | 0028 | 1 | 0 | 0 | 1 | 64.3 | OK | | Cotinine |
| 05111460000031 | 2 | 0028 | 2 | 0 | 0 | 1 | 20.8 | OK | | Cotinine |
| 05111460000032 | 1 | 0028 | 3 | 0 | 0 | 1 | 8.02 | OK | | Cotinine |
| 05111460000033 | | 0028 | 4 | 0 | 0 | 1 | . | Other | Not Reportable | Cotinine |
| 05111460000034 | 1 | 0028 | 5 | 0 | 0 | 1 | 2.63 | OK | | Cotinine |
| 05111460000035 | 1 | 0028 | 6 | 0 | 0 | 1 | 1.42 | OK | | Cotinine |
| 05111460000036 | 2 | 0049 | 0 | 0 | 0 | 1 | 332 | OK | | Cotinine |
| 05111460000037 | 2 | 0049 | 1 | 0 | 0 | 1 | 130 | OK | | Cotinine |
| 05111460000038 | 1 | 0049 | 2 | 0 | 0 | 1 | 46.8 | OK | | Cotinine |
| 05111460000039 | 1 | 0049 | 3 | 0 | 0 | 1 | 19.5 | OK | | Cotinine |
| 05111460000040 | 1 | 0049 | 4 | 0 | 0 | 1 | 7.99 | OK | | Cotinine |
| 05111460000041 | 1 | 0049 | 5 | 0 | 0 | 1 | 5.49 | OK | | Cotinine |
| 05111460000042 | 1 | 0049 | 6 | 0 | 0 | 1 | 2.38 | OK | | Cotinine |
| 05111460000043 | 2 | 0051 | 0 | 0 | 0 | 1 | 206 | OK | | Cotinine |
| 05111460000044 | 1 | 0051 | 1 | 0 | 0 | 1 | 75.0 | OK | | Cotinine |
| 05111460000045 | 1 | 0051 | 2 | 0 | 0 | 1 | 24.3 | OK | | Cotinine |
| 05111460000046 | 1 | 0051 | 3 | 0 | 0 | 1 | 9.45 | OK | | Cotinine |
| 05111460000047 | 1 | 0051 | 4 | 0 | 0 | 1 | 3.43 | OK | | Cotinine |
| 05111460000048 | 1 | 0051 | 5 | 0 | 0 | 1 | 1.55 | OK | | Cotinine |
| 05111460000049 | 1 | 0051 | 6 | 0 | 0 | 1 | 1.42 | OK | | Cotinine |
| 05111460000050 | 2 | 0052 | 0 | 0 | 0 | 1 | 260 | OK | | Cotinine |
| 05111460000051 | 2 | 0052 | 1 | 0 | 0 | 1 | 102 | OK | | Cotinine |
| 05111460000052 | 1 | 0052 | 2 | 0 | 0 | 1 | 38.4 | OK | | Cotinine |
| 05111460000053 | 1 | 0052 | 3 | 0 | 0 | 1 | 18.6 | OK | | Cotinine |
| 05111460000054 | 1 | 0052 | 4 | 0 | 0 | 1 | 6.60 | OK | | Cotinine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000055 | 1 | 0052 | 5 | 0 | 0 | 1 | 4.82 | OK | | Cotinine |
| 05111460000056 | 1 | 0052 | 6 | 0 | 0 | 1 | 2.63 | OK | | Cotinine |
| 05111460000057 | 2 | 0062 | 0 | 0 | 0 | 1 | 211 | OK | | Cotinine |
| 05111460000058 | 2 | 0062 | 1 | 0 | 0 | 1 | 81.1 | OK | SVD for Nicotine only | Cotinine |
| 05111460000059 | 1 | 0062 | 2 | 0 | 0 | 1 | 25.6 | OK | | Cotinine |
| 05111460000060 | 1 | 0062 | 3 | 0 | 0 | 1 | 9.69 | OK | | Cotinine |
| 05111460000061 | 2 | 0062 | 4 | 0 | 0 | 1 | 3.30 | OK | | Cotinine |
| 05111460000062 | 1 | 0062 | 5 | 0 | 0 | 1 | 2.40 | OK | | Cotinine |
| 05111460000063 | 1 | 0062 | 6 | 0 | 0 | 1 | 1.37 | OK | | Cotinine |
| 05111460000064 | 2 | 0063 | 0 | 0 | 0 | 1 | 277 | OK | | Cotinine |
| 05111460000065 | 1 | 0063 | 1 | 0 | 0 | 1 | 92.2 | OK | | Cotinine |
| 05111460000066 | 1 | 0063 | 2 | 0 | 0 | 1 | 28.0 | OK | | Cotinine |
| 05111460000067 | 1 | 0063 | 3 | 0 | 0 | 1 | 8.99 | OK | | Cotinine |
| 05111460000068 | 1 | 0063 | 4 | 0 | 0 | 1 | 3.36 | OK | | Cotinine |
| 05111460000069 | 1 | 0063 | 5 | 0 | 0 | 1 | 1.74 | OK | | Cotinine |
| 05111460000070 | 1 | 0063 | 6 | 0 | 0 | 1 | 1.46 | OK | | Cotinine |
| 05111460000071 | 2 | 0071 | 0 | 0 | 0 | 1 | 328 | OK | | Cotinine |
| 05111460000072 | 2 | 0071 | 1 | 0 | 0 | 1 | 130 | OK | | Cotinine |
| 05111460000073 | 1 | 0071 | 2 | 0 | 0 | 1 | 47.6 | OK | | Cotinine |
| 05111460000074 | 1 | 0071 | 3 | 0 | 0 | 1 | 18.2 | OK | | Cotinine |
| 05111460000075 | 1 | 0071 | 4 | 0 | 0 | 1 | 6.21 | OK | | Cotinine |
| 05111460000076 | 1 | 0071 | 5 | 0 | 0 | 1 | 2.66 | OK | | Cotinine |
| 05111460000077 | 1 | 0071 | 6 | 0 | 0 | 1 | 2.27 | OK | | Cotinine |
| 05111460000078 | 2 | 0076 | 0 | 0 | 0 | 1 | 246 | OK | | Cotinine |
| 05111460000079 | 2 | 0076 | 1 | 0 | 0 | 1 | 124 | OK | | Cotinine |
| 05111460000080 | 1 | 0076 | 2 | 0 | 0 | 1 | 49.3 | OK | | Cotinine |
| 05111460000081 | 1 | 0076 | 3 | 0 | 0 | 1 | 21.7 | OK | | Cotinine |
| 05111460000082 | 1 | 0076 | 4 | 0 | 0 | 1 | 9.12 | OK | | Cotinine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000083 | 1 | 0076 | 5 | 0 | 0 | 1 | 4.17 | OK | | Cotinine |
| 05111460000084 | 1 | 0076 | 6 | 0 | 0 | 1 | 3.51 | OK | | Cotinine |
| 05111460000085 | 2 | 0086 | 0 | 0 | 0 | 1 | 247 | OK | | Cotinine |
| 05111460000086 | 2 | 0086 | 1 | 0 | 0 | 1 | 119 | OK | | Cotinine |
| 05111460000087 | 1 | 0086 | 2 | 0 | 0 | 1 | 43.9 | OK | | Cotinine |
| 05111460000088 | 1 | 0086 | 3 | 0 | 0 | 1 | 19.9 | OK | | Cotinine |
| 05111460000089 | 1 | 0086 | 4 | 0 | 0 | 1 | 8.33 | OK | | Cotinine |
| 05111460000090 | 1 | 0086 | 5 | 0 | 0 | 1 | 4.09 | OK | | Cotinine |
| 05111460000091 | 1 | 0086 | 6 | 0 | 0 | 1 | 3.52 | OK | | Cotinine |
| 05111460000092 | 2 | 0104 | 0 | 0 | 0 | 1 | 134 | OK | | Cotinine |
| 05111460000093 | 1 | 0104 | 1 | 0 | 0 | 1 | 41.3 | OK | | Cotinine |
| 05111460000094 | 1 | 0104 | 2 | 0 | 0 | 1 | 10.4 | OK | | Cotinine |
| 05111460000095 | 1 | 0104 | 3 | 0 | 0 | 1 | 3.10 | OK | | Cotinine |
| 05111460000096 | 1 | 0104 | 4 | 0 | 0 | 1 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000097 | 1 | 0104 | 5 | 0 | 0 | 1 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000098 | 1 | 0104 | 6 | 0 | 0 | 1 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000099 | 2 | 0114 | 0 | 0 | 0 | 1 | 179 | OK | | Cotinine |
| 05111460000100 | 1 | 0114 | 1 | 0 | 0 | 1 | 92.3 | OK | | Cotinine |
| 05111460000101 | 1 | 0114 | 2 | 0 | 0 | 1 | 35.5 | OK | | Cotinine |
| 05111460000102 | 1 | 0114 | 3 | 0 | 0 | 1 | 14.3 | OK | | Cotinine |
| 05111460000103 | 1 | 0114 | 4 | 0 | 0 | 1 | 5.56 | OK | | Cotinine |
| 05111460000104 | 1 | 0114 | 5 | 0 | 0 | 1 | 2.30 | OK | | Cotinine |
| 05111460000105 | 1 | 0114 | 6 | 0 | 0 | 1 | 2.05 | OK | | Cotinine |
| 05111460000106 | 2 | 0123 | 0 | 0 | 0 | 1 | 207 | OK | | Cotinine |
| 05111460000107 | 1 | 0123 | 1 | 0 | 0 | 1 | 96.3 | OK | | Cotinine |
| 05111460000108 | 1 | 0123 | 2 | 0 | 0 | 1 | 36.7 | OK | | Cotinine |
| 05111460000109 | 1 | 0123 | 3 | 0 | 0 | 1 | 16.1 | OK | | Cotinine |
| 05111460000110 | 1 | 0123 | 4 | 0 | 0 | 1 | 6.38 | OK | | Cotinine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000111 | 1 | 0123 | 5 | 0 | 0 | 1 | 2.67 | OK | | Cotinine |
| 05111460000112 | 1 | 0123 | 6 | 0 | 0 | 1 | 2.20 | OK | | Cotinine |
| 05111460000120 | 2 | 0127 | 0 | 0 | 0 | 1 | 185 | OK | | Cotinine |
| 05111460000121 | 1 | 0127 | 1 | 0 | 0 | 1 | 98.8 | OK | | Cotinine |
| 05111460000122 | 1 | 0127 | 2 | 0 | 0 | 1 | 41.2 | OK | | Cotinine |
| 05111460000123 | 1 | 0127 | 3 | 0 | 0 | 1 | 22.8 | OK | | Cotinine |
| 05111460000124 | 1 | 0127 | 4 | 0 | 0 | 1 | 11.0 | OK | | Cotinine |
| 05111460000125 | 1 | 0127 | 5 | 0 | 0 | 1 | 5.42 | OK | | Cotinine |
| 05111460000126 | 1 | 0127 | 6 | 0 | 0 | 1 | 5.13 | OK | | Cotinine |
| 05111460000127 | 2 | 0128 | 0 | 0 | 0 | 1 | 175 | OK | | Cotinine |
| 05111460000128 | 1 | 0128 | 1 | 0 | 0 | 1 | 76.3 | OK | | Cotinine |
| 05111460000129 | 1 | 0128 | 2 | 0 | 0 | 1 | 29.8 | OK | | Cotinine |
| 05111460000130 | 1 | 0128 | 3 | 0 | 0 | 1 | 13.3 | OK | | Cotinine |
| 05111460000131 | 1 | 0128 | 4 | 0 | 0 | 1 | 5.67 | OK | | Cotinine |
| 05111460000132 | 1 | 0128 | 5 | 0 | 0 | 1 | 2.51 | OK | | Cotinine |
| 05111460000133 | 1 | 0128 | 6 | 0 | 0 | 1 | 2.39 | OK | | Cotinine |
| 05111460000134 | 2 | 0133 | 0 | 0 | 0 | 1 | 315 | OK | | Cotinine |
| 05111460000135 | 2 | 0133 | 1 | 0 | 0 | 1 | 106 | OK | | Cotinine |
| 05111460000136 | 1 | 0133 | 2 | 0 | 0 | 1 | 31.9 | OK | | Cotinine |
| 05111460000137 | 1 | 0133 | 3 | 0 | 0 | 1 | 11.8 | OK | | Cotinine |
| 05111460000138 | 1 | 0133 | 4 | 0 | 0 | 1 | 4.17 | OK | | Cotinine |
| 05111460000139 | 1 | 0133 | 5 | 0 | 0 | 1 | 1.74 | OK | | Cotinine |
| 05111460000140 | 1 | 0133 | 6 | 0 | 0 | 1 | 1.99 | OK | | Cotinine |
| 05111460000141 | 2 | 0137 | 0 | 0 | 0 | 1 | 134 | OK | | Cotinine |
| 05111460000142 | 1 | 0137 | 1 | 0 | 0 | 1 | 50.2 | OK | | Cotinine |
| 05111460000143 | 1 | 0137 | 2 | 0 | 0 | 1 | 14.9 | OK | | Cotinine |
| 05111460000144 | 1 | 0137 | 3 | 0 | 0 | 1 | 5.33 | OK | | Cotinine |
| 05111460000145 | 1 | 0137 | 4 | 0 | 0 | 1 | 1.66 | OK | | Cotinine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000146 | 1 | 0137 | 5 | 0 | 0 | 1 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000147 | 2 | 0137 | 6 | 0 | 0 | 1 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000148 | 2 | 0145 | 0 | 0 | 0 | 1 | 143 | OK | | Cotinine |
| 05111460000149 | 1 | 0145 | 1 | 0 | 0 | 1 | 30.5 | OK | | Cotinine |
| 05111460000150 | 1 | 0145 | 2 | 0 | 0 | 1 | 4.82 | OK | | Cotinine |
| 05111460000151 | 1 | 0145 | 3 | 0 | 0 | 1 | 1.32 | OK | | Cotinine |
| 05111460000152 | 1 | 0145 | 4 | 0 | 0 | 1 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000153 | 1 | 0145 | 5 | 0 | 0 | 1 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000154 | 1 | 0145 | 6 | 0 | 0 | 1 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000155 | 2 | 0150 | 0 | 0 | 0 | 1 | 237 | OK | | Cotinine |
| 05111460000156 | 2 | 0150 | 1 | 0 | 0 | 1 | 148 | OK | | Cotinine |
| 05111460000157 | 1 | 0150 | 2 | 0 | 0 | 1 | 68.7 | OK | | Cotinine |
| 05111460000158 | 1 | 0150 | 3 | 0 | 0 | 1 | 35.4 | OK | | Cotinine |
| 05111460000159 | 1 | 0150 | 4 | 0 | 0 | 1 | 15.8 | OK | | Cotinine |
| 05111460000160 | 1 | 0150 | 5 | 0 | 0 | 1 | 7.99 | OK | | Cotinine |
| 05111460000161 | 1 | 0150 | 6 | 0 | 0 | 1 | 6.86 | OK | | Cotinine |
| 05111460000163 | 2 | 0169 | 1 | 0 | 0 | 1 | 54.2 | OK | | Cotinine |
| 05111460000164 | 2 | 0169 | 2 | 0 | 0 | 1 | 17.3 | OK | | Cotinine |
| 05111460000165 | 2 | 0169 | 3 | 0 | 0 | 1 | 6.80 | OK | | Cotinine |
| 05111460000166 | 2 | 0169 | 4 | 0 | 0 | 1 | 2.25 | OK | | Cotinine |
| 05111460000167 | 2 | 0169 | 5 | 0 | 0 | 1 | 1.06 | OK | SVD for Nicotine only | Cotinine |
| 05111460000168 | 2 | 0169 | 6 | 0 | 0 | 1 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000170 | 2 | 0185 | 1 | 0 | 0 | 1 | 60.9 | OK | | Cotinine |
| 05111460000171 | 2 | 0185 | 2 | 0 | 0 | 1 | 16.1 | OK | | Cotinine |
| 05111460000172 | 2 | 0185 | 3 | 0 | 0 | 1 | 5.87 | OK | | Cotinine |
| 05111460000173 | 2 | 0185 | 4 | 0 | 0 | 1 | 2.01 | OK | | Cotinine |
| 05111460000174 | 2 | 0185 | 5 | 0 | 0 | 1 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000175 | 2 | 0185 | 6 | 0 | 0 | 1 | BLQ<(1.00) | OK | | Cotinine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000236 | 5 | 0266 | 4 | 0 | 0 | 1 | 2.59 | OK | | Cotinine |
| 05111460000243 | 5 | 0273 | 4 | 0 | 0 | 1 | 5.50 | OK | | Cotinine |
| 05111460000245 | 5 | 0273 | 6 | 0 | 0 | 1 | 2.21 | OK | | Cotinine |
| 05111460000250 | 5 | 0289 | 4 | 0 | 0 | 1 | 4.09 | OK | | Cotinine |
| 05111460000257 | 5 | 0292 | 4 | 0 | 0 | 1 | 14.0 | OK | | Cotinine |
| 05111460000264 | 5 | 0306 | 4 | 0 | 0 | 1 | 21.1 | OK | | Cotinine |
| 05111460000271 | 5 | 0317 | 4 | 0 | 0 | 1 | 2.77 | OK | | Cotinine |
| 05111460000272 | 5 | 0317 | 5 | 0 | 0 | 1 | 1.36 | OK | | Cotinine |
| 05111460000273 | 5 | 0317 | 6 | 0 | 0 | 1 | 1.37 | OK | | Cotinine |
| 05111460000278 | 5 | 0325 | 4 | 0 | 0 | 1 | 18.5 | OK | | Cotinine |
| 05111460000313 | | 0028 | 4 | 0 | 0 | 2 | . | Other | Not Reportable | Cotinine |
| 05111460000442 | 5 | 0169 | 0 | 0 | 0 | 2 | 120 | OK | | Cotinine |
| 05111460000449 | 5 | 0185 | 0 | 0 | 0 | 2 | 185 | OK | | Cotinine |
| 05111460000456 | 5 | 0197 | 0 | 0 | 0 | 2 | 174 | OK | | Cotinine |
| 05111460000457 | 5 | 0197 | 1 | 0 | 0 | 2 | 56.1 | OK | | Cotinine |
| 05111460000458 | 5 | 0197 | 2 | 0 | 0 | 2 | 18.0 | OK | | Cotinine |
| 05111460000459 | 5 | 0197 | 3 | 0 | 0 | 2 | 7.03 | OK | | Cotinine |
| 05111460000460 | 5 | 0197 | 4 | 0 | 0 | 2 | 3.34 | OK | | Cotinine |
| 05111460000461 | 5 | 0197 | 5 | 0 | 0 | 2 | 1.58 | OK | | Cotinine |
| 05111460000462 | 5 | 0197 | 6 | 0 | 0 | 2 | 1.56 | OK | | Cotinine |
| 05111460000463 | 5 | 0203 | 0 | 0 | 0 | 2 | 169 | OK | | Cotinine |
| 05111460000464 | 5 | 0203 | 1 | 0 | 0 | 2 | 60.5 | OK | | Cotinine |
| 05111460000465 | 5 | 0203 | 2 | 0 | 0 | 2 | 19.1 | OK | | Cotinine |
| 05111460000466 | 5 | 0203 | 3 | 0 | 0 | 2 | 7.86 | OK | | Cotinine |
| 05111460000467 | 5 | 0203 | 4 | 0 | 0 | 2 | 2.98 | OK | | Cotinine |
| 05111460000468 | 5 | 0203 | 5 | 0 | 0 | 2 | 1.34 | OK | | Cotinine |
| 05111460000469 | 5 | 0203 | 6 | 0 | 0 | 2 | 1.19 | OK | | Cotinine |
| 05111460000470 | 5 | 0218 | 0 | 0 | 0 | 2 | 198 | OK | | Cotinine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000471 | 5 | 0218 | 1 | 0 | 0 | 2 | 81.1 | OK | | Cotinine |
| 05111460000472 | 5 | 0218 | 2 | 0 | 0 | 2 | 26.3 | OK | | Cotinine |
| 05111460000473 | 5 | 0218 | 3 | 0 | 0 | 2 | 10.6 | OK | | Cotinine |
| 05111460000474 | 5 | 0218 | 4 | 0 | 0 | 2 | 3.41 | OK | | Cotinine |
| 05111460000475 | 5 | 0218 | 5 | 0 | 0 | 2 | 1.36 | OK | | Cotinine |
| 05111460000476 | 5 | 0218 | 6 | 0 | 0 | 2 | 1.21 | OK | | Cotinine |
| 05111460000477 | 5 | 0240 | 0 | 0 | 0 | 2 | 277 | OK | | Cotinine |
| 05111460000478 | 5 | 0240 | 1 | 0 | 0 | 2 | 92.5 | OK | | Cotinine |
| 05111460000479 | 5 | 0240 | 2 | 0 | 0 | 2 | 27.3 | OK | | Cotinine |
| 05111460000480 | 5 | 0240 | 3 | 0 | 0 | 2 | 10.2 | OK | | Cotinine |
| 05111460000481 | 5 | 0240 | 4 | 0 | 0 | 2 | 3.68 | OK | | Cotinine |
| 05111460000482 | 5 | 0240 | 5 | 0 | 0 | 2 | 1.73 | OK | | Cotinine |
| 05111460000483 | 5 | 0240 | 6 | 0 | 0 | 2 | 1.64 | OK | | Cotinine |
| 05111460000484 | 5 | 0249 | 0 | 0 | 0 | 2 | 310 | OK | | Cotinine |
| 05111460000485 | 5 | 0249 | 1 | 0 | 0 | 2 | 98.0 | OK | | Cotinine |
| 05111460000486 | 5 | 0249 | 2 | 0 | 0 | 2 | 33.0 | OK | | Cotinine |
| 05111460000487 | 5 | 0249 | 3 | 0 | 0 | 2 | 13.1 | OK | | Cotinine |
| 05111460000488 | 5 | 0249 | 4 | 0 | 0 | 2 | 4.40 | OK | | Cotinine |
| 05111460000489 | 5 | 0249 | 5 | 0 | 0 | 2 | 1.79 | OK | | Cotinine |
| 05111460000490 | 5 | 0249 | 6 | 0 | 0 | 2 | 1.76 | OK | | Cotinine |
| 05111460000491 | 5 | 0251 | 0 | 0 | 0 | 2 | 283 | OK | | Cotinine |
| 05111460000492 | 5 | 0251 | 1 | 0 | 0 | 2 | 87.3 | OK | | Cotinine |
| 05111460000493 | 5 | 0251 | 2 | 0 | 0 | 2 | 23.4 | OK | | Cotinine |
| 05111460000494 | 5 | 0251 | 3 | 0 | 0 | 2 | 7.42 | OK | | Cotinine |
| 05111460000495 | 5 | 0251 | 4 | 0 | 0 | 2 | 2.41 | OK | | Cotinine |
| 05111460000496 | 5 | 0251 | 5 | 0 | 0 | 2 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000497 | 5 | 0251 | 6 | 0 | 0 | 2 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000498 | 5 | 0252 | 0 | 0 | 0 | 2 | 252 | OK | | Cotinine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000499 | 5 | 0252 | 1 | 0 | 0 | 2 | 68.7 | OK | | Cotinine |
| 05111460000500 | 5 | 0252 | 2 | 0 | 0 | 2 | 15.1 | OK | | Cotinine |
| 05111460000501 | 5 | 0252 | 3 | 0 | 0 | 2 | 5.36 | OK | | Cotinine |
| 05111460000502 | 5 | 0252 | 4 | 0 | 0 | 2 | 1.52 | OK | | Cotinine |
| 05111460000503 | 5 | 0252 | 5 | 0 | 0 | 2 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000504 | 5 | 0252 | 6 | 0 | 0 | 2 | BLQ<(1.00) | OK | | Cotinine |
| 05111460000505 | 5 | 0265 | 0 | 0 | 0 | 2 | 195 | OK | | Cotinine |
| 05111460000506 | 5 | 0265 | 1 | 0 | 0 | 2 | 80.5 | OK | | Cotinine |
| 05111460000507 | 5 | 0265 | 2 | 0 | 0 | 2 | 28.3 | OK | | Cotinine |
| 05111460000508 | 5 | 0265 | 3 | 0 | 0 | 2 | 12.1 | OK | | Cotinine |
| 05111460000509 | 5 | 0265 | 4 | 0 | 0 | 2 | 4.42 | OK | | Cotinine |
| 05111460000510 | 5 | 0265 | 5 | 0 | 0 | 2 | 2.02 | OK | | Cotinine |
| 05111460000511 | 5 | 0265 | 6 | 0 | 0 | 2 | 1.76 | OK | | Cotinine |
| 05111460000512 | 5 | 0266 | 0 | 0 | 0 | 2 | 245 | OK | | Cotinine |
| 05111460000513 | 5 | 0266 | 1 | 0 | 0 | 2 | 93.9 | OK | | Cotinine |
| 05111460000514 | 5 | 0266 | 2 | 0 | 0 | 2 | 25.5 | OK | | Cotinine |
| 05111460000515 | 7 | 0266 | 3 | 0 | 0 | 2 | 8.39 | OK | | Cotinine |
| 05111460000517 | 7 | 0266 | 5 | 0 | 0 | 2 | 1.15 | OK | | Cotinine |
| 05111460000518 | 7 | 0266 | 6 | 0 | 0 | 2 | 1.12 | OK | | Cotinine |
| 05111460000519 | 5 | 0273 | 0 | 0 | 0 | 2 | 264 | OK | | Cotinine |
| 05111460000520 | 7 | 0273 | 1 | 0 | 0 | 2 | 116 | OK | | Cotinine |
| 05111460000521 | 5 | 0273 | 2 | 0 | 0 | 2 | 42.3 | OK | | Cotinine |
| 05111460000522 | 7 | 0273 | 3 | 0 | 0 | 2 | 15.9 | OK | | Cotinine |
| 05111460000524 | 7 | 0273 | 5 | 0 | 0 | 2 | 2.61 | OK | | Cotinine |
| 05111460000526 | 5 | 0289 | 0 | 0 | 0 | 2 | 186 | OK | | Cotinine |
| 05111460000527 | 5 | 0289 | 1 | 0 | 0 | 2 | 77.0 | OK | | Cotinine |
| 05111460000528 | 5 | 0289 | 2 | 0 | 0 | 2 | 25.8 | OK | | Cotinine |
| 05111460000529 | 7 | 0289 | 3 | 0 | 0 | 2 | 9.99 | OK | | Cotinine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

| Custom ID | Run ID | Subject | Day Nominal | Hour Nominal | Minute Nominal | Split | Concentration (ng/mL) | Sample Condition | Sample Comments | Analyte |
|---|---|---|---|---|---|---|---|---|---|---|
| 05111460000531 | 7 | 0289 | 5 | 0 | 0 | 2 | 1.94 | OK | | Cotinine |
| 05111460000532 | 7 | 0289 | 6 | 0 | 0 | 2 | 1.80 | OK | | Cotinine |
| 05111460000533 | 5 | 0292 | 0 | 0 | 0 | 2 | 244 | OK | | Cotinine |
| 05111460000534 | 7 | 0292 | 1 | 0 | 0 | 2 | 141 | OK | | Cotinine |
| 05111460000535 | 5 | 0292 | 2 | 0 | 0 | 2 | 61.0 | OK | | Cotinine |
| 05111460000536 | 7 | 0292 | 3 | 0 | 0 | 2 | 31.5 | OK | | Cotinine |
| 05111460000538 | 7 | 0292 | 5 | 0 | 0 | 2 | 6.51 | OK | | Cotinine |
| 05111460000539 | 7 | 0292 | 6 | 0 | 0 | 2 | 5.80 | OK | | Cotinine |
| 05111460000540 | 5 | 0306 | 0 | 0 | 0 | 2 | 301 | OK | | Cotinine |
| 05111460000541 | 7 | 0306 | 1 | 0 | 0 | 2 | 189 | OK | | Cotinine |
| 05111460000542 | 5 | 0306 | 2 | 0 | 0 | 2 | 83.0 | OK | | Cotinine |
| 05111460000543 | 7 | 0306 | 3 | 0 | 0 | 2 | 41.5 | OK | | Cotinine |
| 05111460000545 | 7 | 0306 | 5 | 0 | 0 | 2 | 10.0 | OK | | Cotinine |
| 05111460000546 | 7 | 0306 | 6 | 0 | 0 | 2 | 9.10 | OK | | Cotinine |
| 05111460000547 | 5 | 0317 | 0 | 0 | 0 | 2 | 192 | OK | | Cotinine |
| 05111460000548 | 5 | 0317 | 1 | 0 | 0 | 2 | 65.2 | OK | | Cotinine |
| 05111460000549 | 5 | 0317 | 2 | 0 | 0 | 2 | 18.4 | OK | | Cotinine |
| 05111460000550 | 7 | 0317 | 3 | 0 | 0 | 2 | 7.09 | OK | | Cotinine |
| 05111460000554 | 5 | 0325 | 0 | 0 | 0 | 2 | 368 | OK | | Cotinine |
| 05111460000555 | 7 | 0325 | 1 | 0 | 0 | 2 | 232 | OK | | Cotinine |
| 05111460000556 | 5 | 0325 | 2 | 0 | 0 | 2 | 90.3 | OK | | Cotinine |
| 05111460000557 | 7 | 0325 | 3 | 0 | 0 | 2 | 45.8 | OK | | Cotinine |
| 05111460000559 | 7 | 0325 | 5 | 0 | 0 | 2 | 8.53 | OK | | Cotinine |
| 05111460000560 | 7 | 0325 | 6 | 0 | 0 | 2 | 7.18 | OK | | Cotinine |
| 05111460000561 | | 0242 | 0 | 0 | 0 | 2 | . | Other | Analysis not required. | Cotinine |
| 05111460000568 | | 0242 | 0 | 0 | 0 | 1 | . | Other | Analysis not required. | Cotinine |
| 05111460000575 | | 0245 | 0 | 0 | 0 | 2 | . | Other | Analysis not required. | Cotinine |
| 05111460000582 | | 0245 | 0 | 0 | 0 | 1 | . | Other | Analysis not required. | Cotinine |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

Table 10 Summary of Reassay for Analytical Reasons for Nicotine

| Run ID | Reason | Sample Name |
|---|---|---|
| 1 | AAR | AA99071-02 05111460000001 0010 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000008 0013 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000015 0015 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000022 0017 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000029 0028 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000033 0028 SA P1 DAY4 / Day 4 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000036 0049 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000050 0052 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000057 0062 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000064 0063 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000071 0071 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000078 0076 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000099 0114 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000106 0123 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000127 0128 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000134 0133 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | UCR | AA99071-02 05111460000148 0145 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000163 0169 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000164 0169 SA P1 DAY2 / Day 2 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000165 0169 SA P1 DAY3 / Day 3 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000166 0169 SA P1 DAY4 / Day 4 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000167 0169 SA P1 DAY5 / Day 5 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000168 0169 SA P1 DAY6 / Day 6 0h 0m PL-1 |
| 4 | AAR | AA99071-02 05111460000169 0185 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000170 0185 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000171 0185 SA P1 DAY2 / Day 2 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000172 0185 SA P1 DAY3 / Day 3 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000173 0185 SA P1 DAY4 / Day 4 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000174 0185 SA P1 DAY5 / Day 5 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000175 0185 SA P1 DAY6 / Day 6 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000023 0017 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000031 0028 SA P1 DAY2 / Day 2 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000058 0062 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 4 | LSR | AA99071-02 05111460000061 0062 SA P1 DAY4 / Day 4 0h 0m PL-1 |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

Table 11 Summary of Reassay for Analytical Reasons for Cotinine

| Run ID | Reason | Sample Name |
|---|---|---|
| 1 | AAR | AA99071-02 05111460000001 0010 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000008 0013 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000009 0013 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000015 0015 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000022 0017 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000029 0028 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000033 0028 SA P1 DAY4 / Day 4 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000036 0049 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000037 0049 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000043 0051 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000050 0052 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000051 0052 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000057 0062 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000064 0063 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000071 0071 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000072 0071 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000078 0076 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000079 0076 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000085 0086 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000086 0086 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000092 0104 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000099 0114 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000106 0123 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000120 0127 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000127 0128 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000134 0133 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000135 0133 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000141 0137 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | UCR | AA99071-02 05111460000147 0137 SA P1 DAY6 / Day 6 0h 0m PL-1 |
| 1 | UCR | AA99071-02 05111460000148 0145 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000155 0150 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 1 | AAR | AA99071-02 05111460000156 0150 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 2 | AAR | AA99071-02 05111460000162 0169 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 2 | AAR | AA99071-02 05111460000169 0185 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 5 | AAR | AA99071-02 05111460000520 0273 SA P1 DAY1 / Day 1 0h 0m PL-2 |
| 5 | AAR | AA99071-02 05111460000534 0292 SA P1 DAY1 / Day 1 0h 0m PL-2 |
| 5 | AAR | AA99071-02 05111460000541 0306 SA P1 DAY1 / Day 1 0h 0m PL-2 |
| 5 | AAR | AA99071-02 05111460000555 0325 SA P1 DAY1 / Day 1 0h 0m PL-2 |
| 6 | AAR | AA99071-02 05111460000009 0013 SA P1 DAY1 / Day 1 0h 0m PL-1 |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

| Run ID | Reason | Sample Name |
|---|---|---|
| 6 | AAR | AA99071-02 05111460000037 0049 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 6 | AAR | AA99071-02 05111460000043 0051 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 6 | AAR | AA99071-02 05111460000121 0127 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 6 | AAR | AA99071-02 05111460000135 0133 SA P1 DAY1 / Day 1 0h 0m PL-1 |
| 6 | AAR | AA99071-02 05111460000155 0150 SA P1 DAY0 / Day 0 0h 0m PL-1 |
| 6 | AAR | AA99071-02 05111460000156 0150 SA P1 DAY1 / Day 1 0h 0m PL-1 |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

Table 12. Incurred Sample Reproducibility Assessment for Nicotine

| Subject | Period | Time Point | Analyte | Units | Original Value | Reassay Value | Mean Value | % Difference | Reproducible? | Event? | % of Passing ISR Samples |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0010 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 11.3 | 11.0 | 11.2 | 2.68 | Pass | No | 100.0 |
| 0013 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 19.2 | 18.3 | 18.8 | 4.79 | Pass | No | |
| 0013 | 1 | Day 1 0h 0m | Nicotine | ng/mL | 0.420 | 0.425 | 0.423 | 1.18 | Pass | No | |
| 0015 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 14.5 | 15.3 | 14.9 | 5.37 | Pass | No | |
| 0017 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 25.3 | 25.6 | 25.5 | 1.18 | Pass | No | |
| 0028 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 13.8 | 14.0 | 13.9 | 1.44 | Pass | No | |
| 0028 | 1 | Day 4 0h 0m | Nicotine | ng/mL | 30.5 | 32.6 | 31.6 | 6.65 | Pass | No | |
| 0049 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 28.1 | 28.5 | 28.3 | 1.41 | Pass | No | |
| 0049 | 1 | Day 1 0h 0m | Nicotine | ng/mL | 0.431 | 0.498 | 0.465 | 14.41 | Pass | No | |
| 0051 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 9.91 | 10.4 | 10.2 | 4.80 | Pass | No | |
| 0052 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 17.6 | 17.6 | 17.6 | 0.00 | Pass | No | |
| 0062 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 19.3 | 19.1 | 19.2 | 1.04 | Pass | No | |
| 0063 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 13.9 | 13.9 | 13.9 | 0.00 | Pass | No | |
| 0071 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 24.0 | 23.9 | 24.0 | 0.42 | Pass | No | |
| 0071 | 1 | Day 1 0h 0m | Nicotine | ng/mL | 0.660 | 0.751 | 0.706 | 12.89 | Pass | No | |
| 0071 | 1 | Day 2 0h 0m | Nicotine | ng/mL | 0.537 | 0.577 | 0.557 | 7.18 | Pass | No | |
| 0076 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 14.5 | 13.9 | 14.2 | 4.23 | Pass | No | |
| 0076 | 1 | Day 1 0h 0m | Nicotine | ng/mL | 0.722 | 0.791 | 0.757 | 9.11 | Pass | No | |
| 0086 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 9.95 | 10.8 | 10.4 | 8.17 | Pass | No | |
| 0086 | 1 | Day 1 0h 0m | Nicotine | ng/mL | 0.994 | 1.08 | 1.04 | 8.27 | Pass | No | |
| 0104 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 8.72 | 8.67 | 8.70 | 0.57 | Pass | No | |
| 0114 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 15.1 | 14.5 | 14.8 | 4.05 | Pass | No | |
| 0123 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 16.5 | 16.3 | 16.4 | 1.22 | Pass | No | |
| 0127 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 9.48 | 9 91 | 9.70 | 4.43 | Pass | No | |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

| Subject | Period | Time Point | Analyte | Units | Original Value | Reassay Value | Mean Value | % Difference | Reproducible? | Event? | % of Passing ISR Samples |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0127 | 1 | Day 1 0h 0m | Nicotine | ng/mL | 0.414 | 0.488 | 0.451 | 16.41 | Pass | No | |
| 0128 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 13.6 | 13.4 | 13.5 | 1.48 | Pass | No | |
| 0128 | 1 | Day 1 0h 0m | Nicotine | ng/mL | 0.534 | 0.577 | 0.556 | 7.73 | Pass | No | |
| 0133 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 25.6 | 26.2 | 25.9 | 2.32 | Pass | No | |
| 0133 | 1 | Day 1 0h 0m | Nicotine | ng/mL | 0.403 | 0.426 | 0.415 | 5.54 | Pass | No | |
| 0137 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 8.35 | 8.76 | 8.56 | 4.79 | Pass | No | |
| 0145 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 10.8 | 10.3 | 10.6 | 4.72 | Pass | No | |
| 0150 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 9.40 | 9.42 | 9.41 | 0.21 | Pass | No | |
| 0150 | 1 | Day 1 0h 0m | Nicotine | ng/mL | 0.495 | 0.602 | 0.549 | 19.49 | Pass | No | |
| 0169 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 4.88 | 4.76 | 4.82 | 2.49 | Pass | No | |
| 0197 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 17.8 | 17.8 | 17.8 | 0.00 | Pass | No | |
| 0203 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 11.8 | 11.9 | 11.9 | 0.84 | Pass | No | |
| 0218 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 15.8 | 17.1 | 16.5 | 7.88 | Pass | No | |
| 0240 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 15.7 | 16.2 | 16.0 | 3.13 | Pass | No | |
| 0249 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 27.7 | 27.9 | 27.8 | 0.72 | Pass | No | |
| 0251 | 1 | Day 0 0h 0m | Nicotine | ng/mL | 19.0 | 20.4 | 19.7 | 7.11 | Pass | No | |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

Table 13 Incurred Sample Reproducibility Assessment for Cotinine

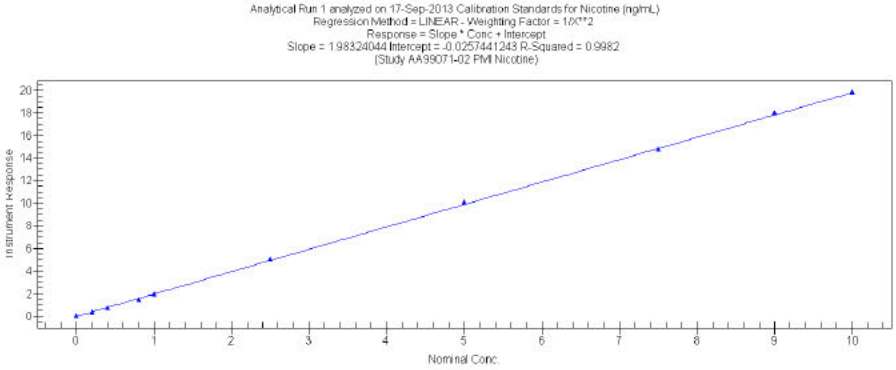
| Subject | Period | Time Point | Analyte | Units | Original Value | Reassay Value | Mean Value | % Difference | Reproducible? | Event? | % of Passing ISR Samples |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0010 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 182 | 185 | 184 | 1.63 | Pass | No | 97.5 |
| 0013 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 289 | 288 | 289 | 0.35 | Pass | No | |
| 0015 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 241 | 242 | 242 | 0.41 | Pass | No | |
| 0017 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 204 | 207 | 206 | 1.46 | Pass | No | |
| 0028 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 212 | 212 | 212 | 0.00 | Pass | No | |
| 0028 | 1 | Day 4 0h 0m | Cotinine | ng/mL | 414 | 404 | 409 | 2.44 | Pass | No | |
| 0049 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 332 | 323 | 328 | 2.74 | Pass | No | |
| 0052 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 260 | 255 | 258 | 1.94 | Pass | No | |
| 0062 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 211 | 213 | 212 | 0.94 | Pass | No | |
| 0063 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 277 | 268 | 273 | 3.30 | Pass | No | |
| 0071 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 328 | 323 | 326 | 1.53 | Pass | No | |
| 0071 | 1 | Day 1 0h 0m | Cotinine | ng/mL | 130 | 133 | 132 | 2.27 | Pass | No | |
| 0071 | 1 | Day 2 0h 0m | Cotinine | ng/mL | 47.6 | 46.2 | 46.9 | 2.99 | Pass | No | |
| 0076 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 246 | 237 | 242 | 3.72 | Pass | No | |
| 0076 | 1 | Day 1 0h 0m | Cotinine | ng/mL | 124 | 120 | 122 | 3.28 | Pass | No | |
| 0086 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 247 | 249 | 248 | 0.81 | Pass | No | |
| 0086 | 1 | Day 1 0h 0m | Cotinine | ng/mL | 119 | 114 | 117 | 4.27 | Pass | No | |
| 0104 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 134 | 127 | 131 | 5.34 | Pass | No | |
| 0114 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 179 | 177 | 178 | 1.12 | Pass | No | |
| 0123 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 207 | 206 | 207 | 0.48 | Pass | No | |
| 0127 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 185 | 179 | 182 | 3.30 | Pass | No | |
| 0128 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 175 | 174 | 175 | 0.57 | Pass | No | |
| 0128 | 1 | Day 1 0h 0m | Cotinine | ng/mL | 76.3 | 75.6 | 76.0 | 0.92 | Pass | No | |
| 0133 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 315 | 303 | 309 | 3.88 | Pass | No | |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

| Subject | Period | Time Point | Analyte | Units | Original Value | Reassay Value | Mean Value | % Difference | Reproducible? | Event? | % of Passing ISR Samples |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0137 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 134 | 132 | 133 | 1.50 | Pass | No | |
| 0145 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 143 | 138 | 141 | 3.55 | Pass | No | |
| 0169 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 120 | 122 | 121 | 1.65 | Pass | No | |
| 0197 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 174 | 173 | 174 | 0.57 | Pass | No | |
| 0203 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 169 | 170 | 170 | 0.59 | Pass | No | |
| 0218 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 198 | 199 | 199 | 0.50 | Pass | No | |
| 0240 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 277 | 277 | 277 | 0.00 | Pass | No | |
| 0249 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 310 | 330 | 320 | 6.25 | Pass | No | |
| 0251 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 283 | 291 | 287 | 2.79 | Pass | No | |
| 0013 | 1 | Day 1 0h 0m | Cotinine | ng/mL | 118 | 119 | 119 | 0.84 | Pass | No | |
| 0049 | 1 | Day 1 0h 0m | Cotinine | ng/mL | 130 | AAR | N/AP | N/AP | Fail | N/AP | |
| 0051 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 206 | 203 | 205 | 1.46 | Pass | No | |
| 0127 | 1 | Day 1 0h 0m | Cotinine | ng/mL | 98.8 | 100 | 99.4 | 1.21 | Pass | No | |
| 0133 | 1 | Day 1 0h 0m | Cotinine | ng/mL | 106 | 103 | 105 | 2.86 | Pass | No | |
| 0150 | 1 | Day 0 0h 0m | Cotinine | ng/mL | 237 | 247 | 242 | 4.13 | Pass | No | |
| 0150 | 1 | Day 1 0h 0m | Cotinine | ng/mL | 148 | 142 | 145 | 4.14 | Pass | No | |

## FIGURES

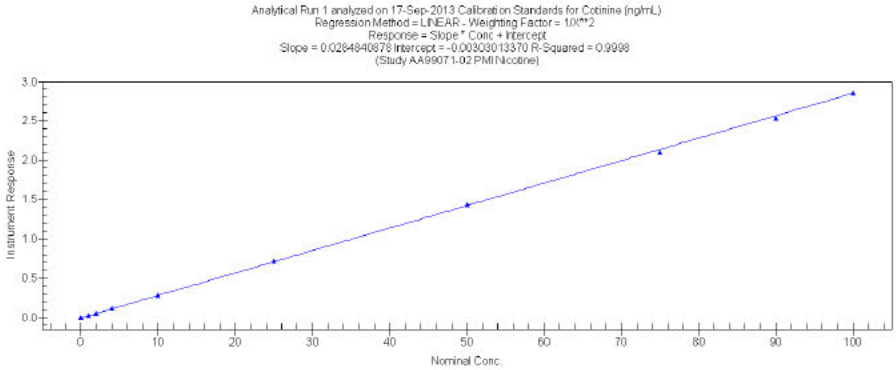
Figure 1 Calibration Curve for Nicotine in Control Matrix, Watson Run ID 1[1]




[1] Note: Though included on the figure above, the Standard 0 (blank sample extracted with internal standard) was not used as a standard to calculate the calibration curve parameters.

**Nicotine and Cotinine in Human Plasma ($K_2EDTA$)**
**Celerion Study AA99071-02**

Figure 2 Calibration Curve for Cotinine in Control Matrix, Watson Run ID 1[2]




[2] Note: Though included on the figure above, the Standard 0 (blank sample extracted with internal standard) was not used as a standard to calculate the calibration curve parameters.

## ATTACHMENTS

Attachment 1 General List of Abbreviations used at Celerion

Abbreviations are used in this document as applicable.

| Abbreviation | Description |
|---|---|
| °C | Degree Celsius (centigrade) |
| µg | Microgram |
| AAR | Above the acceptable range |
| AB | Applied Biosystems |
| API | Atmospheric pressure ionization |
| ASCII | American standard code for information interchange |
| BAM | Bioanalytical method |
| BLK | Blank |
| BLQ | Below limit of quantification |
| CC | Conventional Cigarette |
| CDER | Center for Drug Evaluation and Research |
| CFR | Code of Federal Regulations |
| CRO | Contract research organisation |
| CV | Coefficient of variation |
| Da | Dalton |
| DCU | Diluted concentration unreliable |
| DFNR | Dilution factor not reliable |
| DQC | Dilution quality control sample |
| ELISA | Enzyme-linked immunosorbent assay |
| EDTA | Ethylenediaminetetraacetic acid |
| EQB | Exceeding quadratic bounds |
| EXT | Extraction |
| fg | Femtogram |
| g | Gram |
| GLP | Good laboratory practices |
| h | Hour |
| HDPE | High density polyethylene |
| HPLC | High performance liquid chromatography |

| Abbreviation | Description |
|---|---|
| HSR | High standard removed |
| ID | Identifier |
| INC | Incongruous |
| INS | Instrumentation |
| IS | Internal standard |
| ISA | Insufficient volume for full analysis |
| ISP | Incomplete sample processing |
| ISR | Incurred sample reproducibility |
| ISV | Insufficient volume |
| IVR | Insufficient volume to reassay |
| L | Litre, liter |
| LC-MS/MS | Liquid chromatography- tandem mass spectrometry |
| LLOQ | Lower limit of quantitation |
| LNK | Celerion, Lincoln site |
| M | Molar |
| mg | Milligram |
| mL | Millilitre, milliliter |
| MRM | Multiple reaction monitoring |
| mol | Mole |
| MS | Mass spectrometry |
| MW | Molecular weight |
| n | Number of data points |
| N/AP | Not applicable |
| N/AV | Not available |
| NFV | Not full volume |
| ng | Nanogram |
| No | Number |
| NU | Not used |
| OECD | Organization for Economic Cooperation and Development |
| PD | Period |
| pg | Picogram |
| QC | Quality control |
| QCs | Quality control samples |

| Abbreviation | Description |
|---|---|
| R E | Relative error |
| REF | Reference |
| RI | Reinjection |
| RIA | Rarioimmunoassay |
| RT | Room temperature |
| RR | Reanalysis |
| RVL | Remaining volume low |
| S A | Smoking Abstinence |
| S D | Standard deviation |
| SOP | Standard operating procedure |
| SPE | Solid-phase extraction |
| SST | System suitability test |
| STD | Standard |
| Sub | Subject |
| SVD | Sample volume depleted |
| TBD | To be determined |
| Temp | Temperature |
| THS | Tobacco Heating System |
| UCR | Unacceptable chromatography |
| UISR | Unacceptable internal standard response |
| ULOQ | Upper limit of quantitation |
| U S FDA | United States Food and Drug Administration |
| USP | US pharmacopeia |
| $\bar{x}$ | Mean |

Attachment 2 Temperature Definitions at Celerion

Values for temperatures are nominal temperatures representing the following temperature ranges:

| Nominal temperature | Temperature Range |
|---|---|
| -80 C | -65 C to -90 C |
| -20 C | -10 C to -30 C |
| 5 C | 2 C to 8 C |
| Room temperature | 15 C to 25 C |
| 24 C | 22 C to 26 C |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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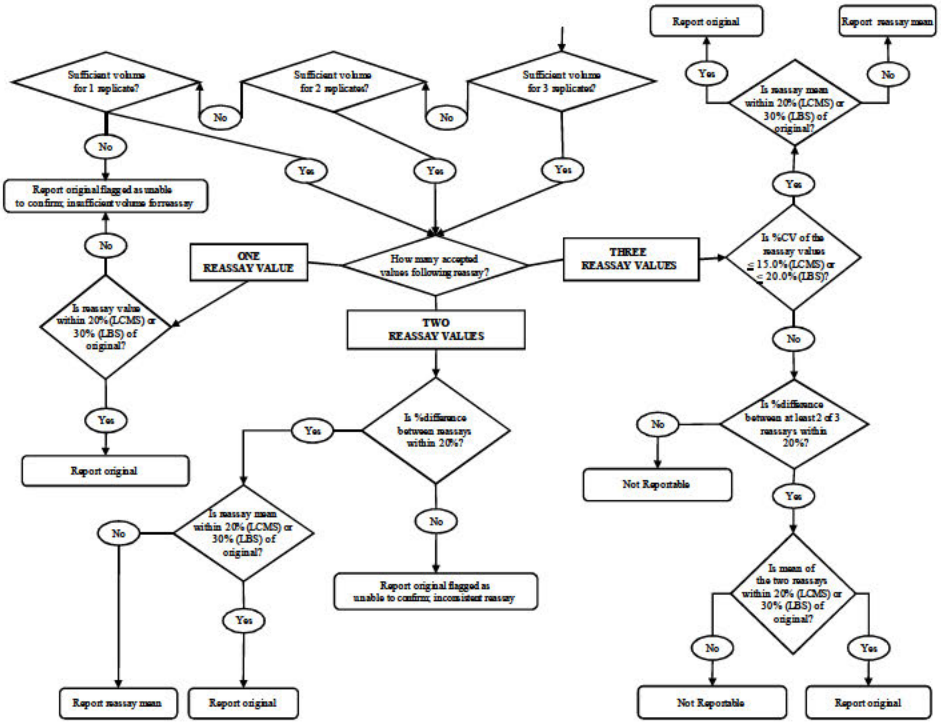
Attachment 3 Procedure for VRC and SSR Reassays and Reporting of Reassay Results




To compare reassays:

$$\frac{|\text{Reassay Value 1} - \text{Reassay Value 2}|}{\text{Mean of Reassay Value 1 and 2}} * 100\%$$

To compare to original:

$$\frac{|\text{Mean of Reassays} - \text{Original Value}|}{\text{Original Value}} * 100\%$$

An LC-MS/MS value as outlined in the decision tree is obtained from a single determination

If BLQ is obtained for a value, the nominal concentration of the LLOQ is used when comparing reassays in this decision tree.

Attachment 4 General List of Calculation Formulae

Mean: $$x_{Mean} = \frac{1}{n}\sum_{i=1}^{n} x_i$$

Standard Deviation (SD): $$SD = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - x_{Mean})^2}$$

Precision (RSD, CV): $CV\ \% = (SD / X_{Mean}) * 100$

Accuracy (% Theoretical): $Accuracy\ \% = (X / X_{Nominal}) * 100$

$Accuracy\ of\ Mean\ \% = (X_{Mean} / X_{Nominal}) * 100$

Inaccuracy (% Bias, % RE): $Bias\ \% = ((X - X_{nominal}) / X_{nominal}) * 100$

$Bias\ of\ Mean\ \% = ((X_{Mean} - X_{nominal}) / X_{nominal}) * 100$

X = value (e.g. analyte concentration, OD value, cpm value, peak signal)
n = number of values X

Attachment 5 Reassay Descriptions

| Analytical Reason (Code) | Description |
|---|---|
| Above the Accepted Range (AAR) | Identifies a study sample whose calculated concentration is greater than the upper limit of quantitation (ULOQ). This study sample will be diluted before being reassayed. |
| Diluted Concentration Unreliable (DCU) | Identifies a study sample that has been diluted and determined to have a concentration below LLOQ (BLQ, below limit of quantification) before correction for the final dilution factor. |
| Dilution Factor Not Reliable (DFNR) | Identifies a study sample that has been diluted, and determined to have a measurable concentration, however >50% of the dilution QC samples (having the same dilution factor) did not meet their acceptance criteria.<br>Identifies a dilution QC sample that does not fulfil the acceptance criterion and is excluded from the DQC statistics. |
| Highest / Lowest Standard Removed (HSR / LSR) | If the working range of the method is truncated as a result of<br>- the ULOQ calibration standard being rejected or unavailable (e.g. incomplete sample processing or incomplete instrument analysis, unacceptable chromatography), all study samples with concentrations greater than the highest acceptable standard are identified as 'highest standard removed' (HSR).<br>- the calibration standard at the LLOQ being rejected or unavailable (e.g. incomplete sample processing or incomplete instrument analysis, unacceptable chromatography), all study samples with concentrations below the lowest acceptable standard are identified as 'lowest standard removed' (LSR). |
| Incomplete Sample Processing (ISP) | Identifies a study sample, calibration standard, or QC sample for which data could not be obtained due to processing problems that occurred during the extraction or assay documented by the analyst prior to instrumental analysis. |
| Insufficient Volume for Reassay (IVR) | Identified a study sample that has insufficient sample volume for reanalysis (including all received splits) |
| Incomplete Instrument Analysis (IIA) | Identifies a study sample, calibration standard, or QC sample for which data could not be obtained due to processing problems that occurred during HPLC injection or instrumental analysis and were documented by the analyst. |
| Unacceptable Chromatography (UCR) | Identifies a study sample, calibration standard, or QC sample judged to demonstrate unacceptable chromatography according to the applicable Celerion procedures (e.g. split peak, poor peak symmetry, unseparated interference). |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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Attachment 6 Certificates of Analysis

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Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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Attachment 7 Bioanalytical Method Summary

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

PMI RESEARCH & DEVELOPMENT

BIOANALYTICAL METHOD SUMMARY (BMS)

Doc No: FOR_QM000496 – CR204A2 | Version N°: 2.0 | Page 1 of 2

| | | | |
|---|---|---|---|
| **Biomarker: Nicotine** | | **Matrix: Plasma** | |
| **MVR/SOP no. & date: AA33664-06 / 22-JUL-2013** | | **CRO/Laboratory: Celerion-Lincoln** | |
| **LLOQ: 0.200 ng/mL** | | **ULOQ: 10.0 ng/mL** | |
| **Validation** | ☑ **Full** ☐ **Partial** ☐ **Cross**<br>**Comments (required for Partial/Cross):** | | |
| **Assay:** | ☑ **Chromatographic** ☐ **Ligand binding** ☐ **Enzymatic** ☐ **Other describe:** | | |
| | ☐ **LC/MS** ☑ **LC/MS/MS** ☐ **GC/MS** ☐ **GC/MS/MS**<br>☐ **ELISA** | | |

**Equipment and short description of extraction and analysis:** An aliquot of human plasma (EDTA) containing the analyte and internal standard was extracted using a solid phase extraction procedure. The extracted samples were analyzed by an HPLC equipped with an AB SCIEX API 4000™ or API 5000™ triple quadrupole mass spectrometer using an ESI source. Positive ions were monitored in the multiple reaction monitoring (MRM) mode. Quantitation was determined using a weighted linear regression analysis (1/concentration$^2$) of peak area ratios of the analyte and internal standard.

| | |
|---|---|
| ***Selectivity/Sensitivity/Matrix effect:*** | **No significant matrix effect was observed in any of the 6 human plasma (EDTA) lots that were fortified with nicotine at the concentration of the low QC (0.600 ng/mL) or in any of the 6 human plasma (EDTA) lots that were fortified with nicotine at the concentration of the high QC (7.50 ng/mL) samples** |
| **Accuracy:** | **Intra-batch: -2.8 to 12.0% R.E.**<br>**Inter-batch: -0.9 to 5.5% R.E.** |
| **Precision:** | **Intra-batch: 0.9 to 7.1% CV**<br>**Inter-batch: 2.6 to 6.2% CV** |
| **Recovery:** | **81% recovery at 0.600 ng/mL in human plasma**<br>**79% recovery at 1.20 ng/mL in human plasma**<br>**84% recovery at 7.50 ng/mL in human plasma** |
| **Freeze and thaw stability:** | **6 freeze (-20°C )-thaw (ambient temperature) cycles in polypropylene tubes under white light**<br>**7 freeze (-20°C )-thaw (ambient temperature) cycles in polypropylene tubes at -20°C under UV-shielded light** |
| **Short-term temperature stability:** | **27 hours in polypropylene tubes at ambient temperature under white light** |
| **Long-term stability:** | **1041 days in polypropylene tubes at -20°C** |
| **Stock solution stability:** | **574 days at approximately 100 µg/mL in water in a polypropylene container at -20°C** |
| **Post-preparative stability:** | **73 hours in a polypropylene 96 well plate at 5°C** |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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PMI RESEARCH & DEVELOPMENT

BIOANALYTICAL METHOD SUMMARY (BMS)

Doc No: FOR_QM000496 – CR204A2 | Version N°: 2.0 | Page 2 of 2

| | |
|---|---|
| ***Accreditation/ GLP compliance/ QA statements:*** | **GLP Compliance as Assay Validation conforms to Celerion Standard Operating Procedures which were written in compliance with FDA: Guidance to Industry "Bioanalytical Method Validation"** |

| **BMS completed by:** | | |
|---|---|---|
| Name: | Date: | Signature: |
| Erica Nach. | 29-AUG-2013 | Erica J Nach |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
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PMI RESEARCH & DEVELOPMENT

BIOANALYTICAL METHOD SUMMARY (BMS)

Doc No: FOR_QM000498 – CR204A2 | Version N°: 2.0 | Page 1 of 2

| | | | |
|---|---|---|---|
| **Biomarker: Cotinine** | | **Matrix: Plasma** | |
| **MVR/SOP no. & date: AA33664-06 / 22-JUL-2013** | | **CRO/Laboratory: Celerion-Lincoln** | |
| **LLOQ: 1.00 ng/mL** | | **ULOQ: 100 ng/mL** | |
| **Validation** | ☑ **Full** ☐ **Partial** ☐ **Cross**<br>**Comments (required for Partial/Cross):** | | |
| **Assay:** | ☑ **Chromatographic** ☐ **Ligand binding** ☐ **Enzymatic** ☐ **Other describe:** | | |
| | ☐ **LC/MS** ☑ **LC/MS/MS** ☐ **GC/MS** ☐ **GC/MS/MS**<br>☐ **ELISA** | | |
| **Equipment and short description of extraction and analysis:** An aliquot of human plasma (EDTA) containing the analyte and internal standard was extracted using a solid phase extraction procedure. The extracted samples were analyzed by an HPLC equipped with an AB SCIEX API 4000™ or API 5000™ triple quadrupole mass spectrometer using an ESI source. Positive ions were monitored in the multiple reaction monitoring (MRM) mode. Quantitation was determined using a weighted linear regression analysis (1/concentration$^2$) of peak area ratios of the analyte and internal standard. | | | |

| | |
|---|---|
| ***Selectivity/Sensitivity/Matrix effect:*** | **No significant matrix effect was observed in 5 of the 6 human plasma (EDTA) lots that were fortified with cotinine at the concentration of the LLOQ (1.00 ng/mL) or in any of the 6 human plasma (EDTA) lots that were fortified with cotinine at the concentration of the high QC (75.0 ng/mL) samples** |
| **Accuracy:** | **Intra-batch: -0.1 to 5.0% R.E.**<br>**Inter-batch: 1.5 to 4.2% R.E.** |
| **Precision:** | **Intra-batch: 0.5 to 2.4% CV**<br>**Inter-batch: 1.1 to 2.2% CV** |
| **Recovery:** | **75% recovery at 3.00 ng/mL in human plasma**<br>**78% recovery at 12.0 ng/mL in human plasma**<br>**83% recovery at 75.0 ng/mL in human plasma** |
| **Freeze and thaw stability:** | **6 freeze (-20°C )-thaw (ambient temperature) cycles in polypropylene tubes under white light**<br>**7 freeze (-20°C )-thaw (ambient temperature) cycles in polypropylene tubes at -20°C under UV-shielded light** |
| **Short-term temperature stability:** | **27 hours in polypropylene tubes at ambient temperature under white light** |
| **Long-term stability:** | **194 days in polypropylene tubes at -20°C** |
| **Stock solution stability:** | **39 days at 200 µg/mL in water in a polypropylene container at -20°C** |
| **Post-preparative stability:** | **73 hours in a polypropylene 96 well plate at 5°C** |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

PMI RESEARCH & DEVELOPMENT

BIOANALYTICAL METHOD SUMMARY (BMS)

Doc No: FOR_QM000496 – CR204A2 | Version N°: 2.0 | Page 2 of 2

| | |
|---|---|
| ***Accreditation/ GLP compliance/ QA statements:*** | **GLP Compliance as Assay Validation conforms to Celerion Standard Operating Procedures which were written in compliance with FDA: Guidance to Industry "Bioanalytical Method Validation"** |

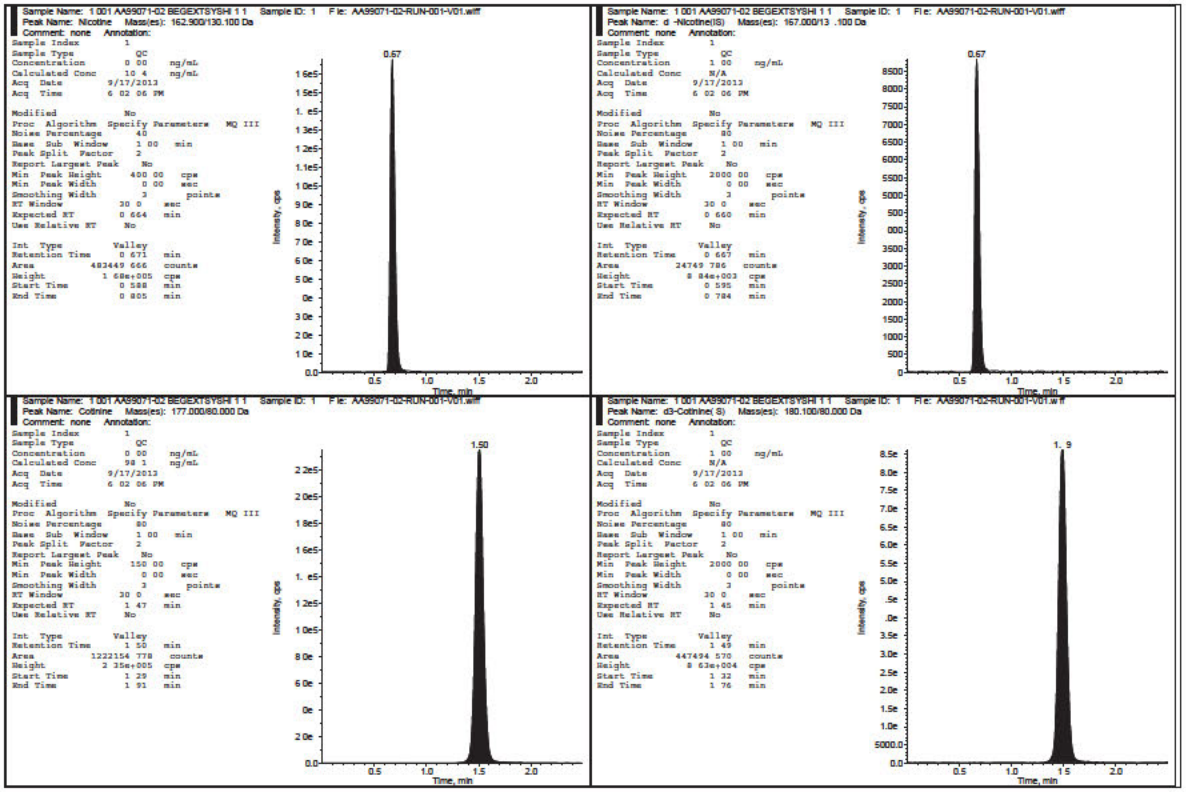
| **BMS completed by:** | | |
|---|---|---|
| Name: | Date: | Signature: |
| Erica Nach. | 29-AUG-2013 | Erica J. Nach |

Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02

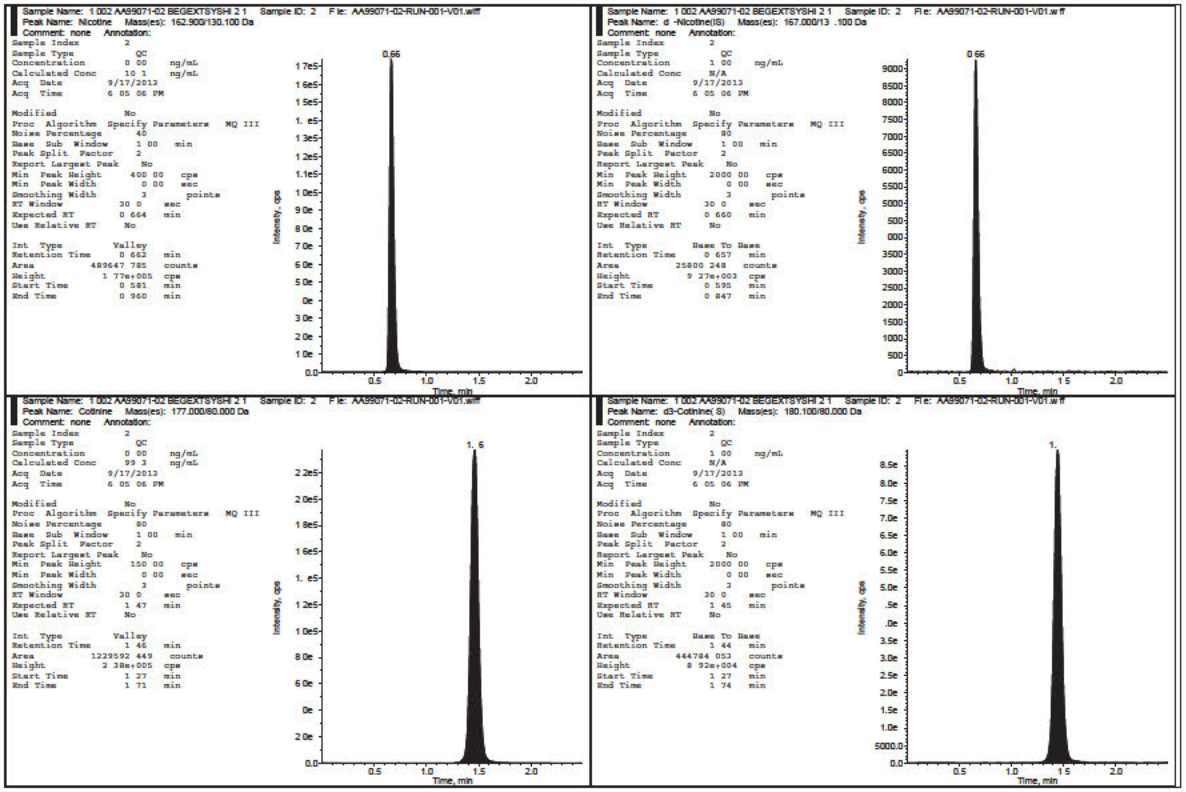
Attachment 8 Chromatograms

Total number of pages including this page: 188

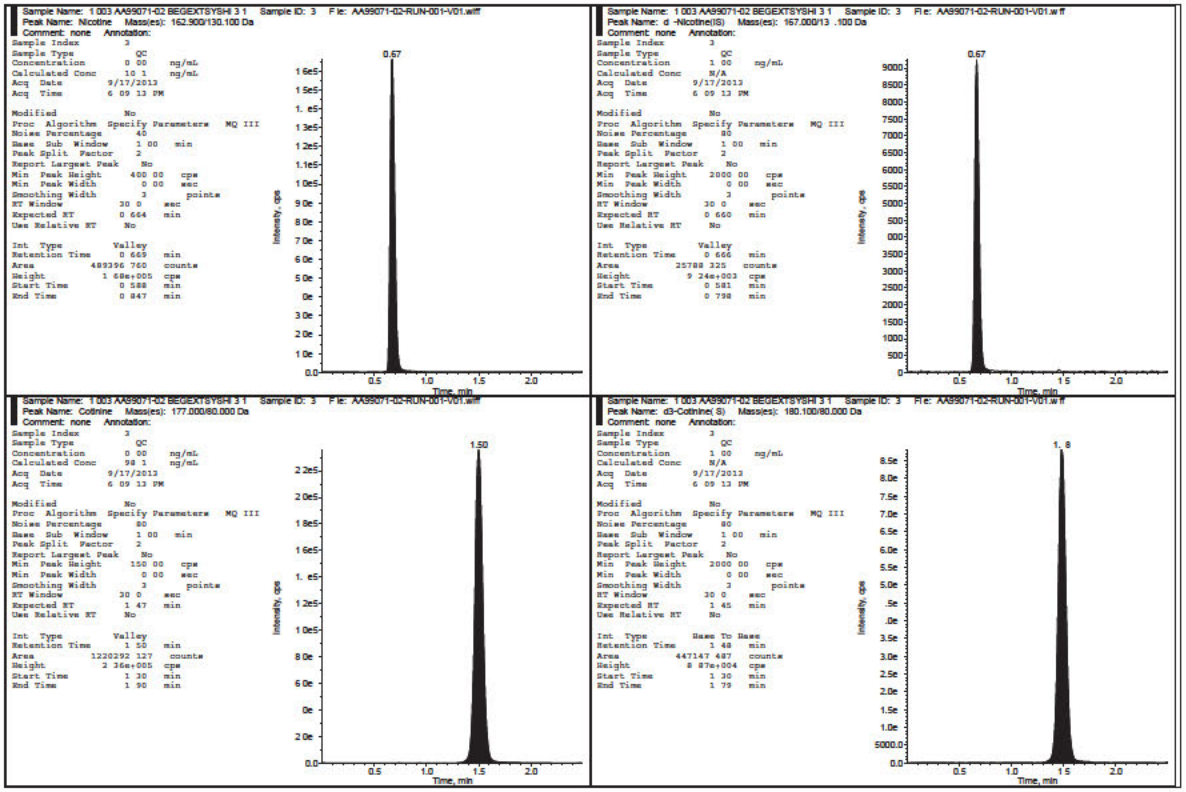
Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02



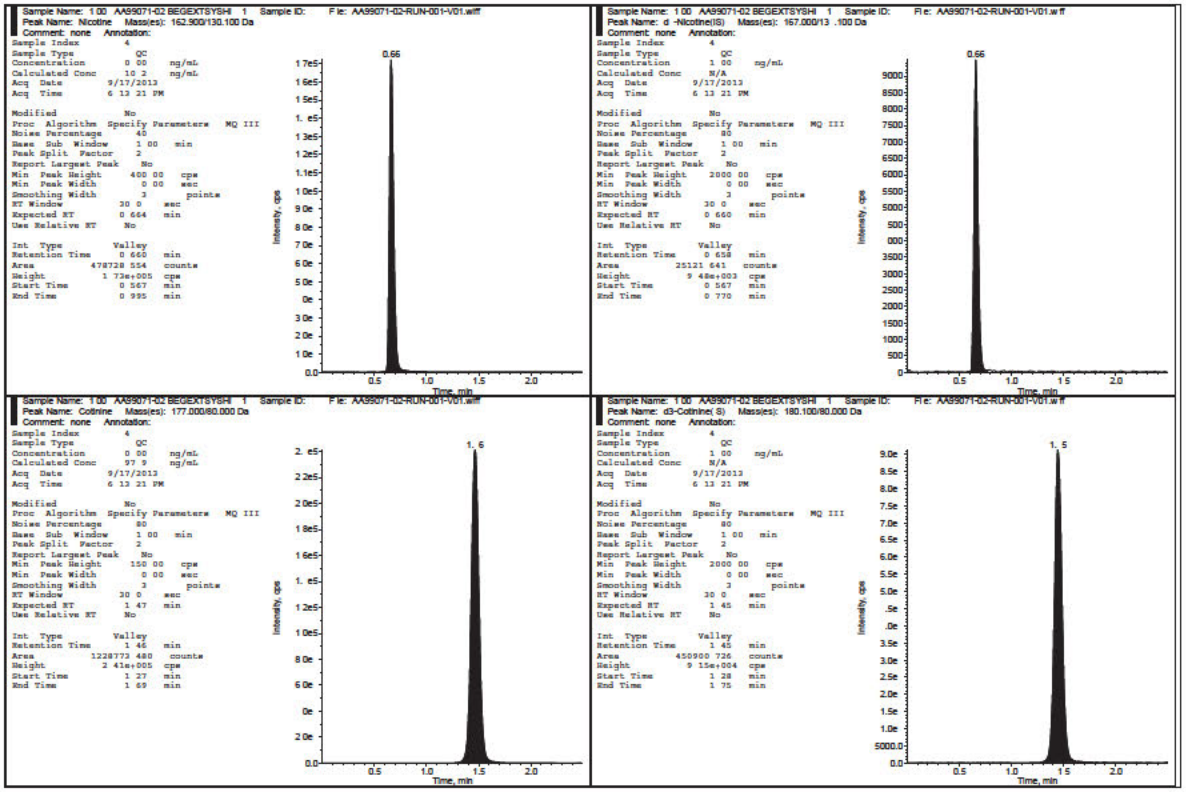
Nicotine and Cotinine in Human Plasma ($K_2$EDTA)
Celerion Study AA99071-02



Nicotine and Cotinine in Human Plasma ($K_2$EDTA)
Celerion Study AA99071-02



Nicotine and Cotinine in Human Plasma ($K_2EDTA$)
Celerion Study AA99071-02



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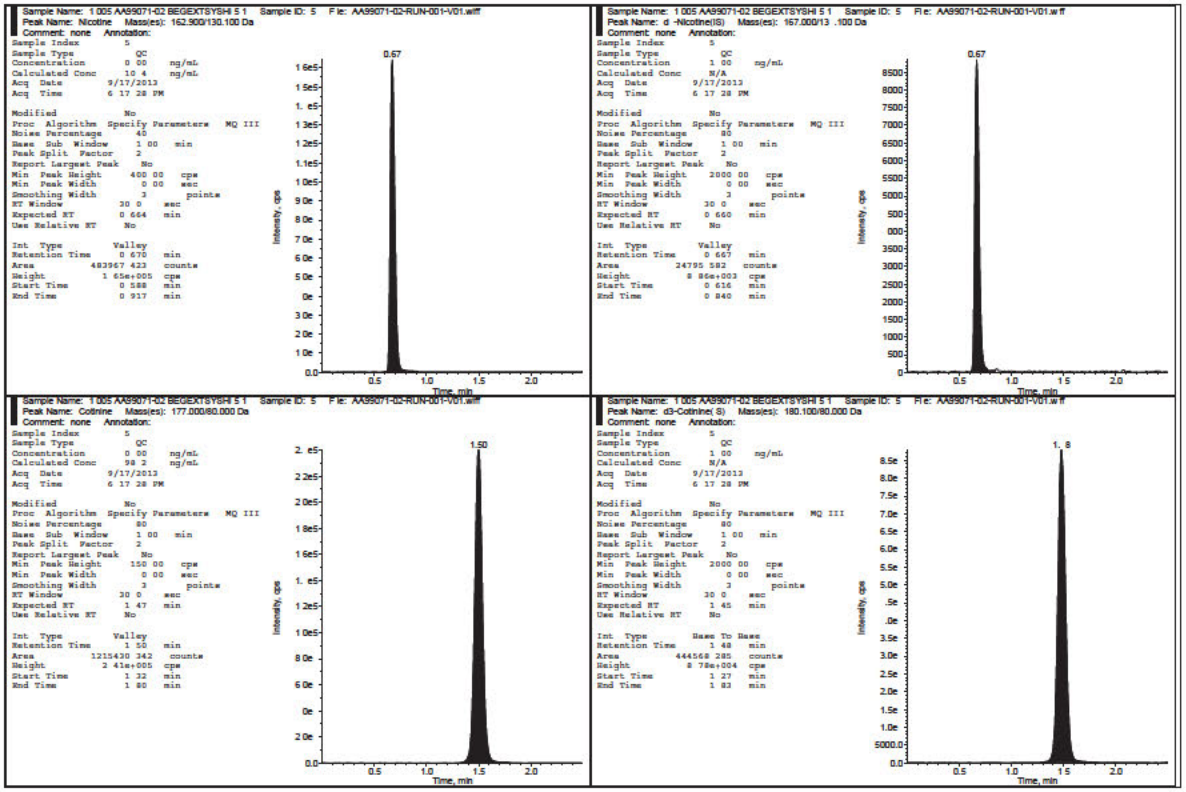
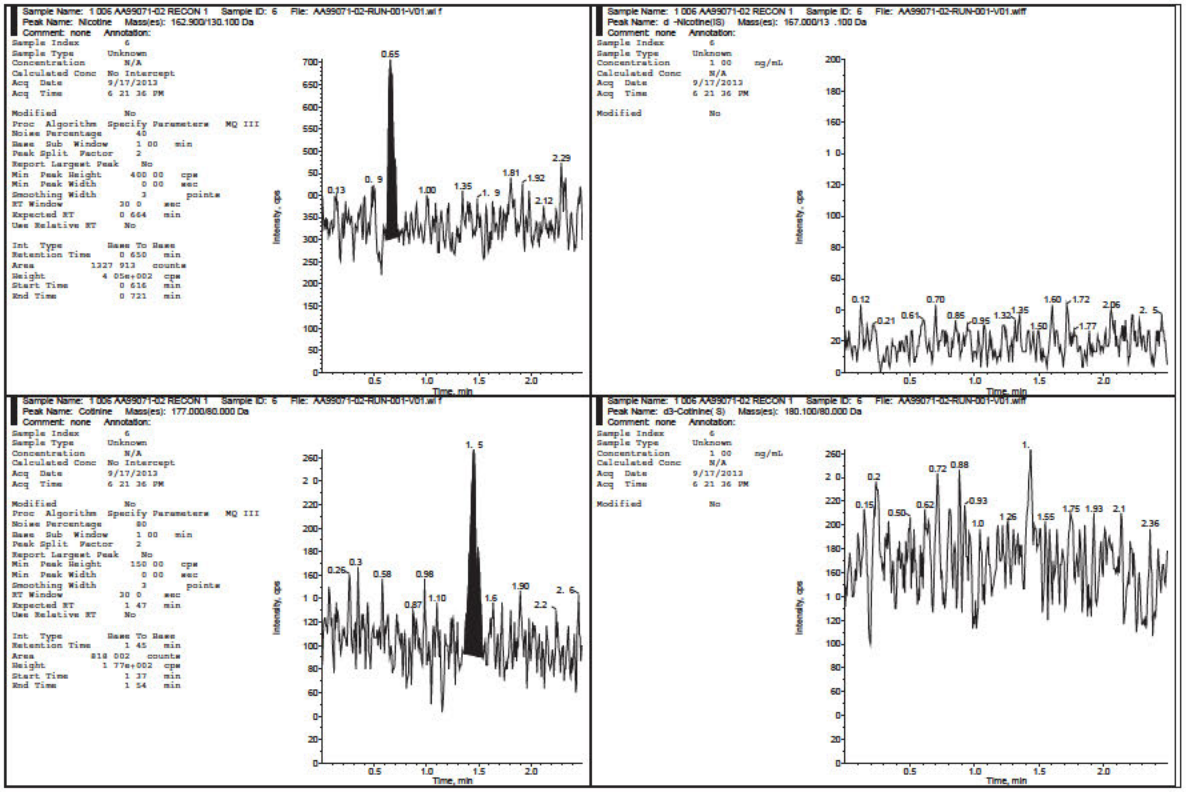


Nicotine and Cotinine in Human Plasma ($K_2$EDTA)
Celerion Study AA99071-02



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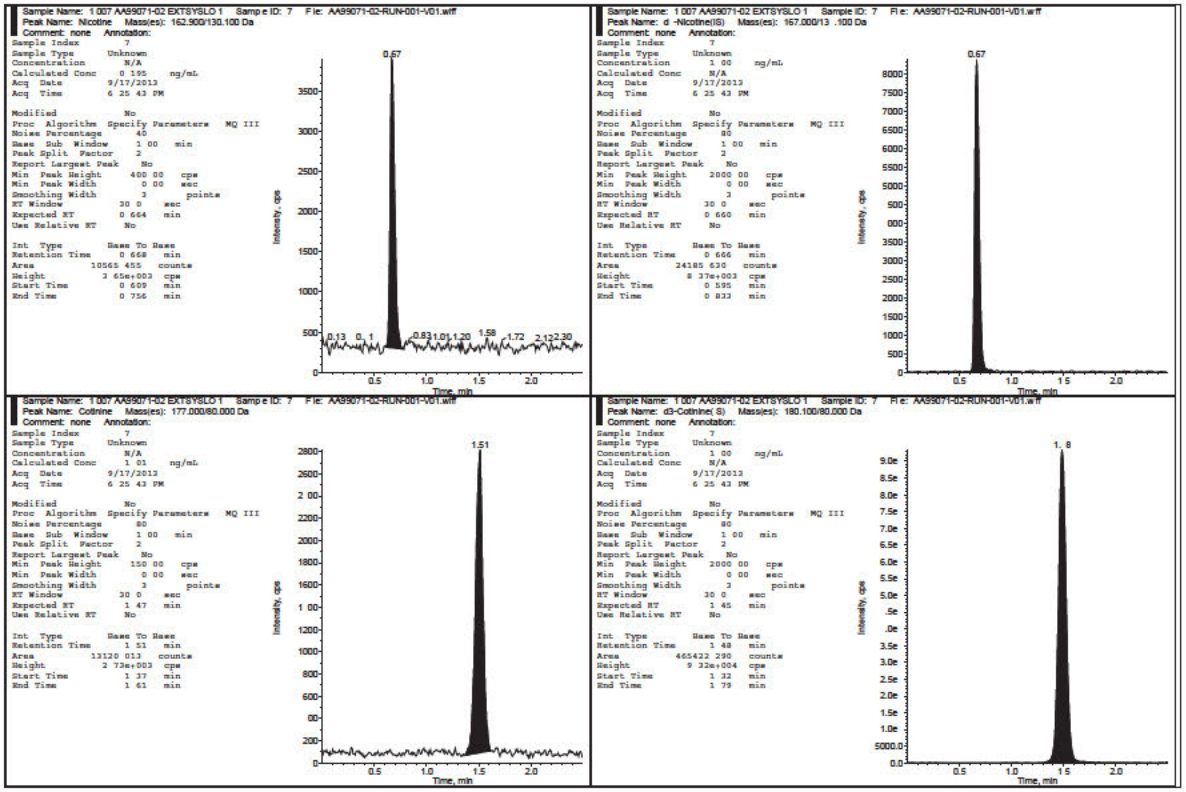
Celerion Study AA99071-02



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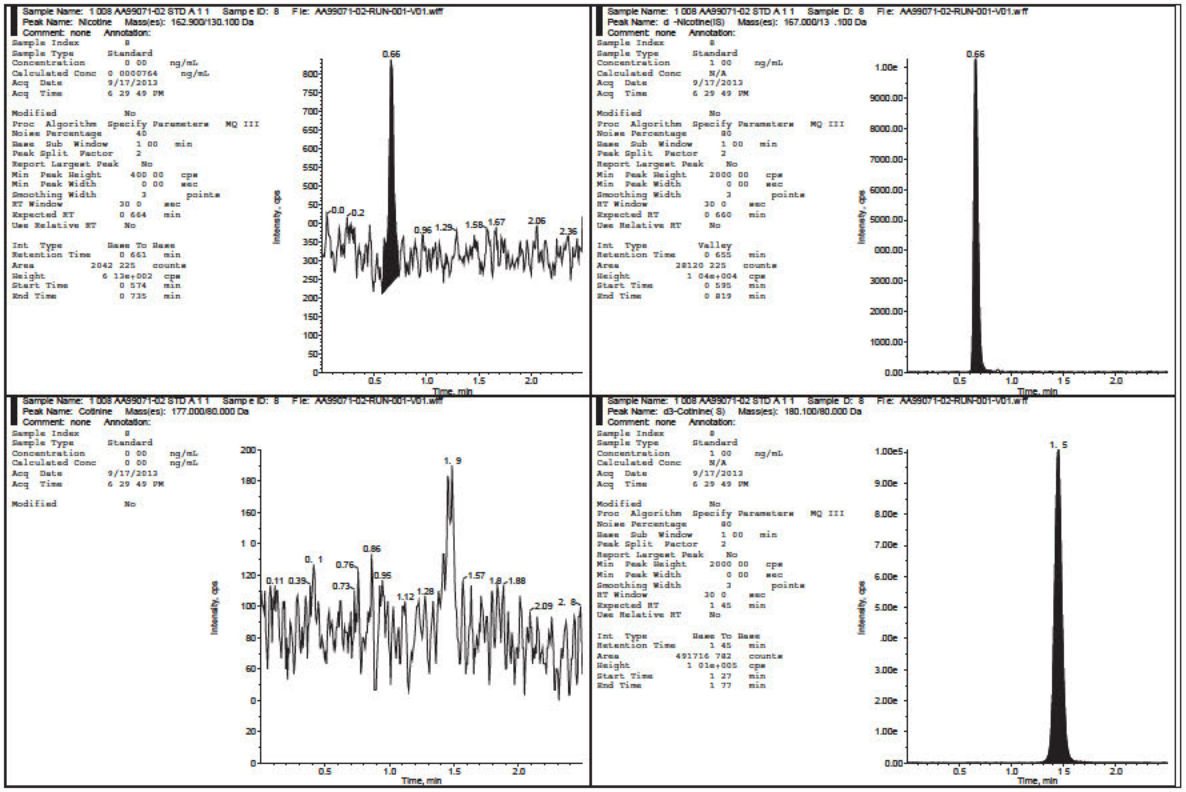

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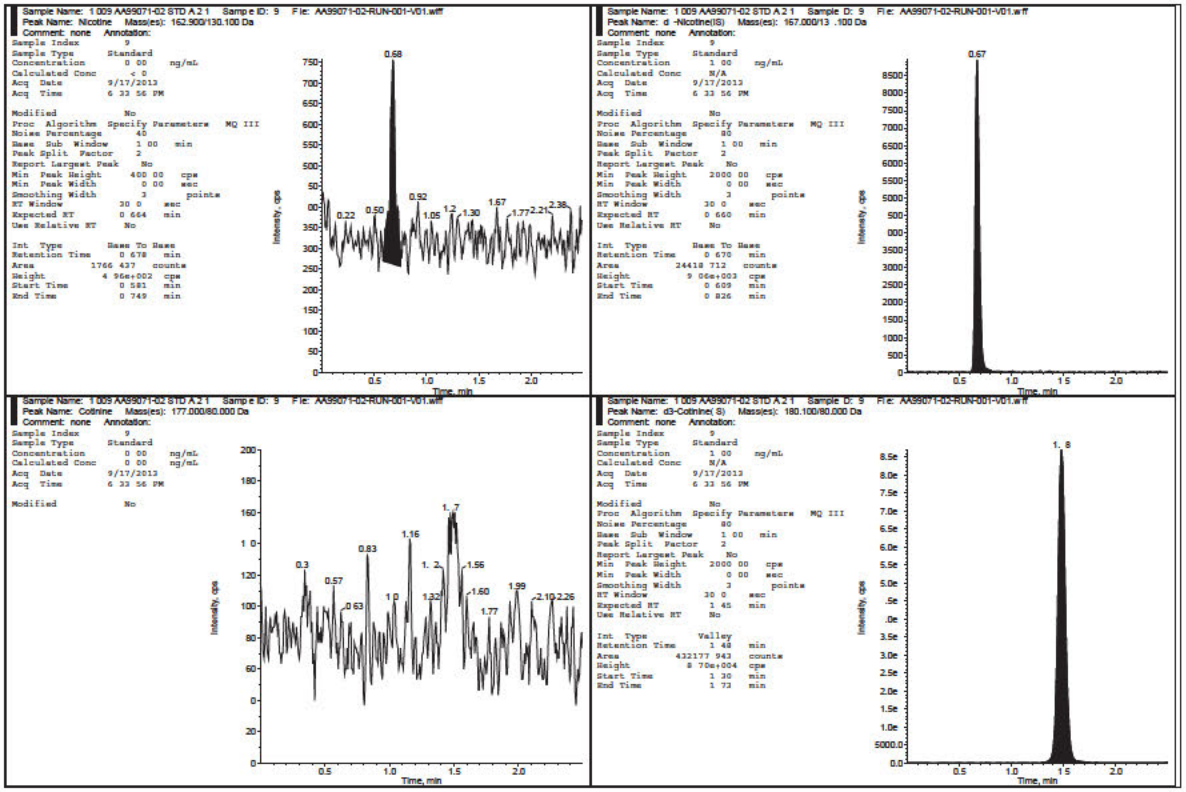

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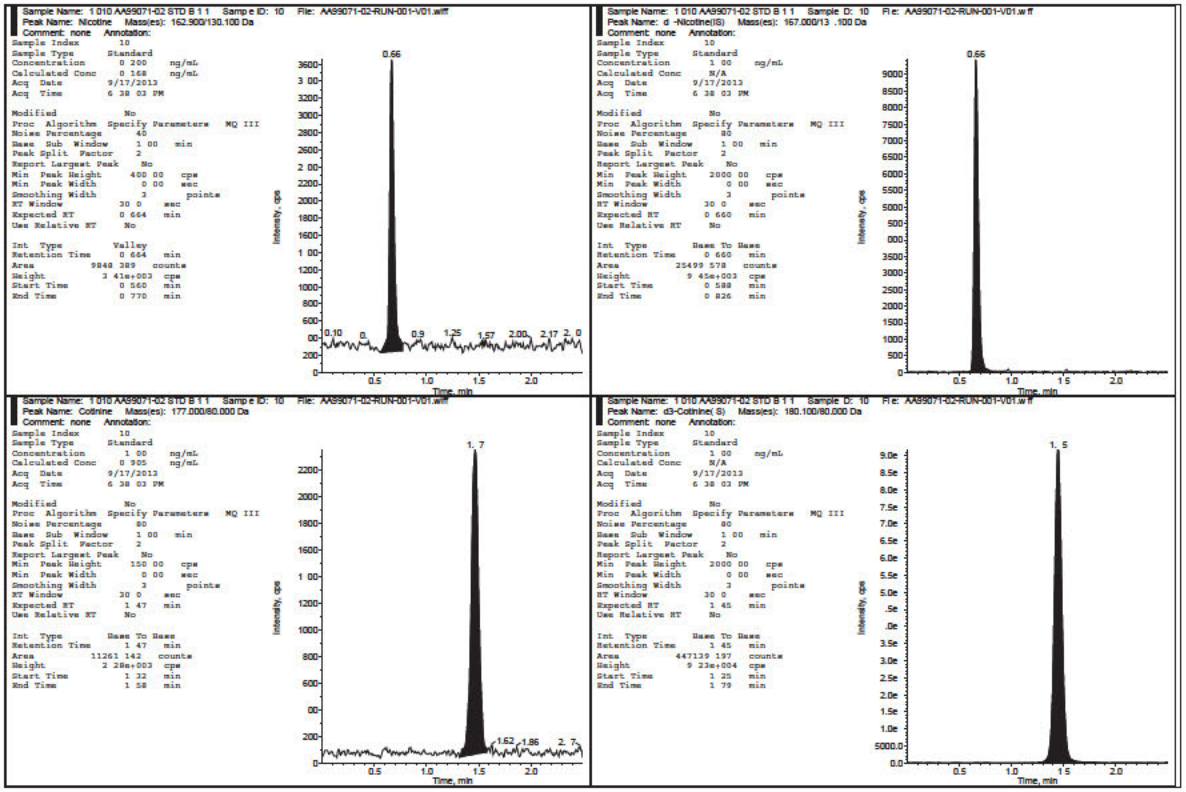

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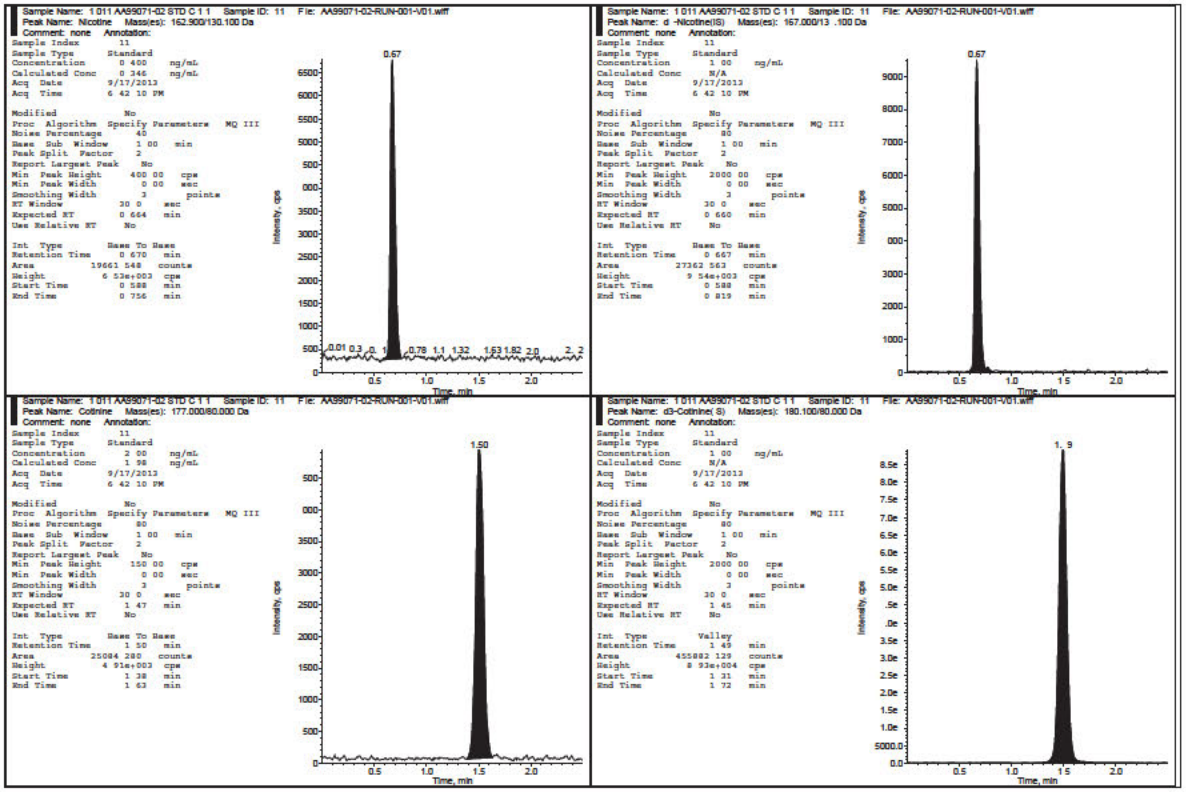

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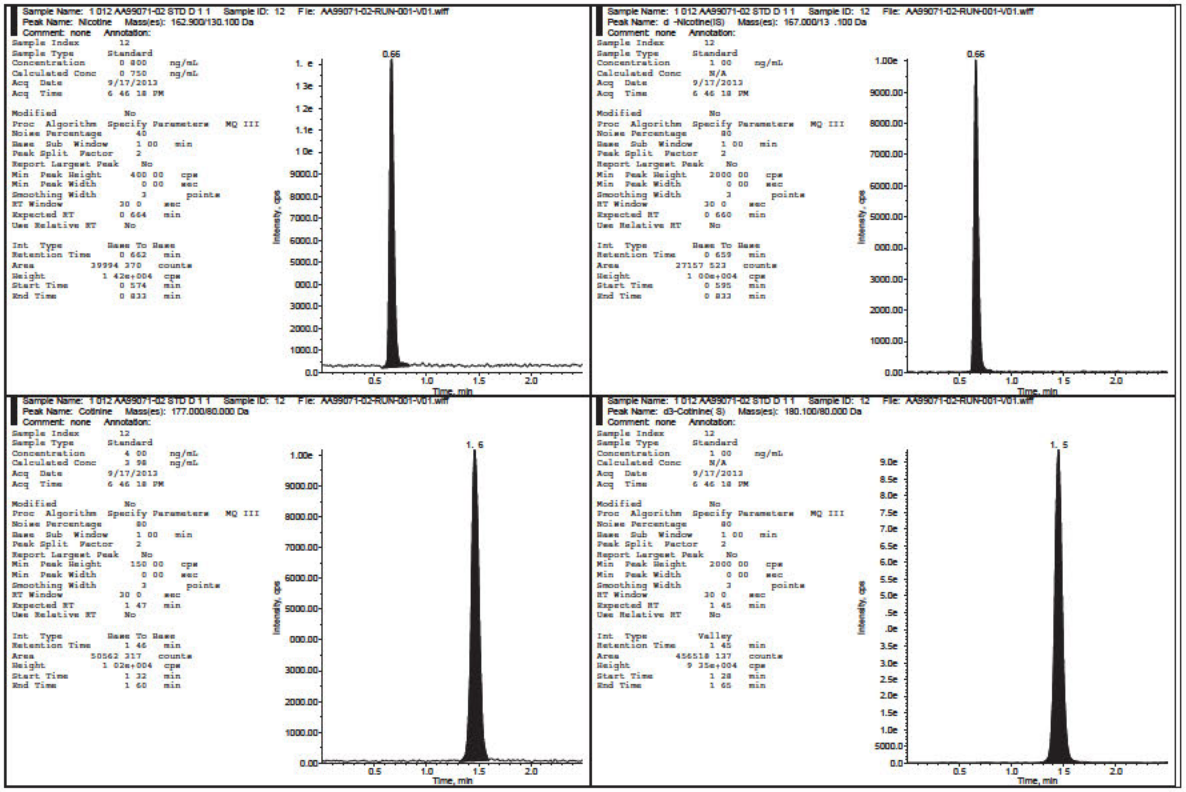

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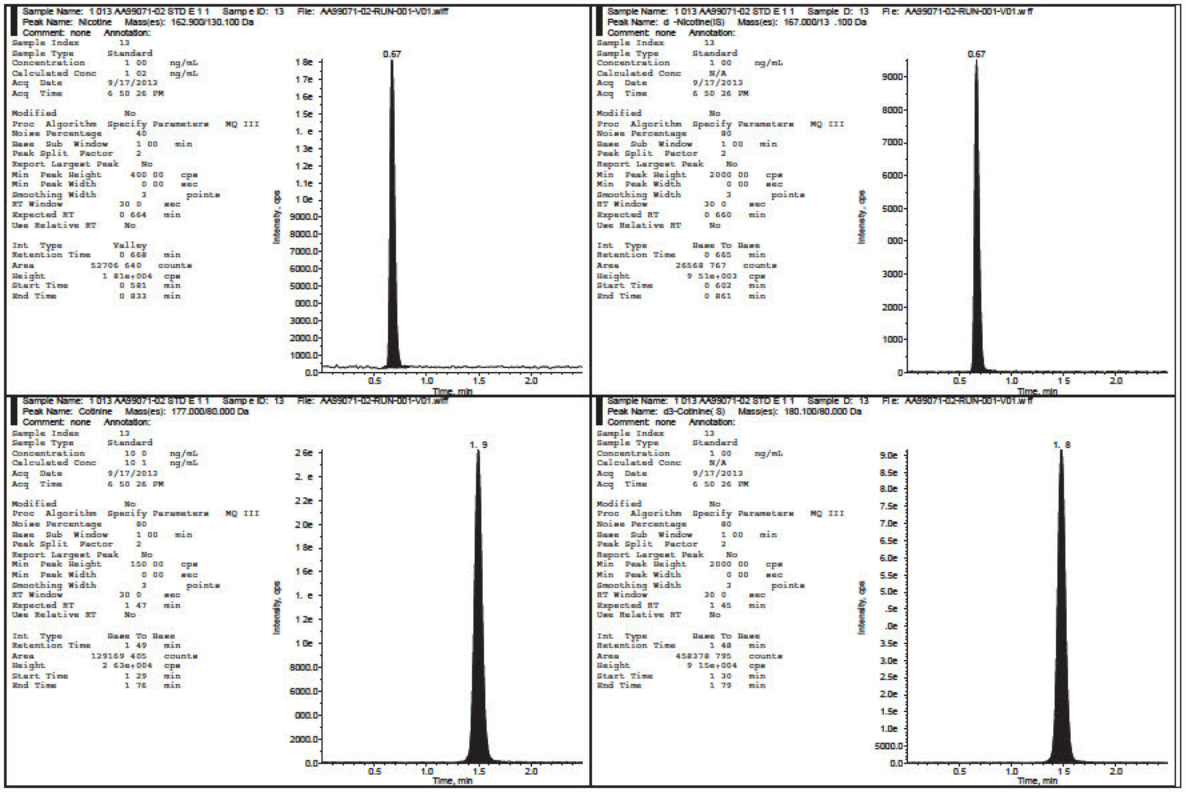

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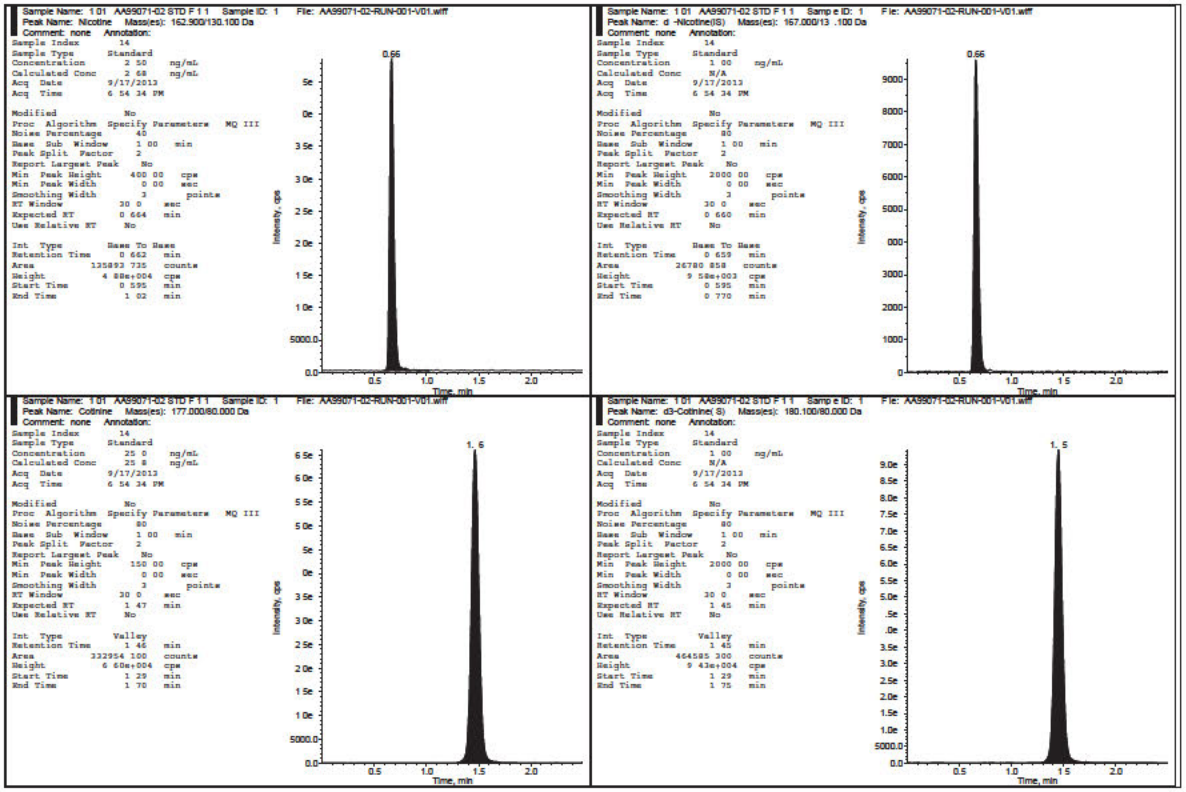

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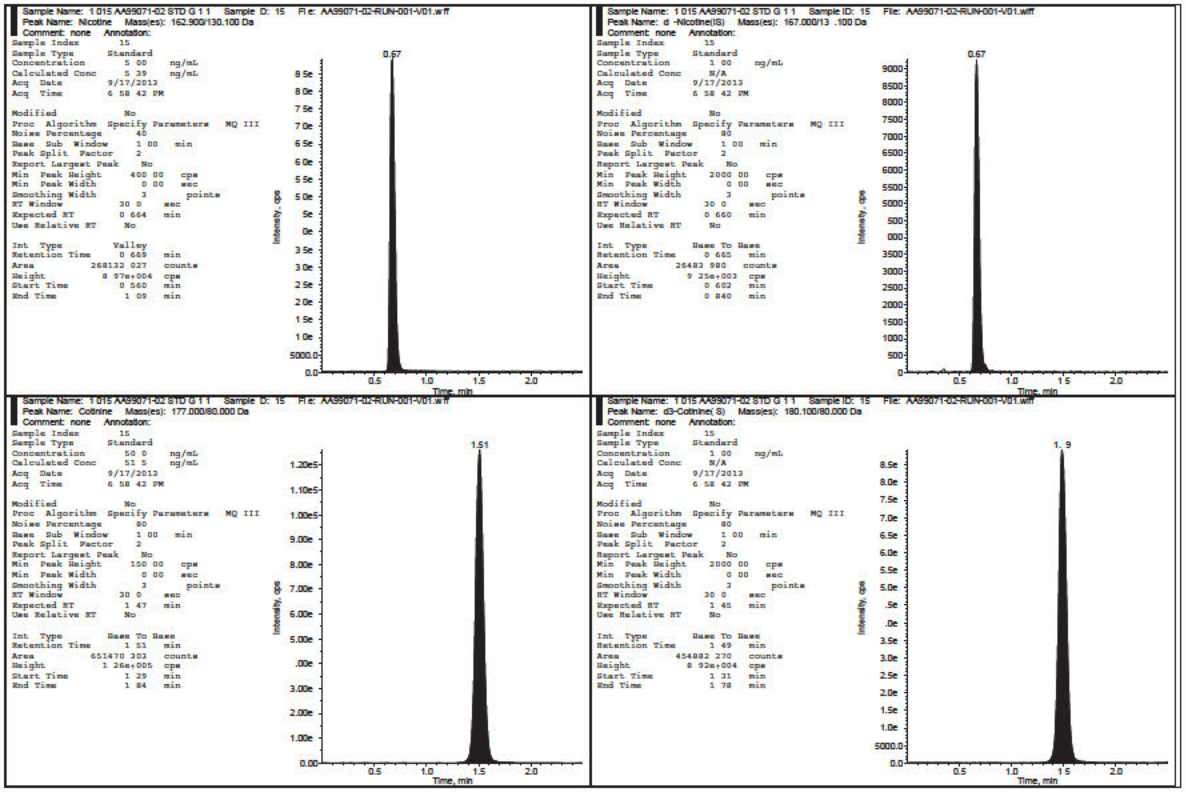

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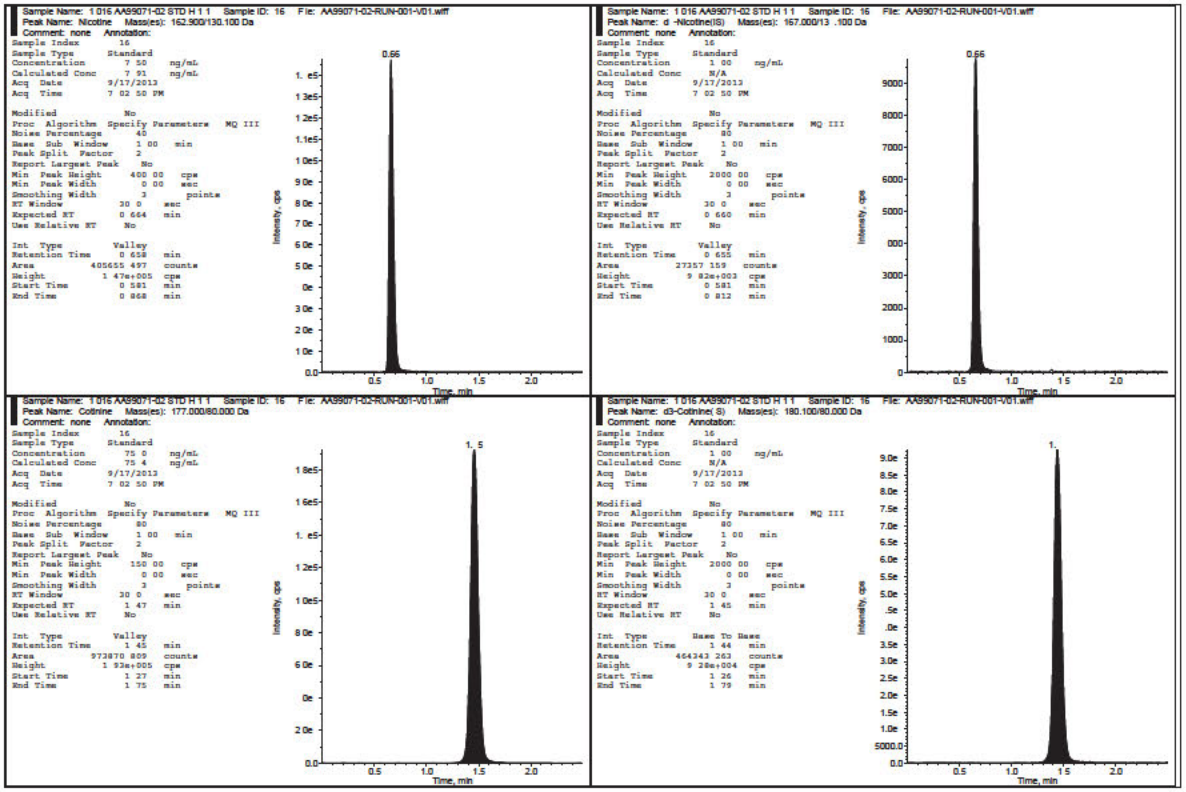

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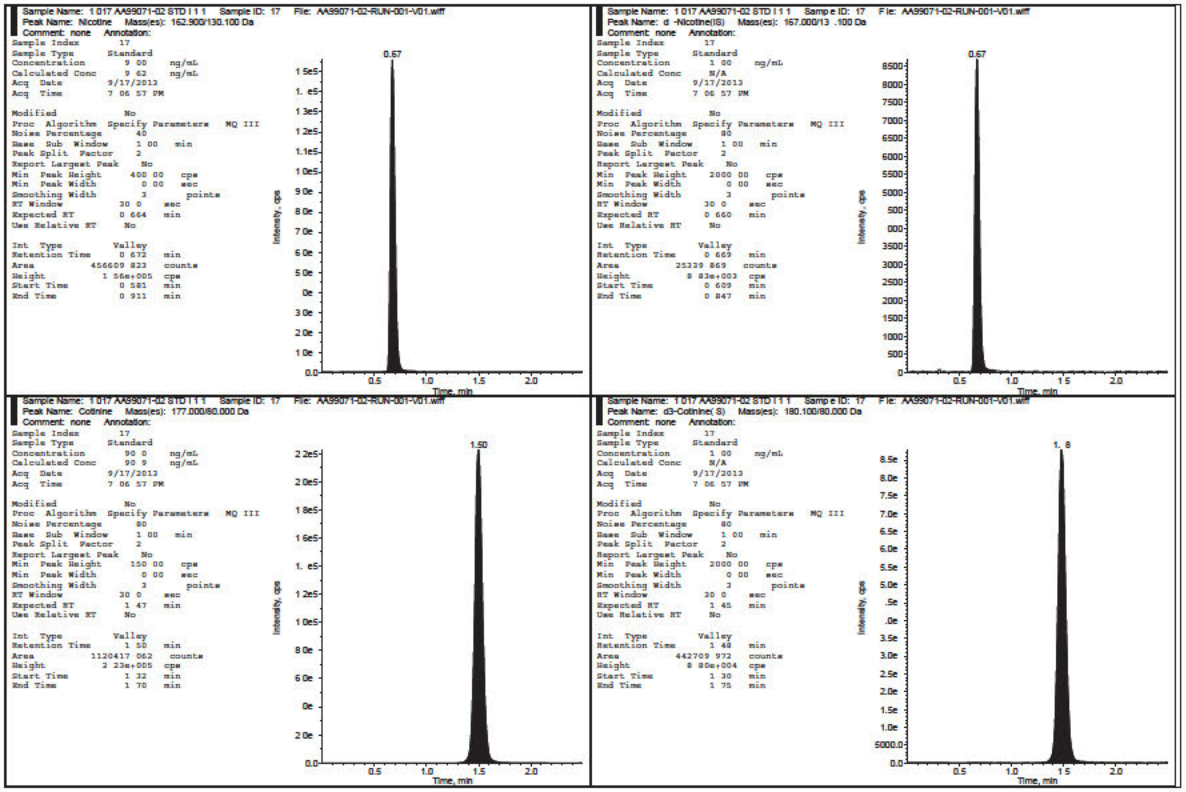
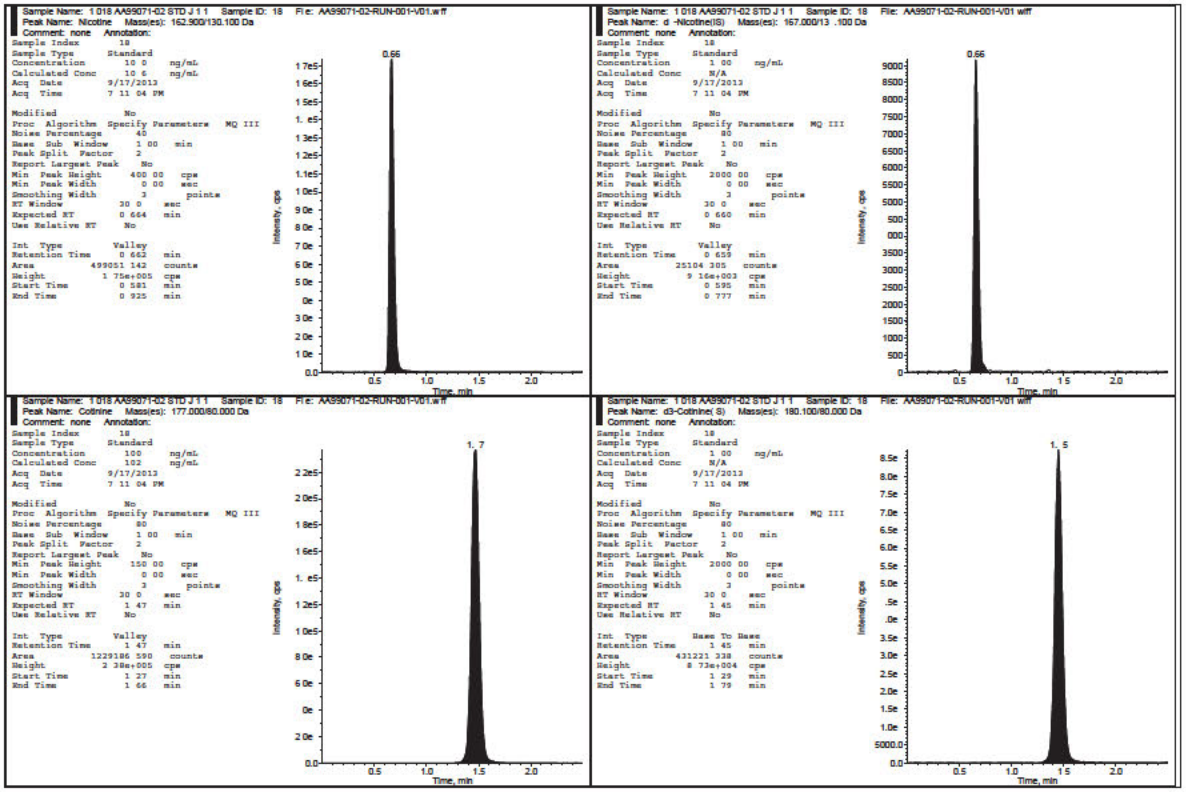


Nicotine and Cotinine in Human Plasma ($K_2$EDTA)
Celerion Study AA99071-02



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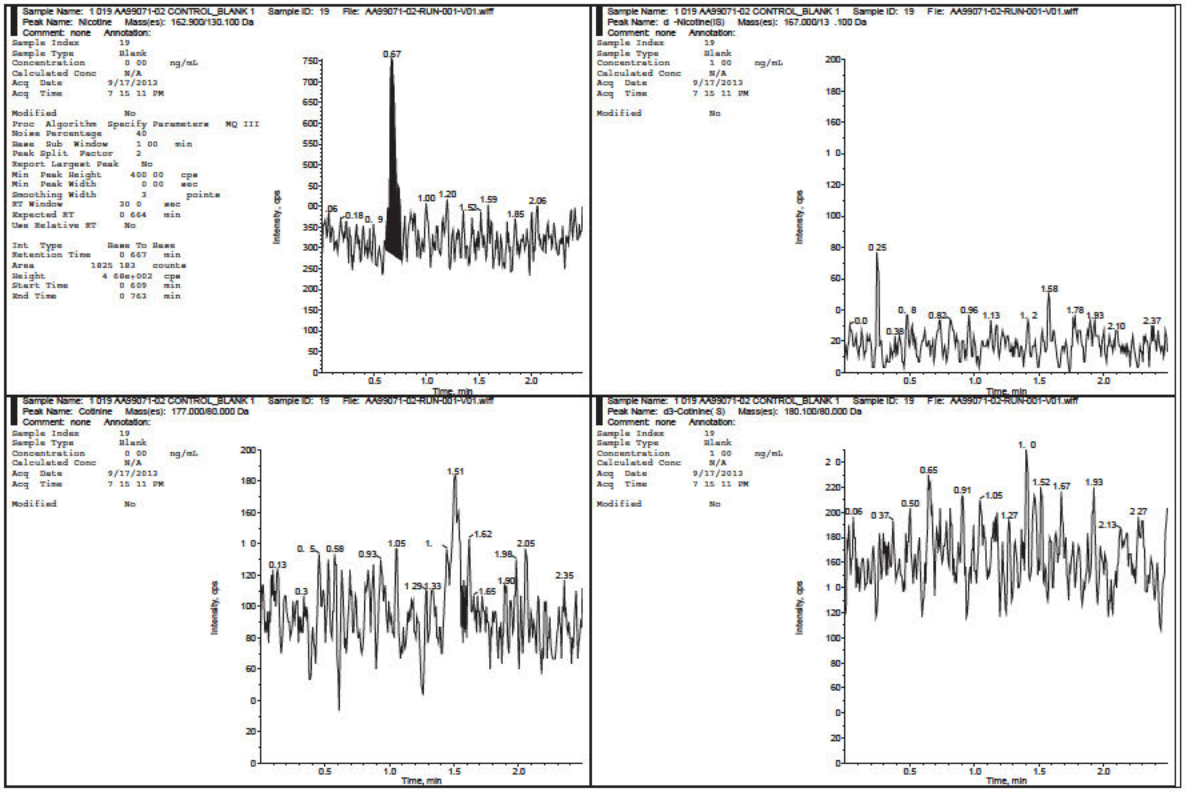

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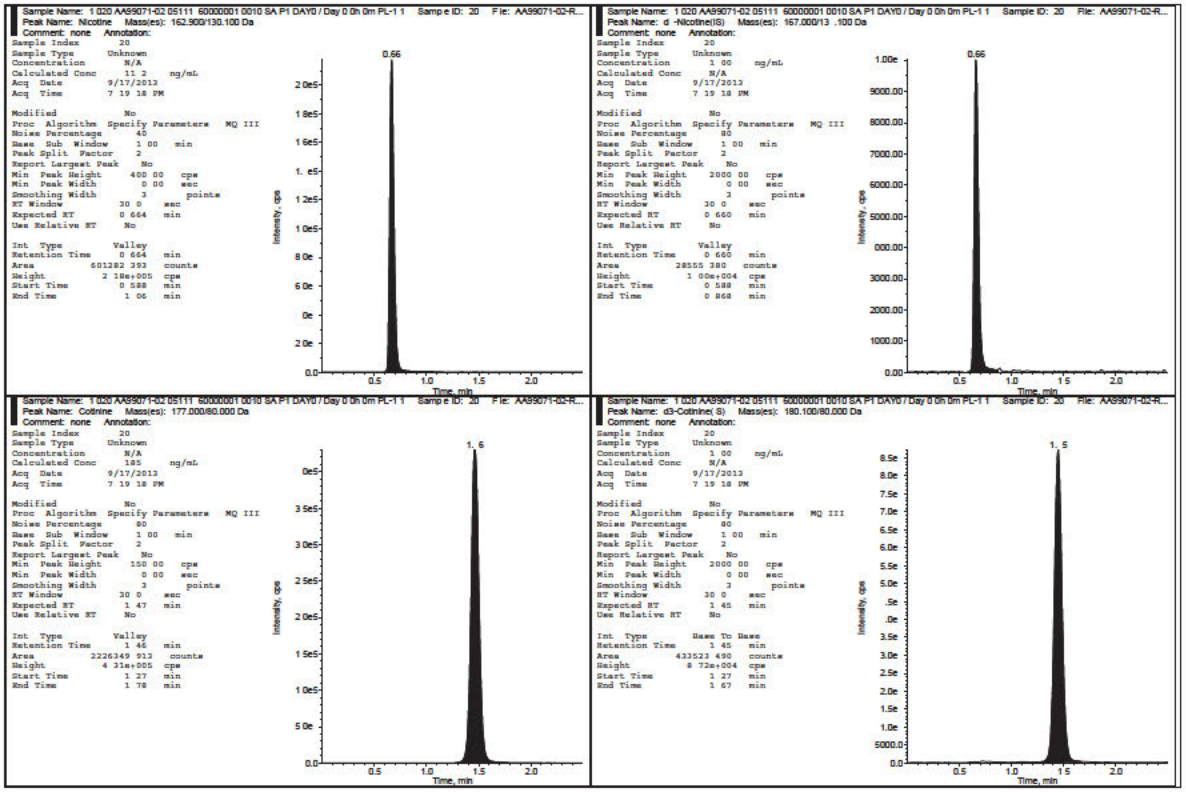

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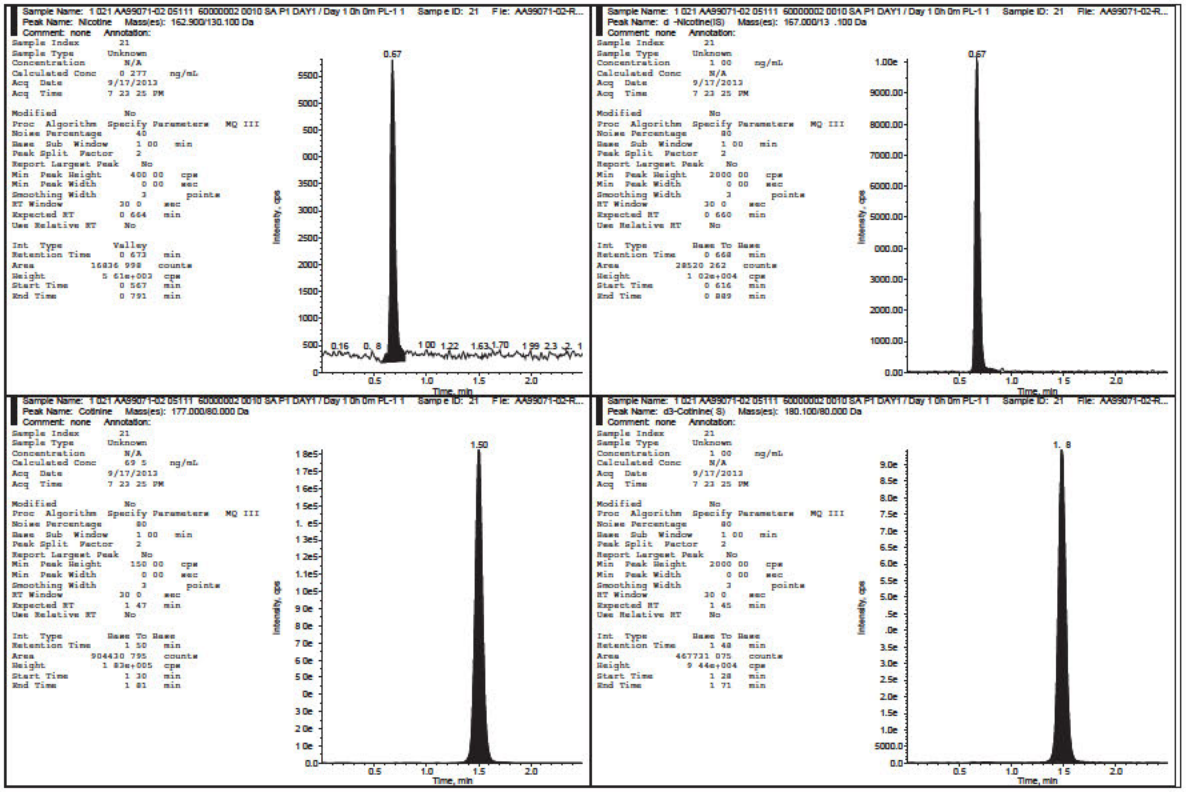

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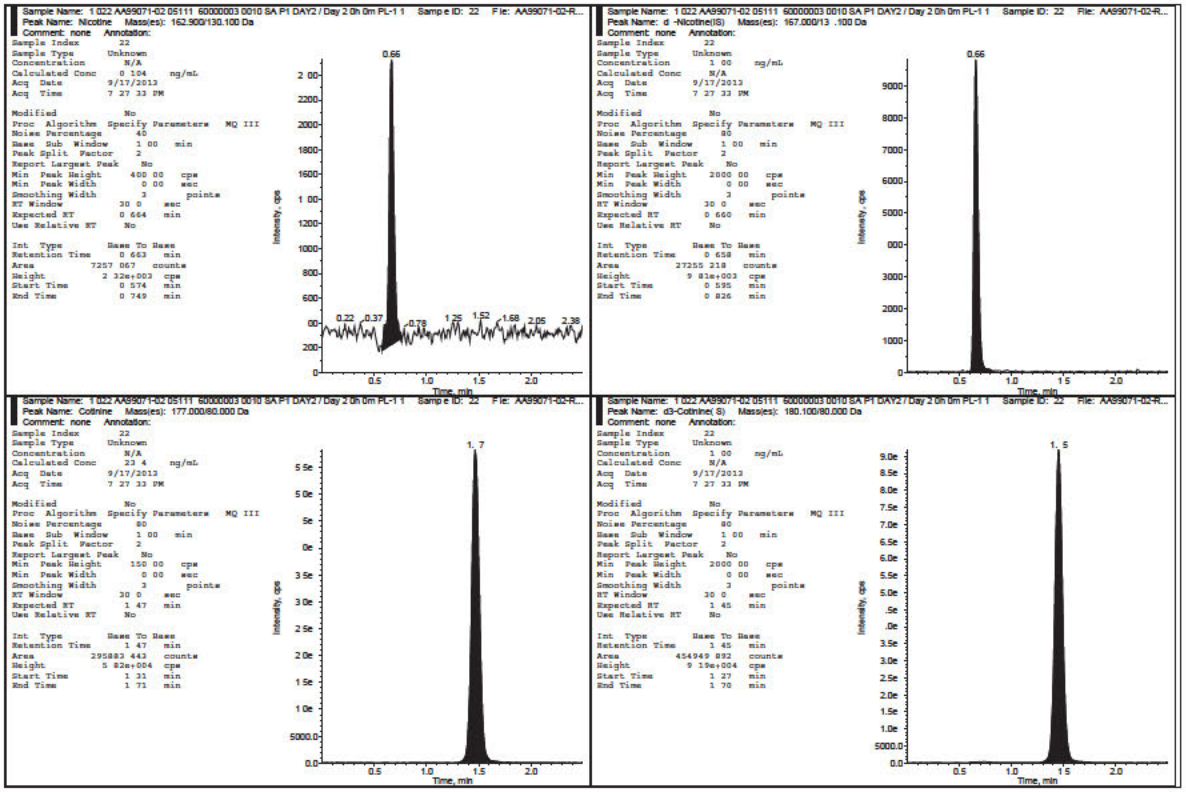

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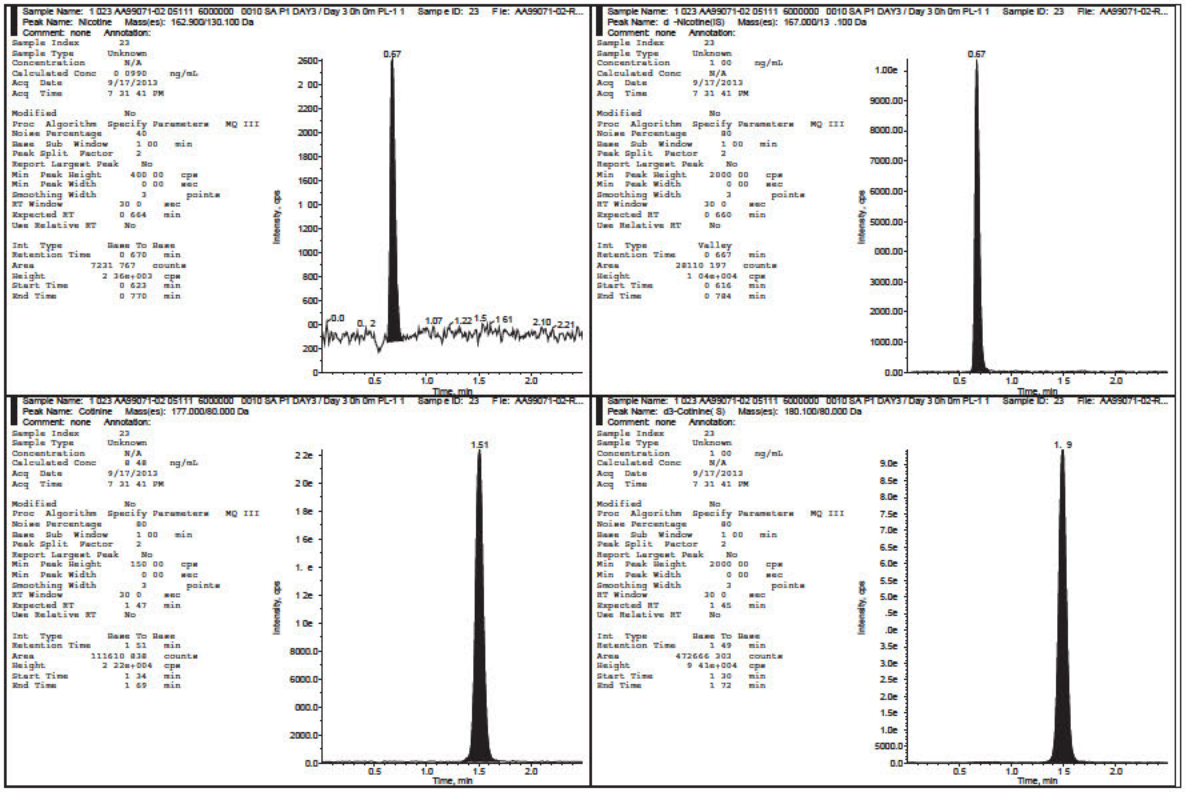

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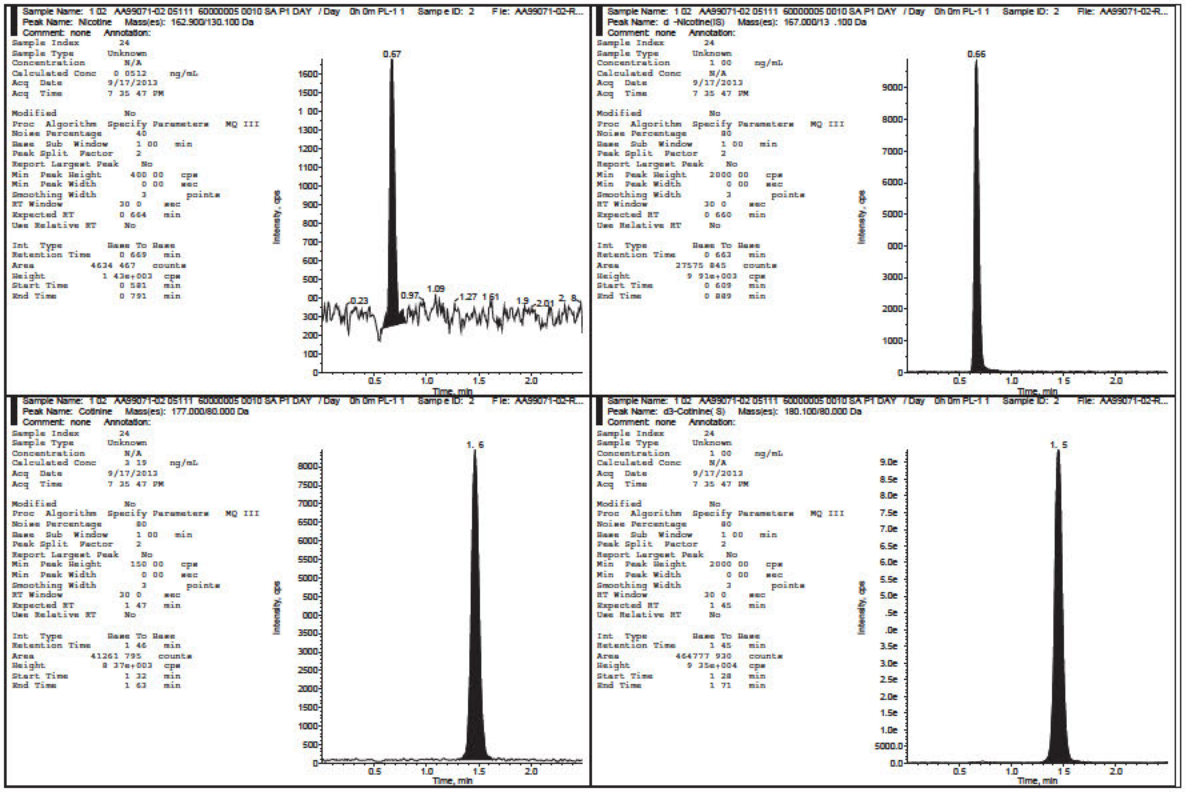

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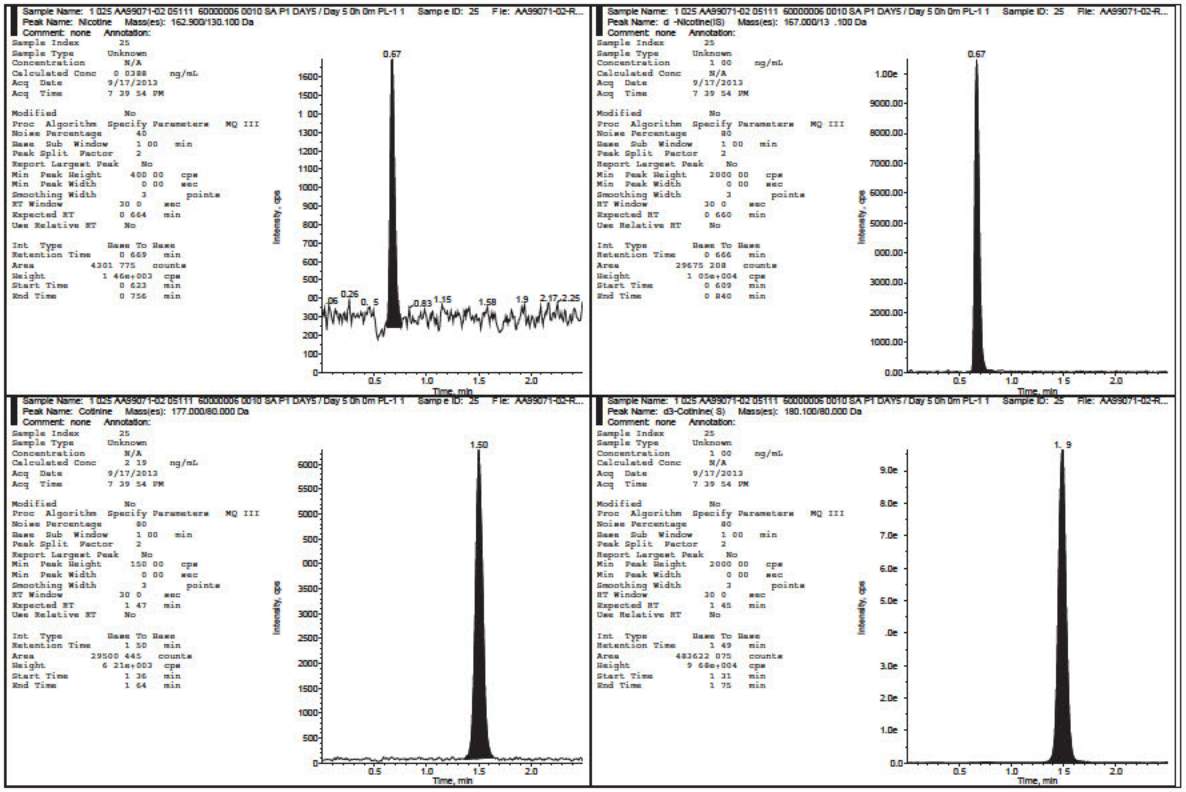

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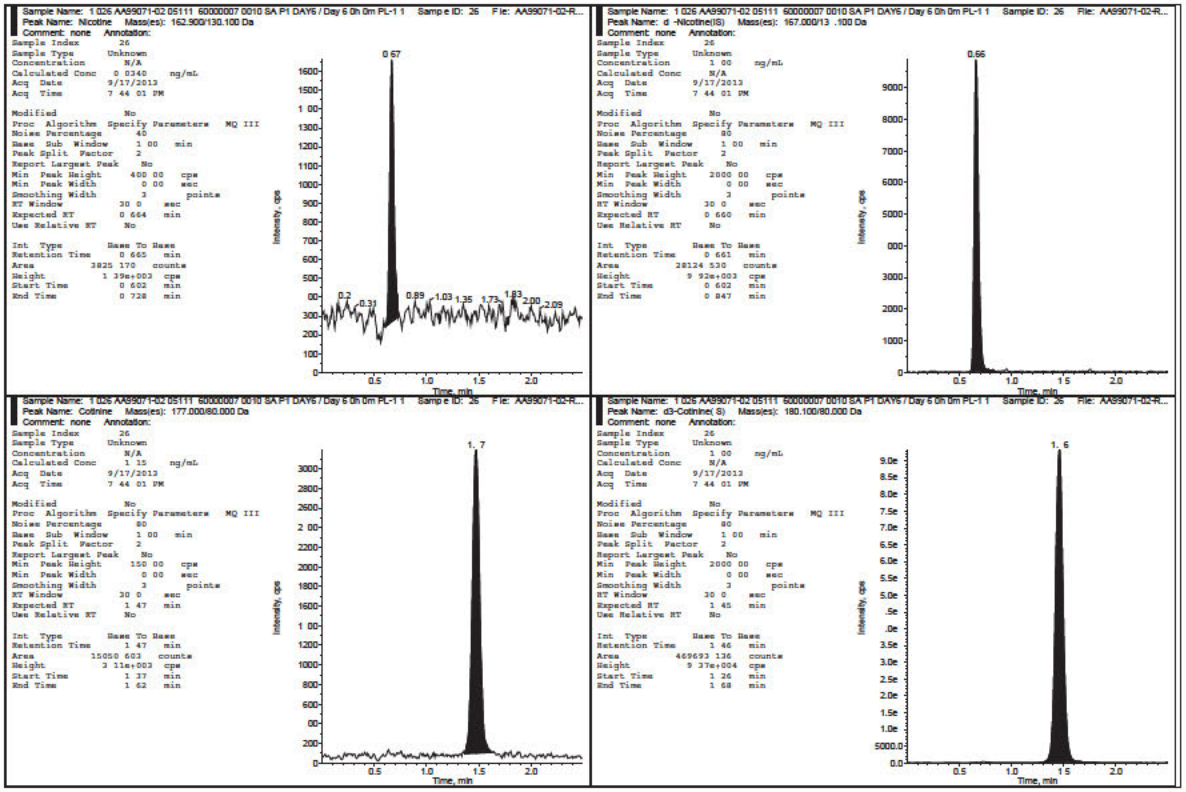

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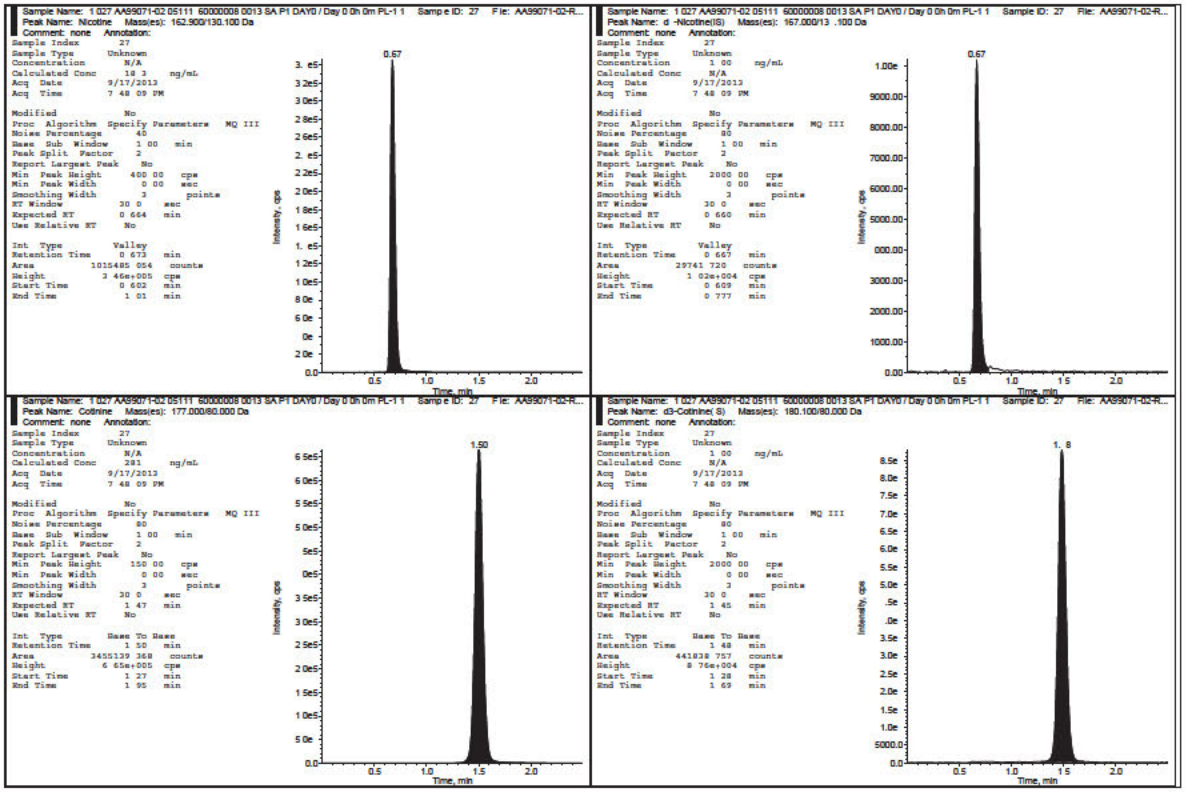

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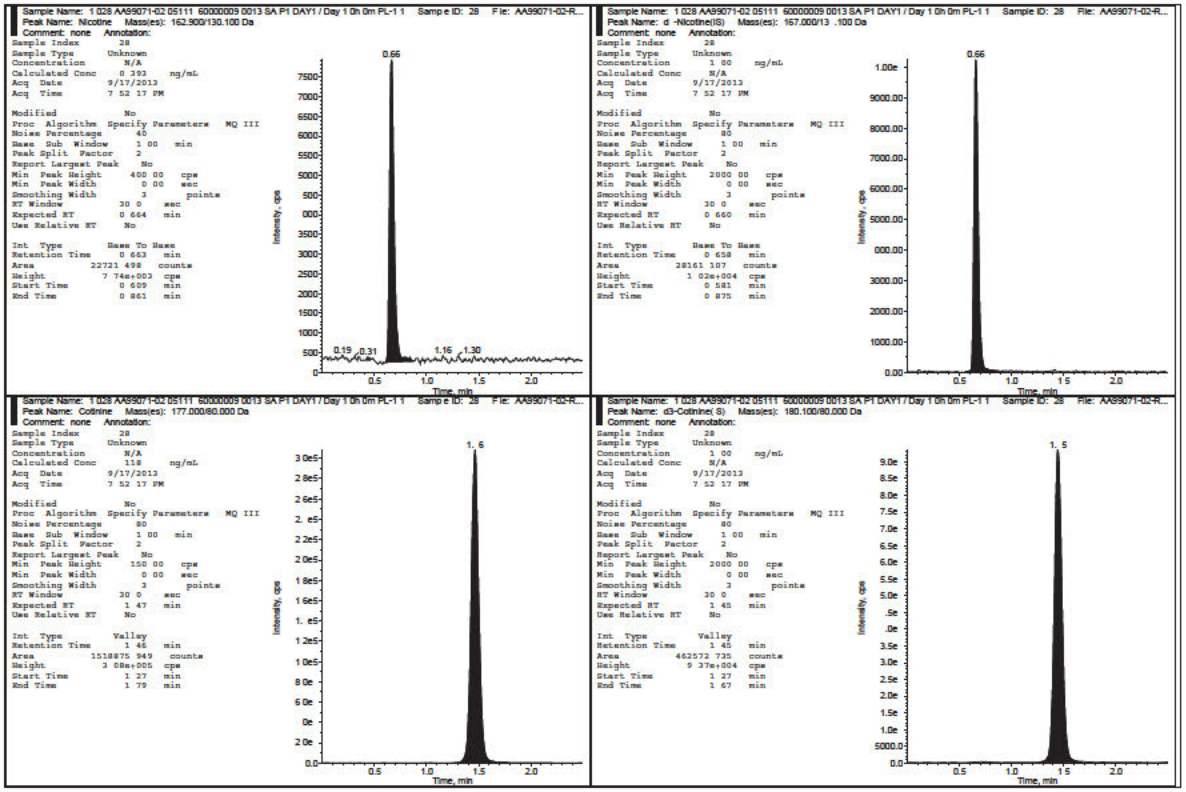

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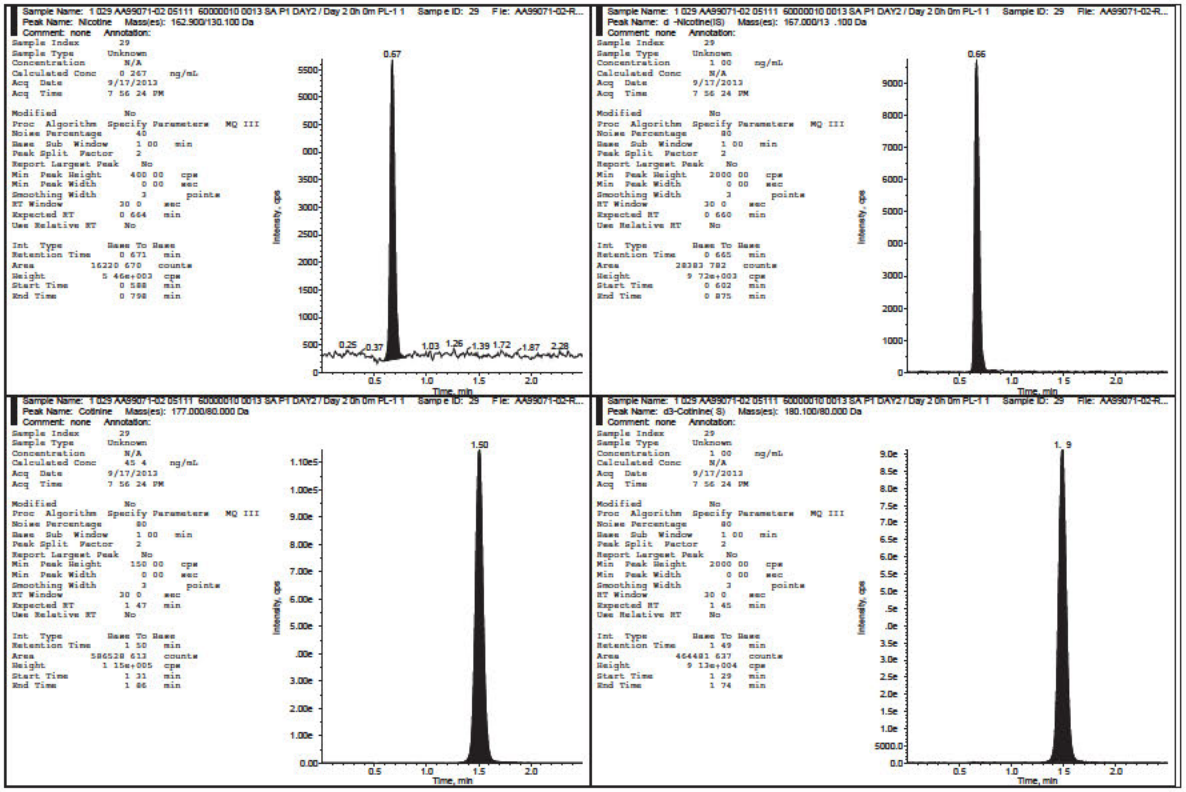

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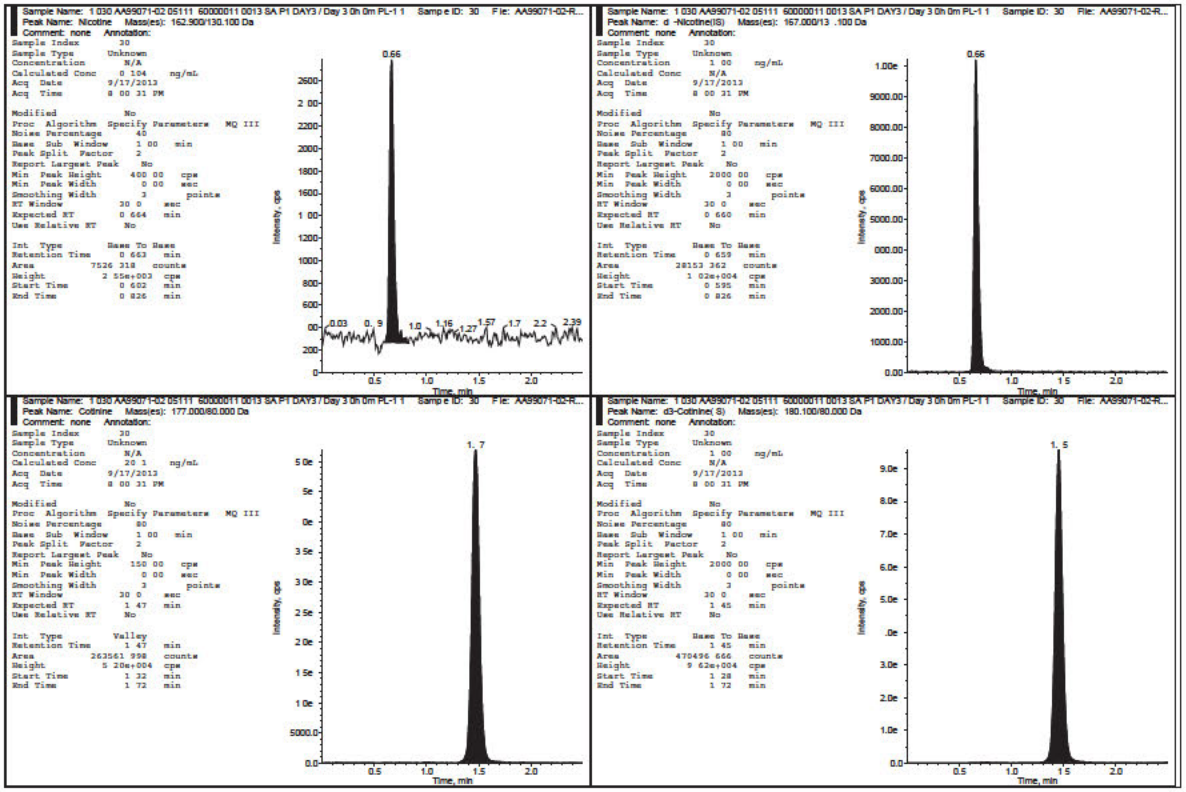

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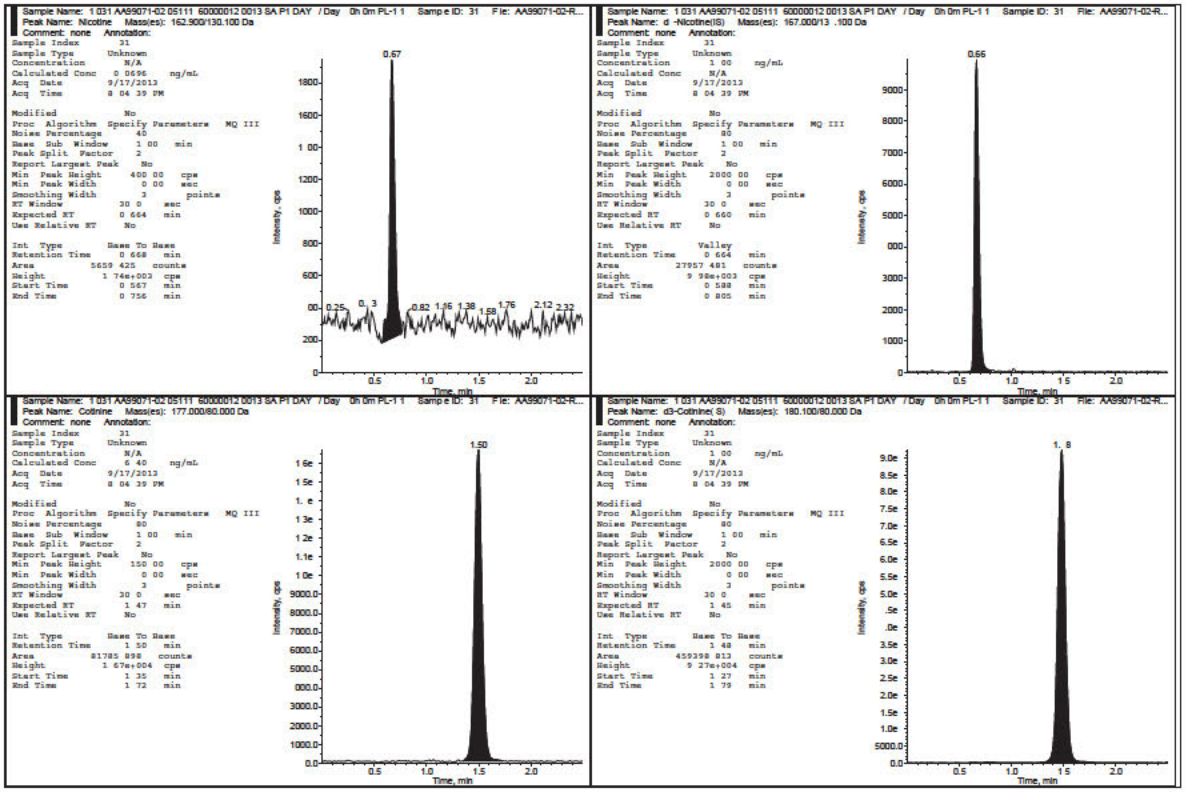

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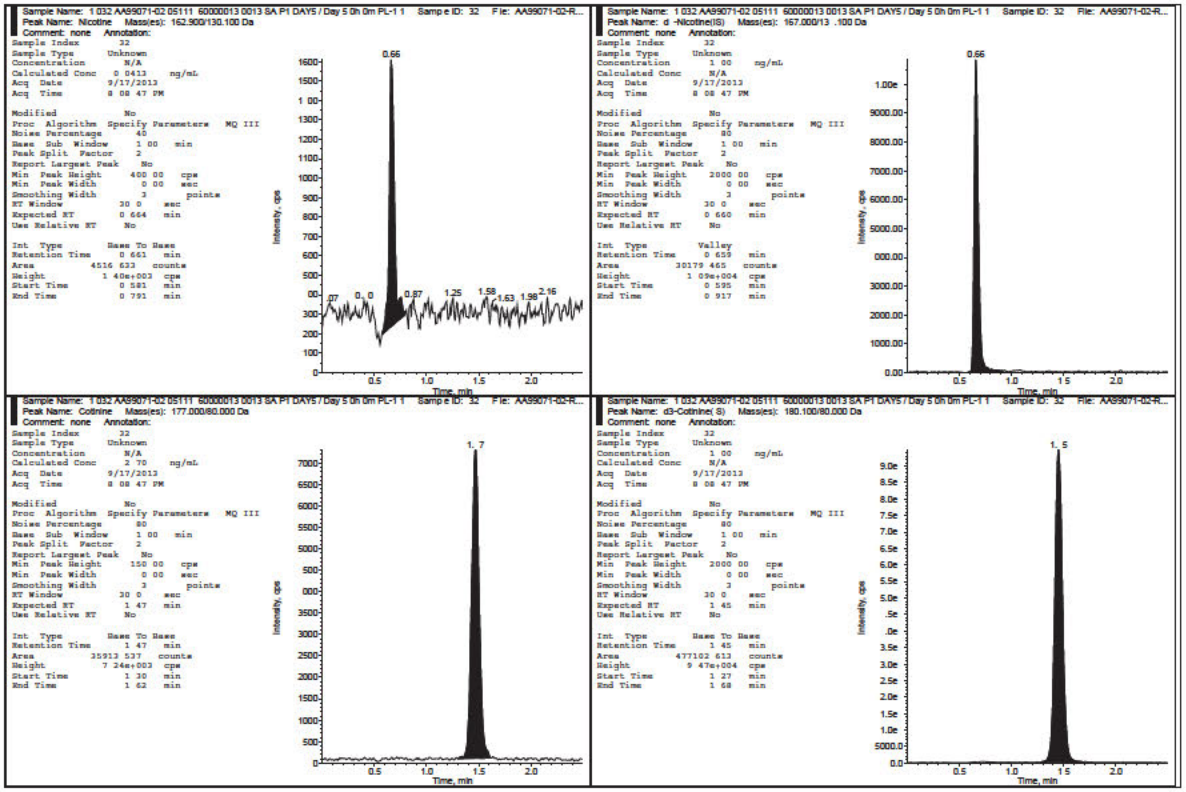

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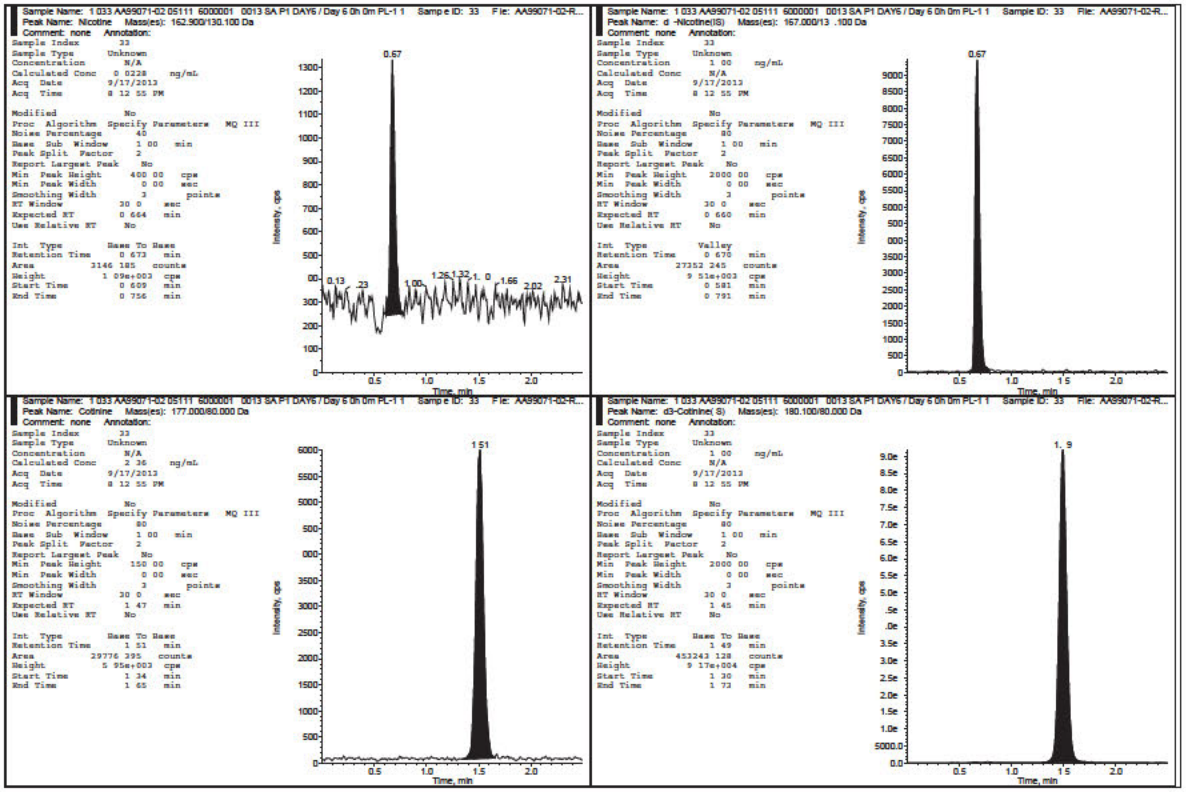

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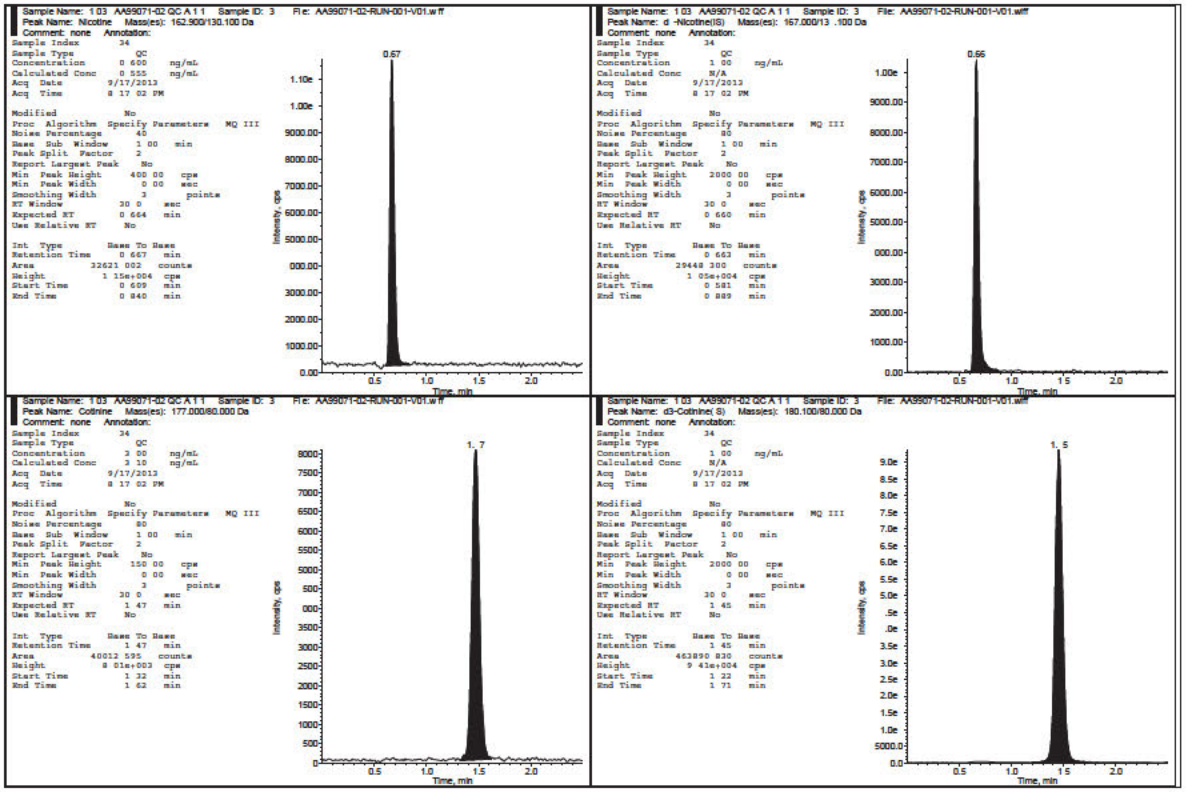

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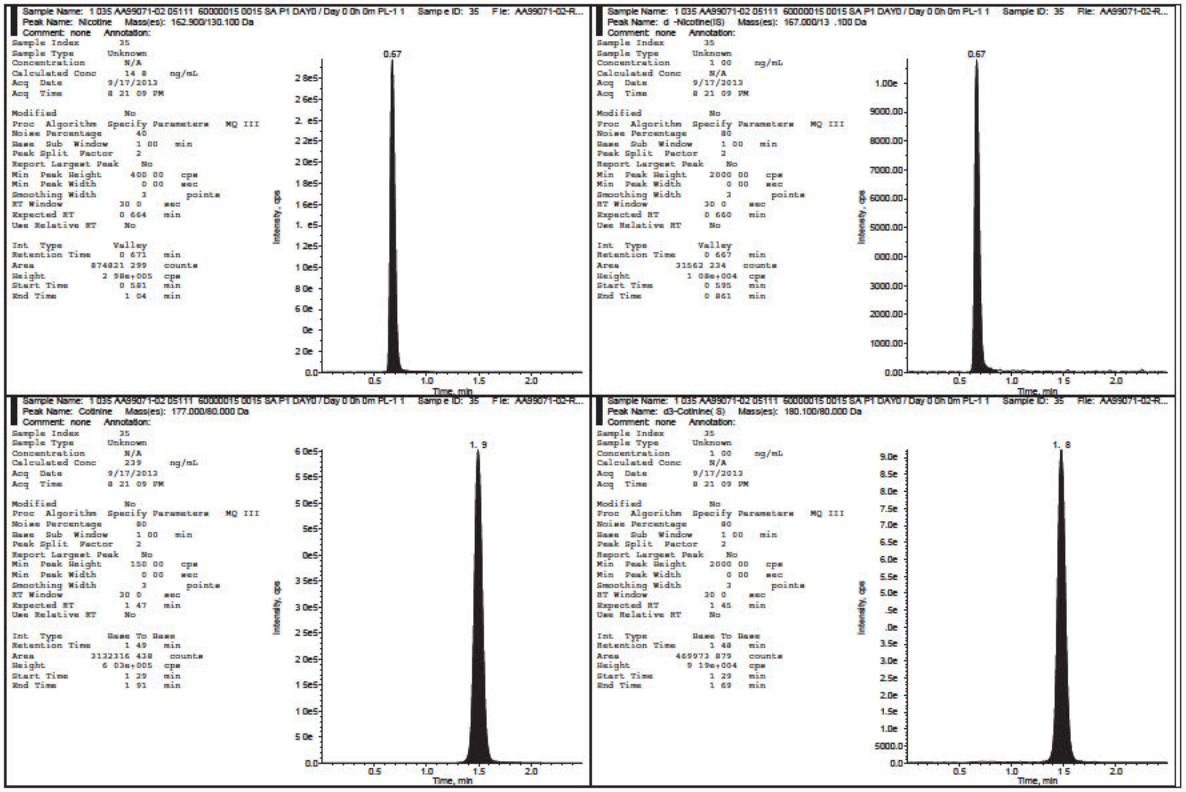

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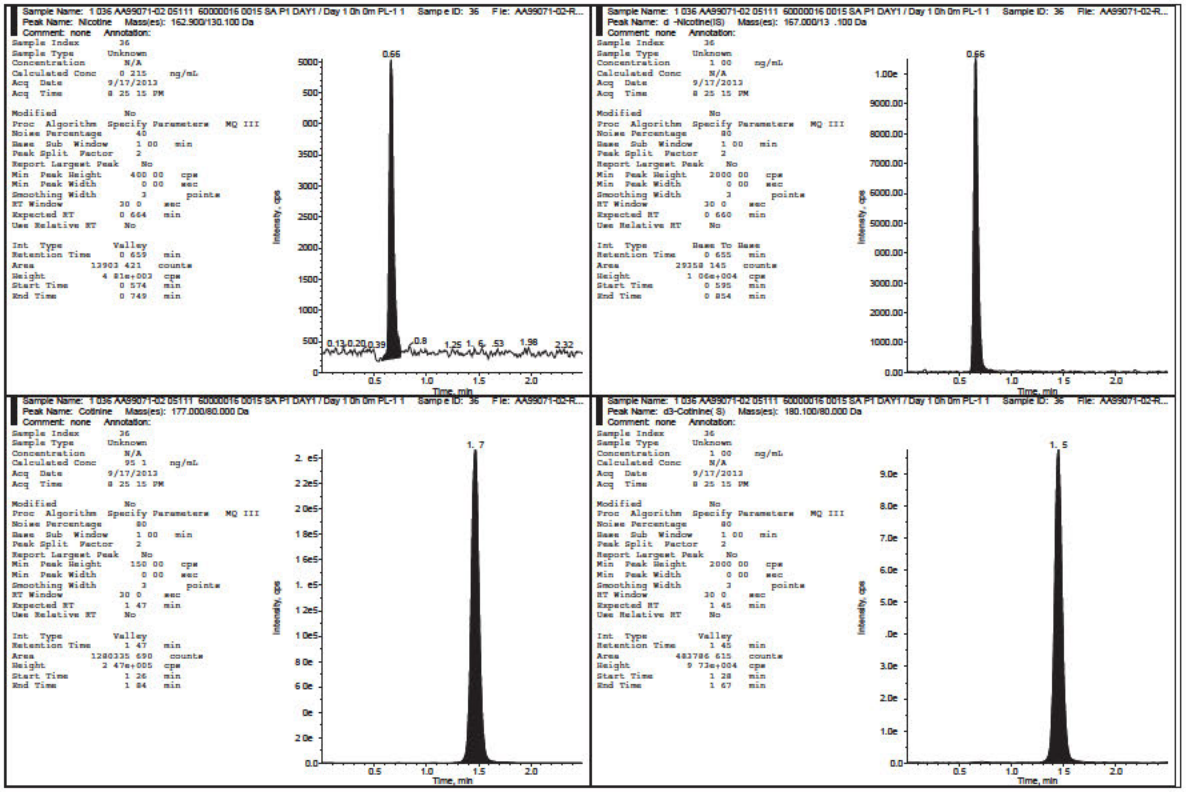

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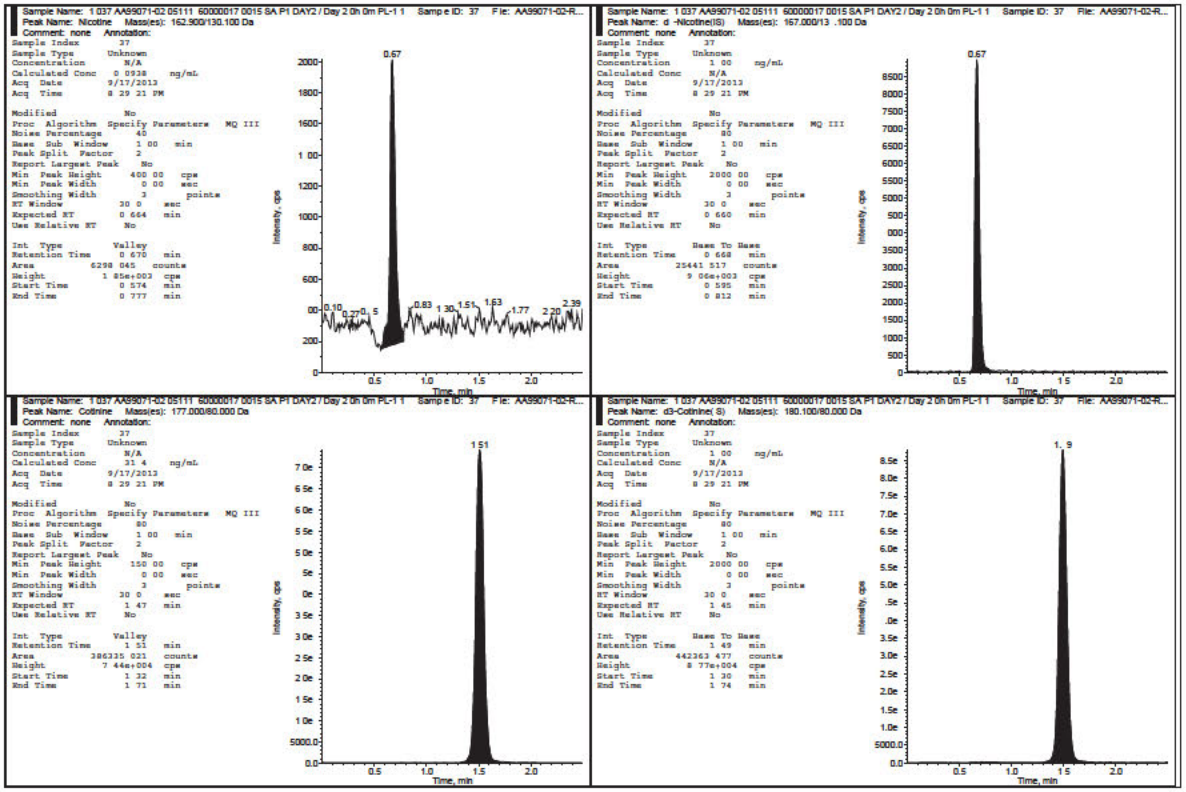

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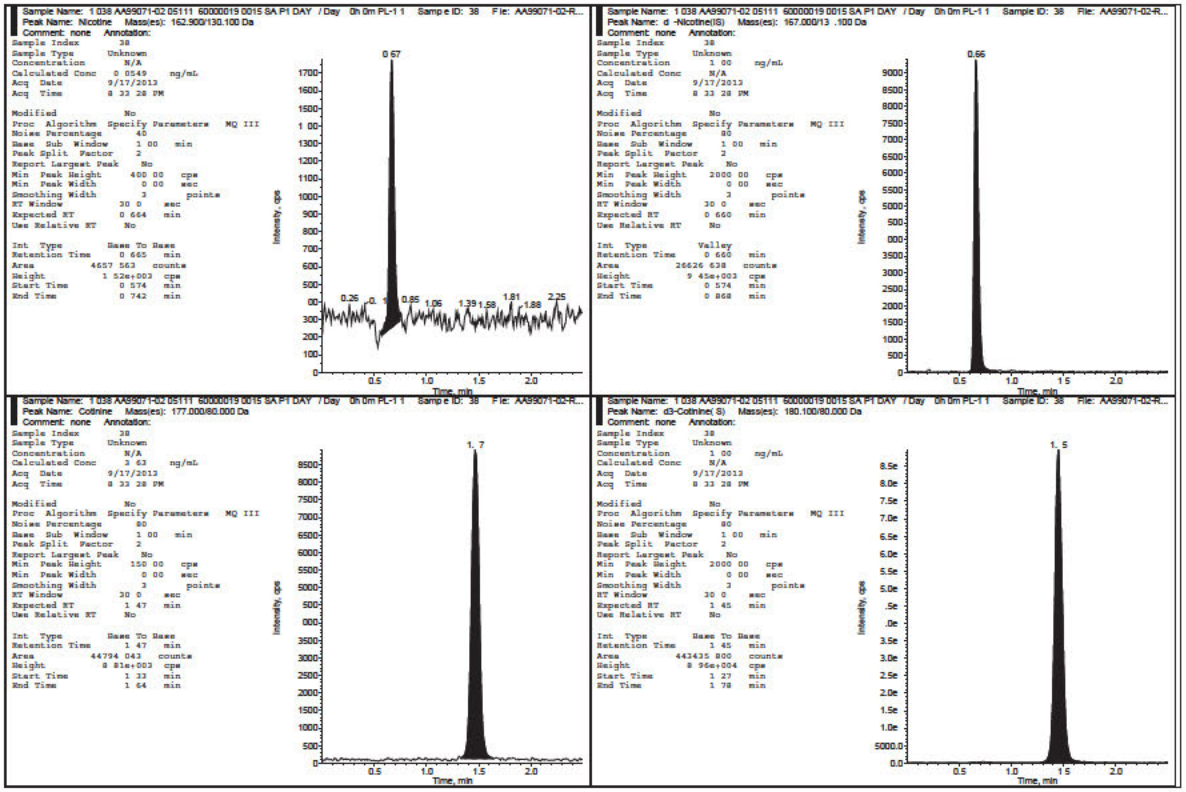

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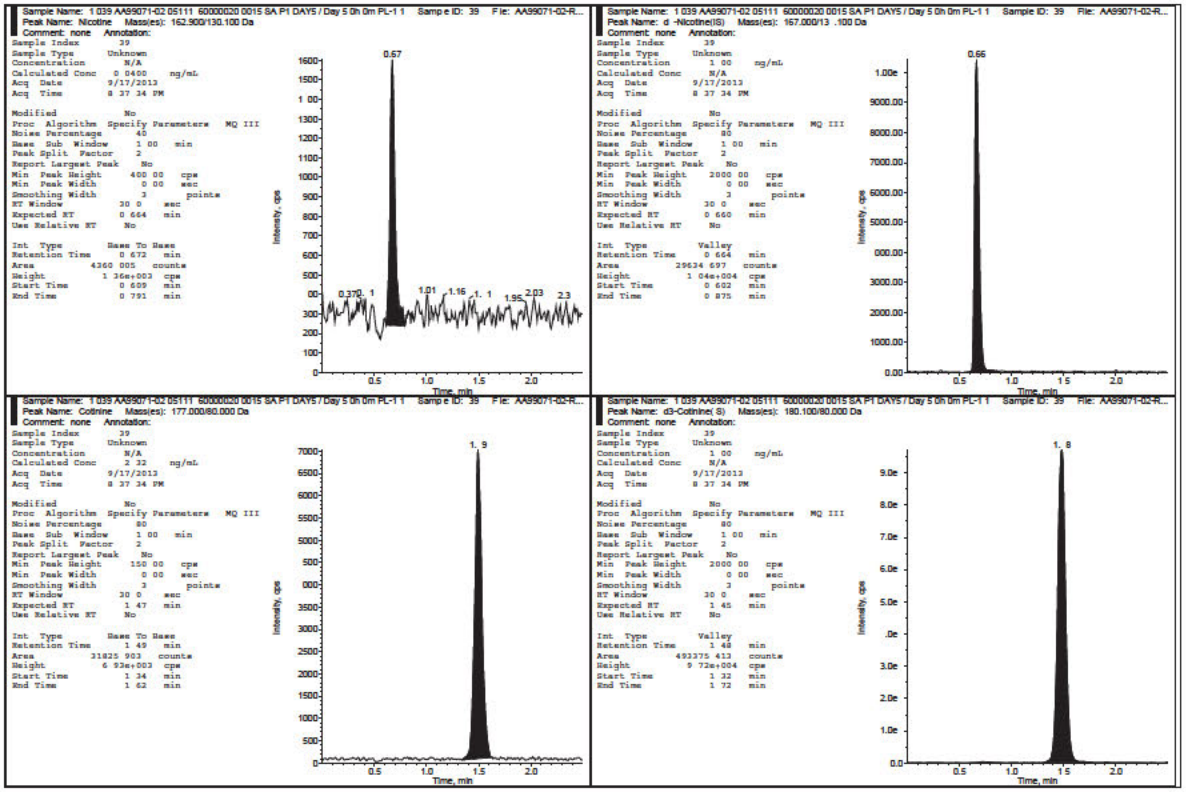

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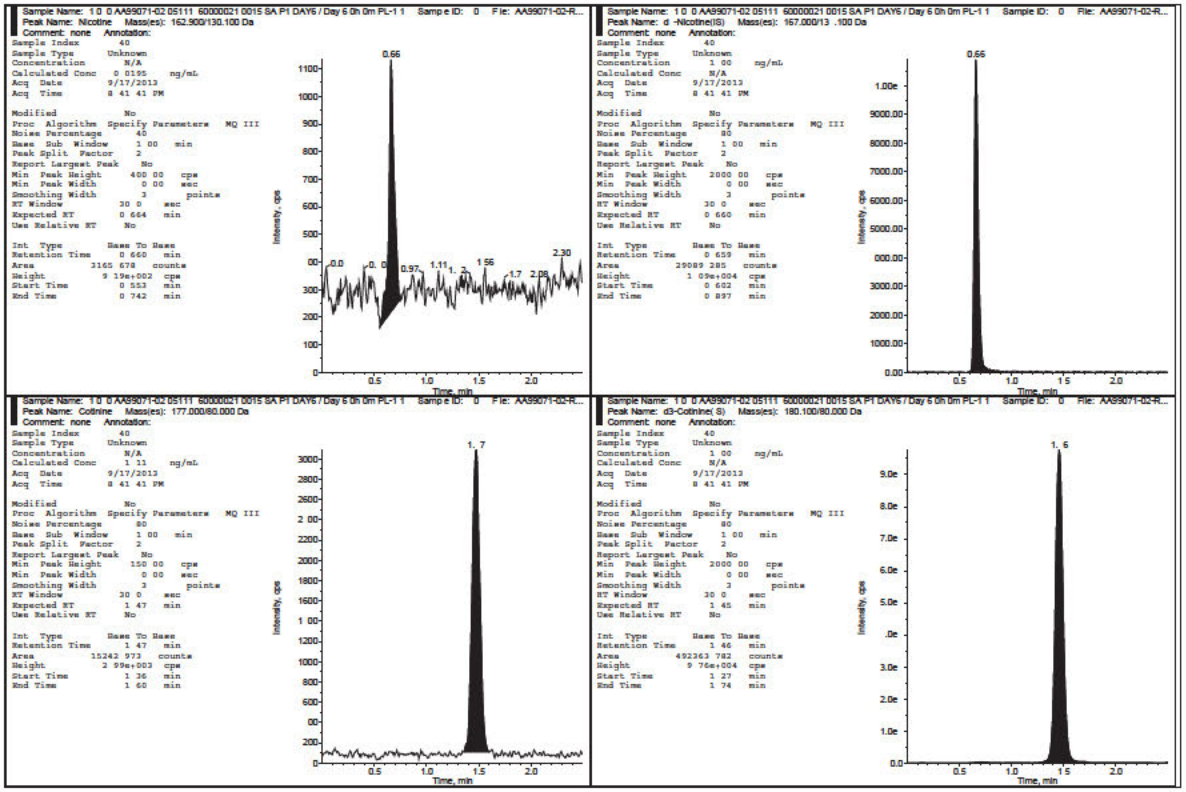

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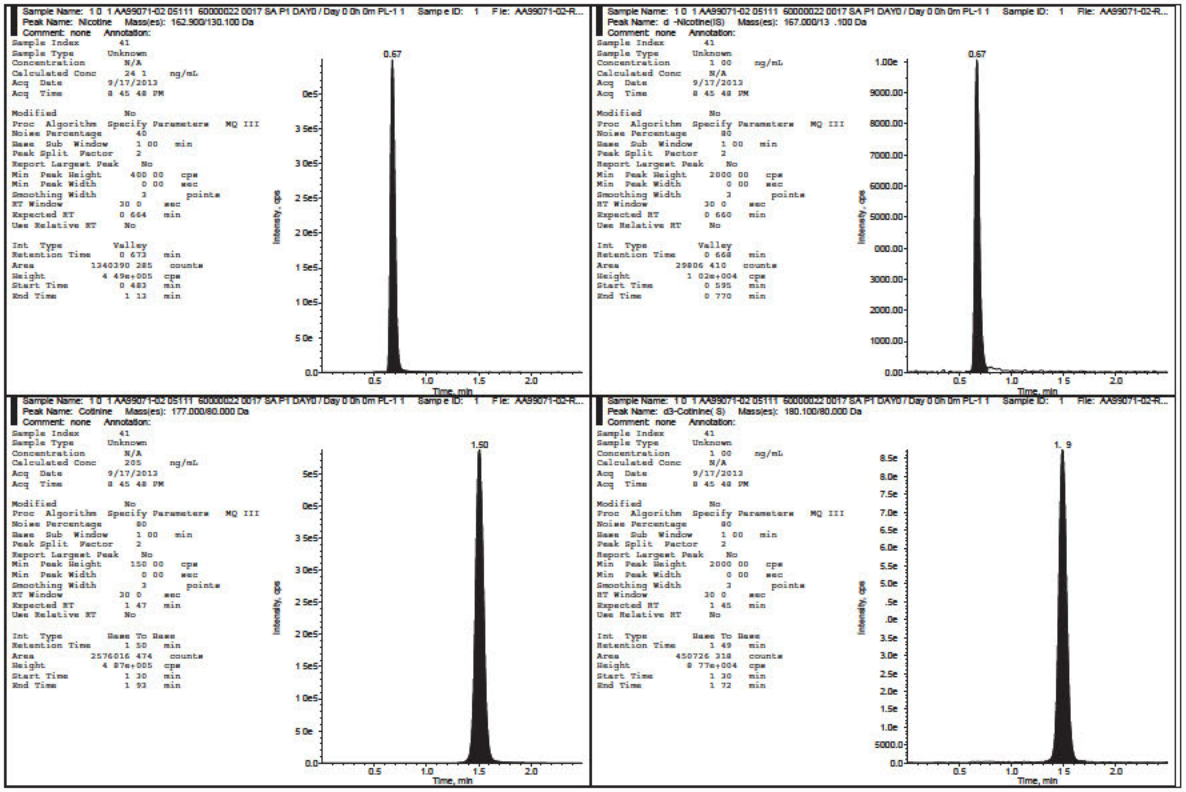

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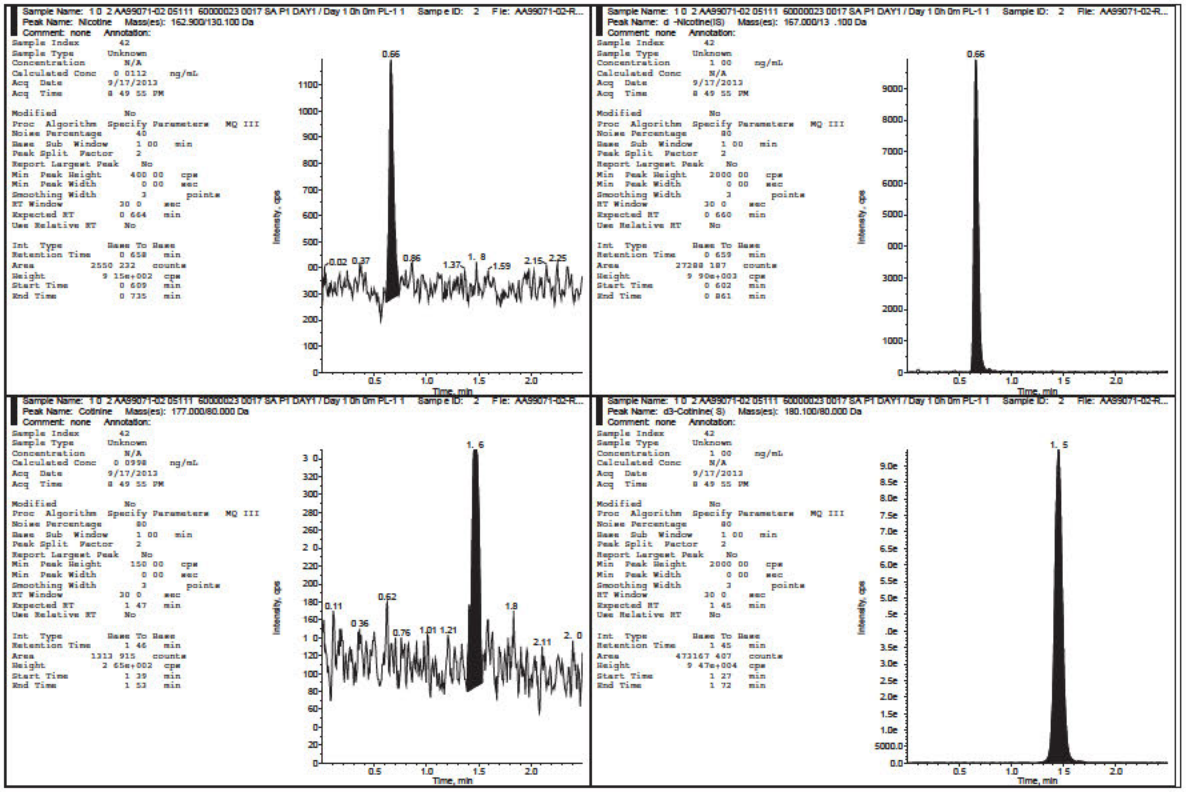

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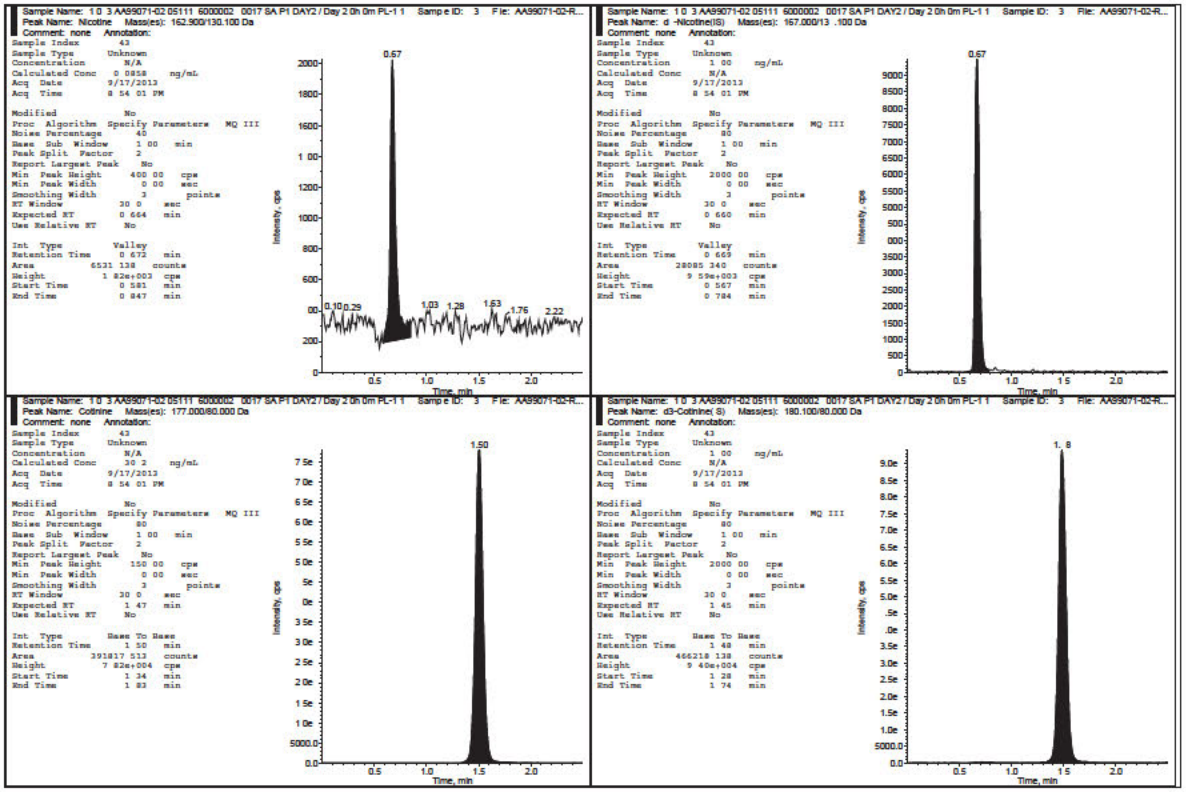

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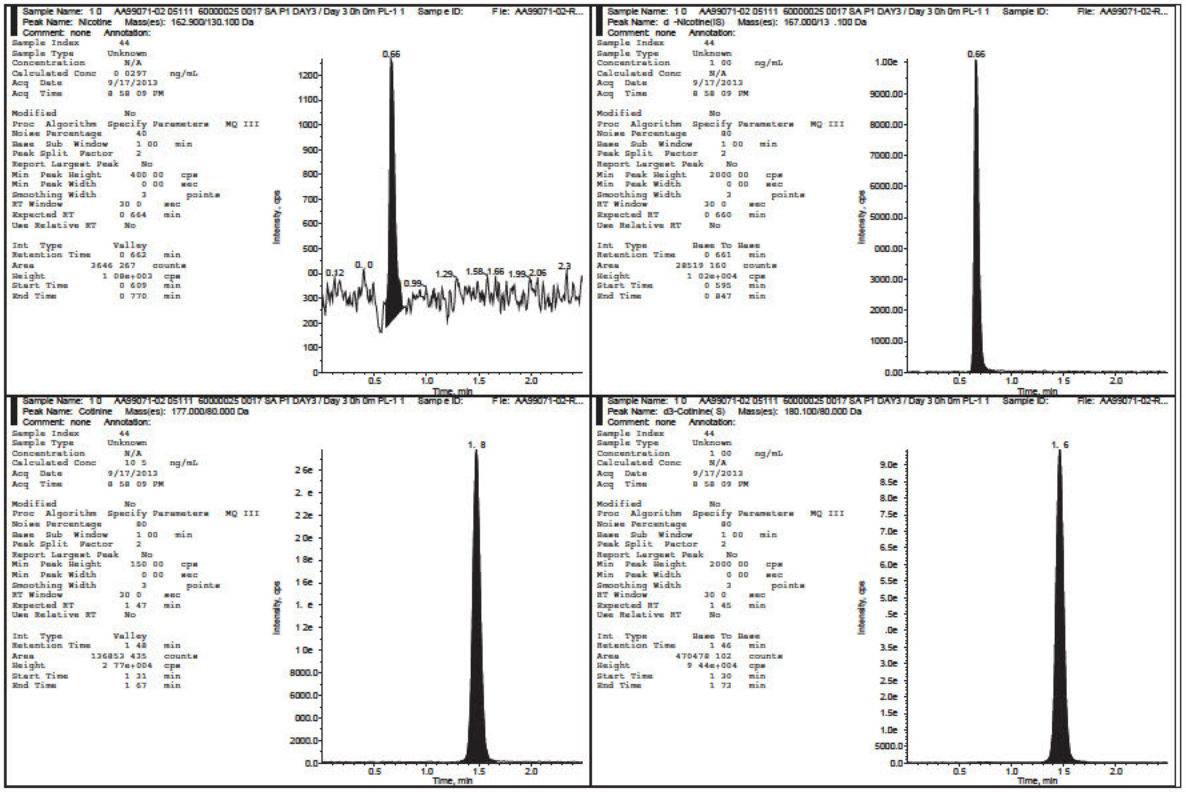

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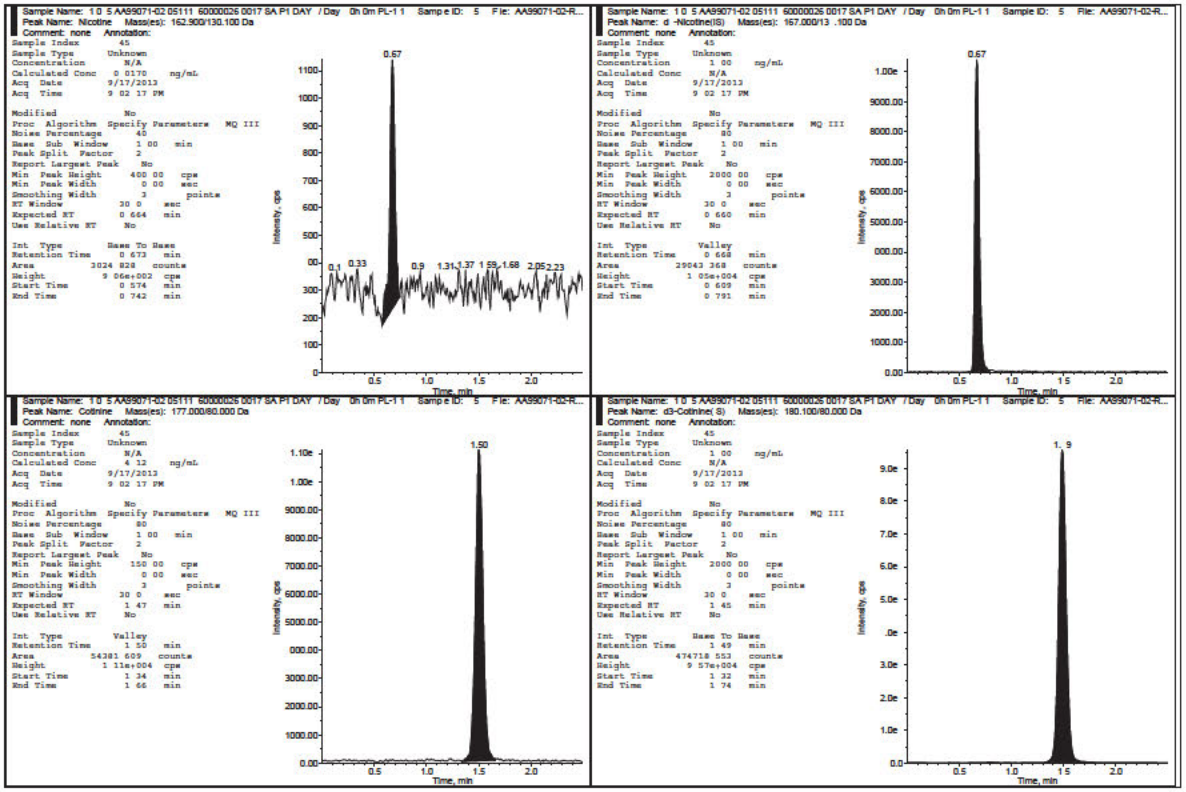

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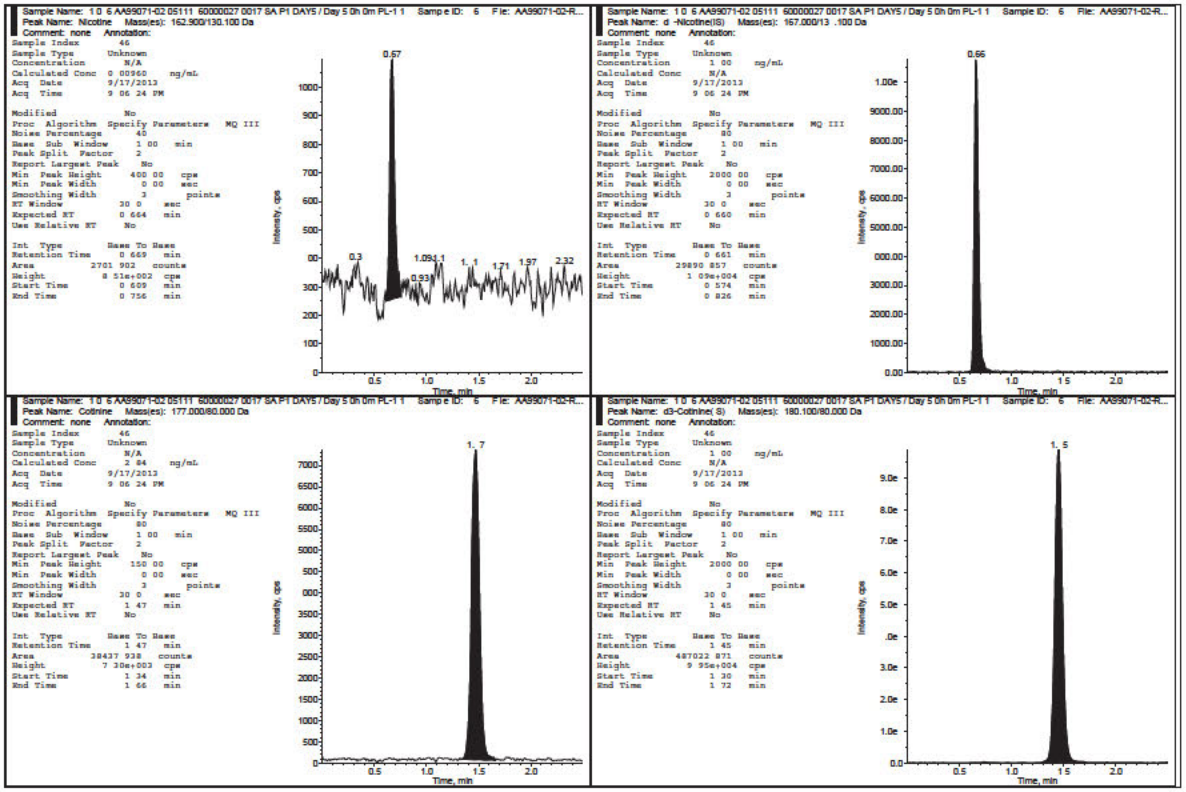

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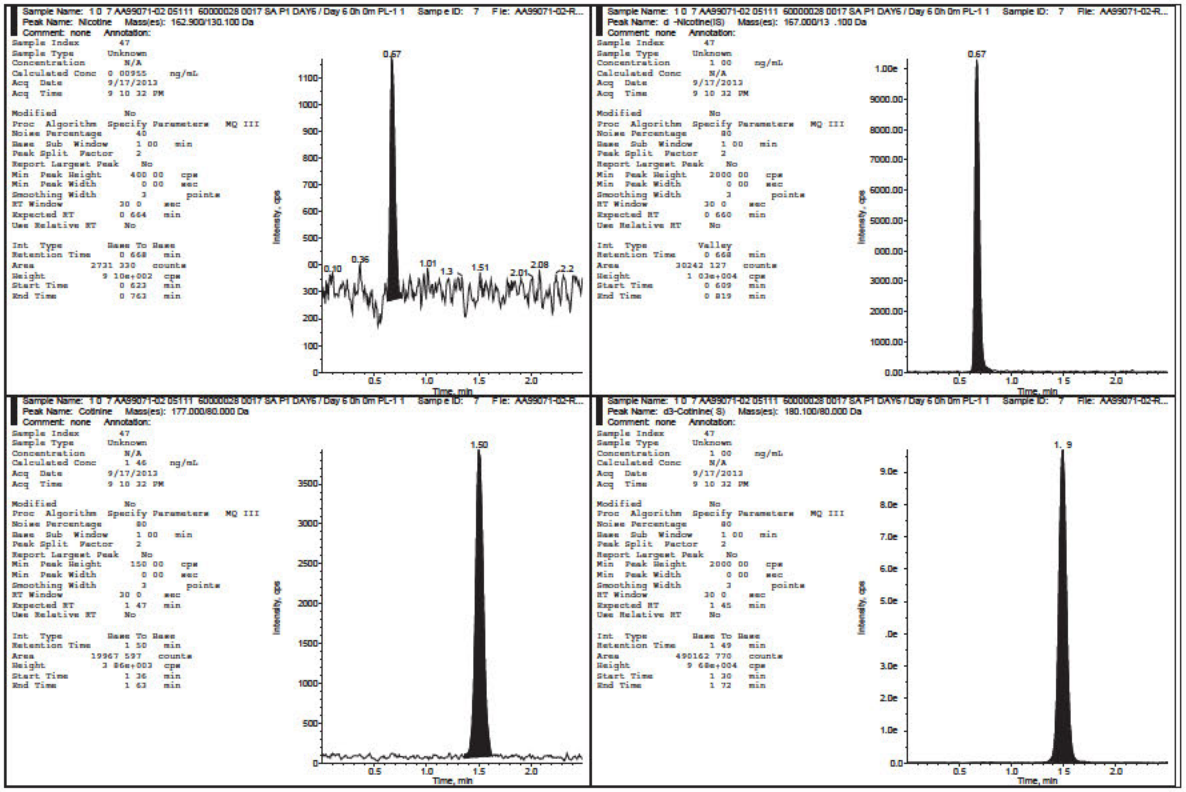

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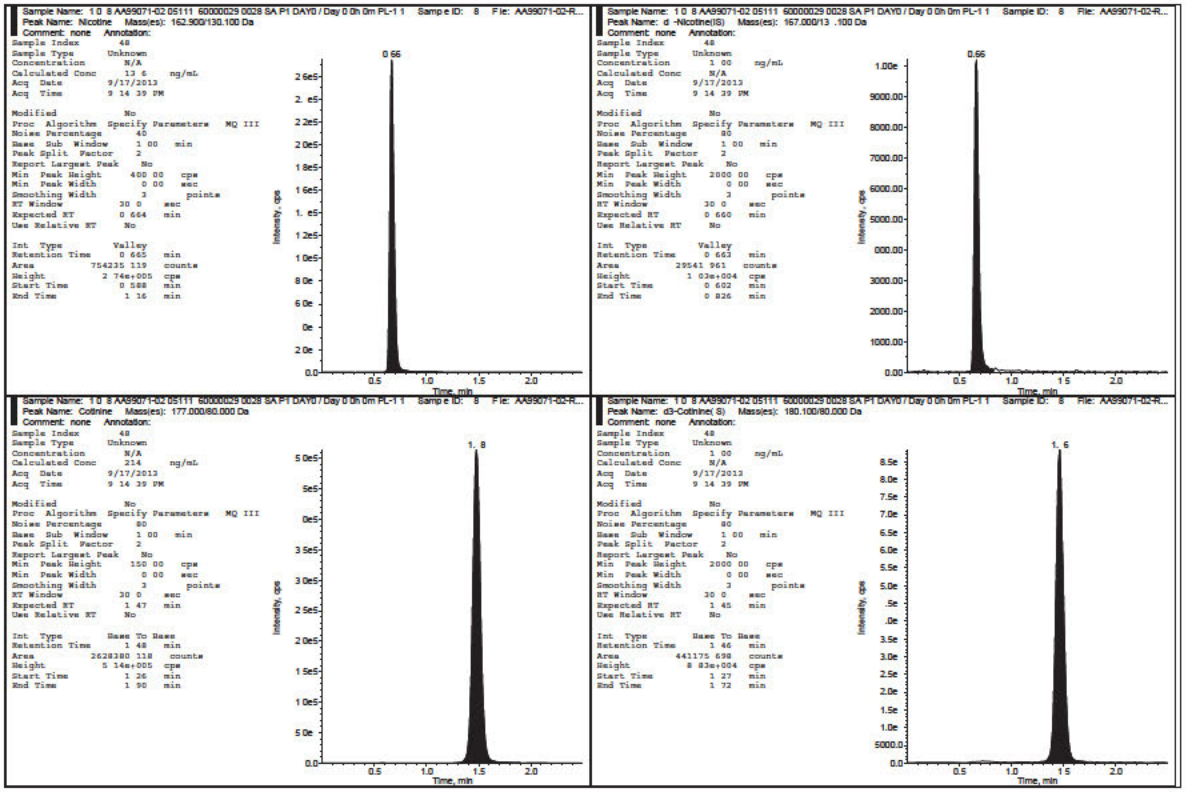

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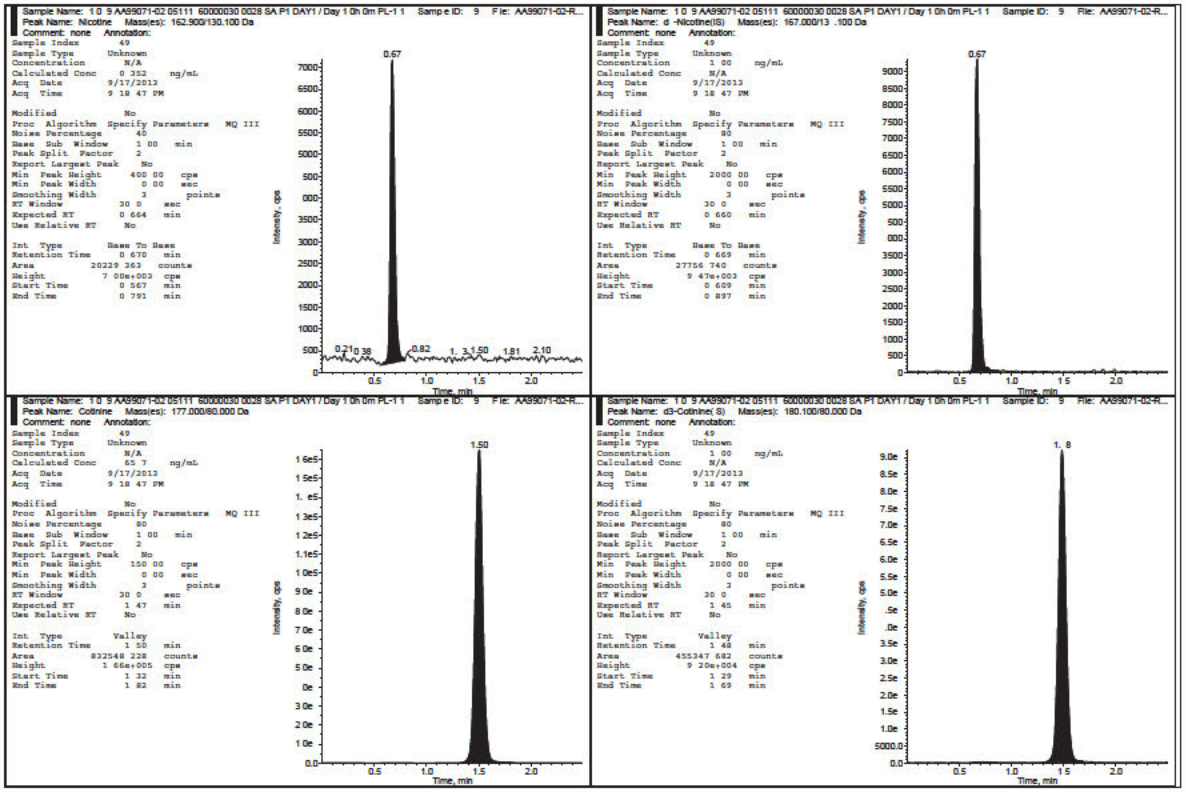

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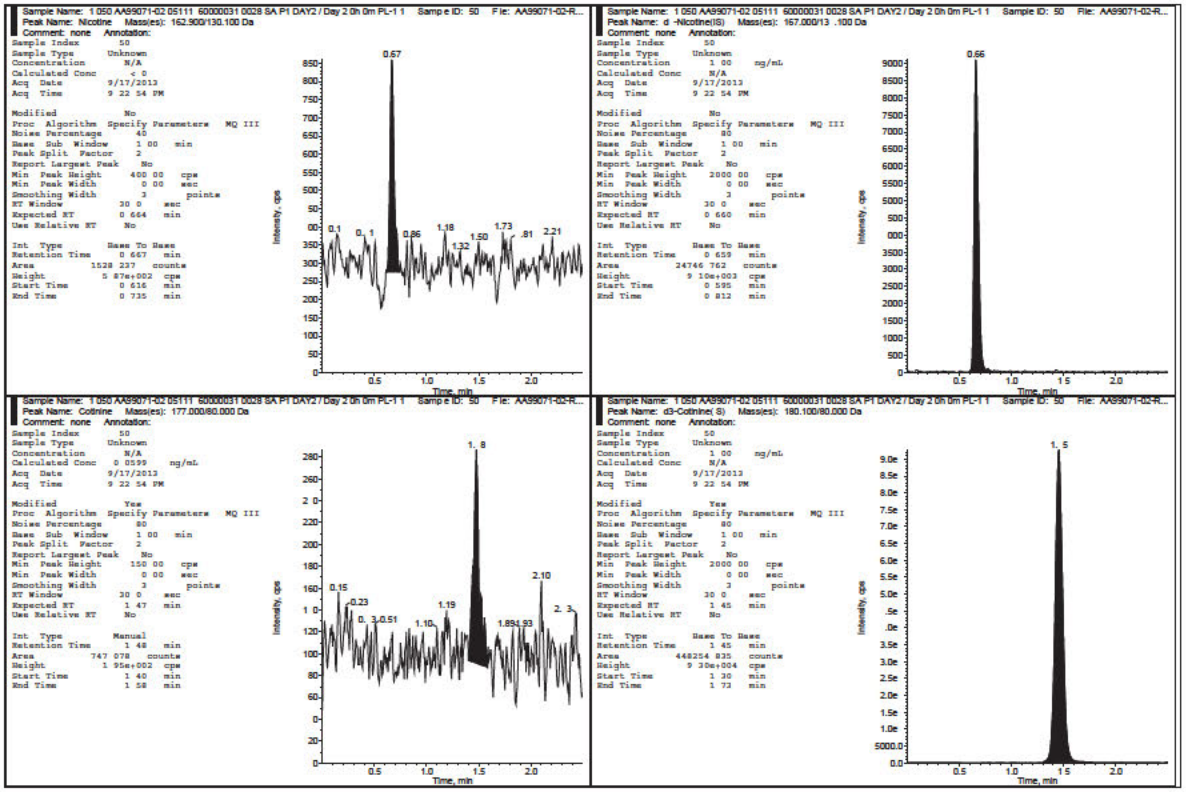

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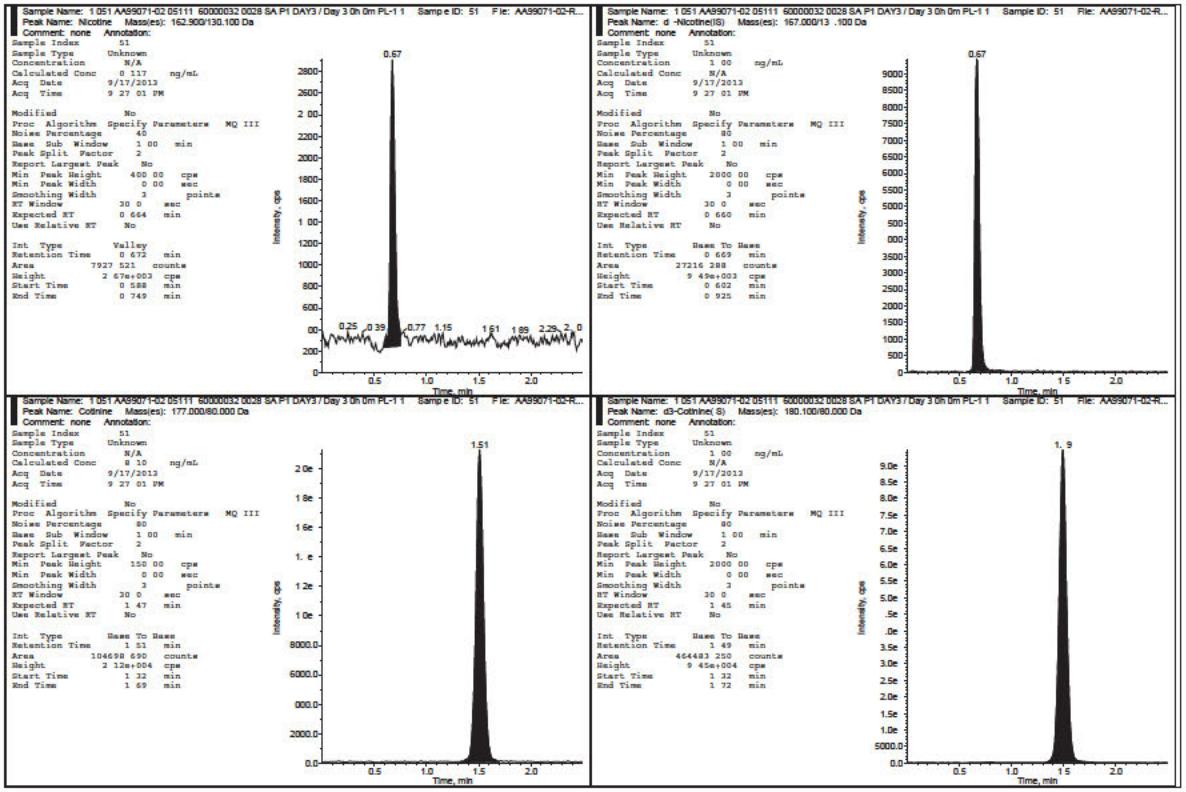

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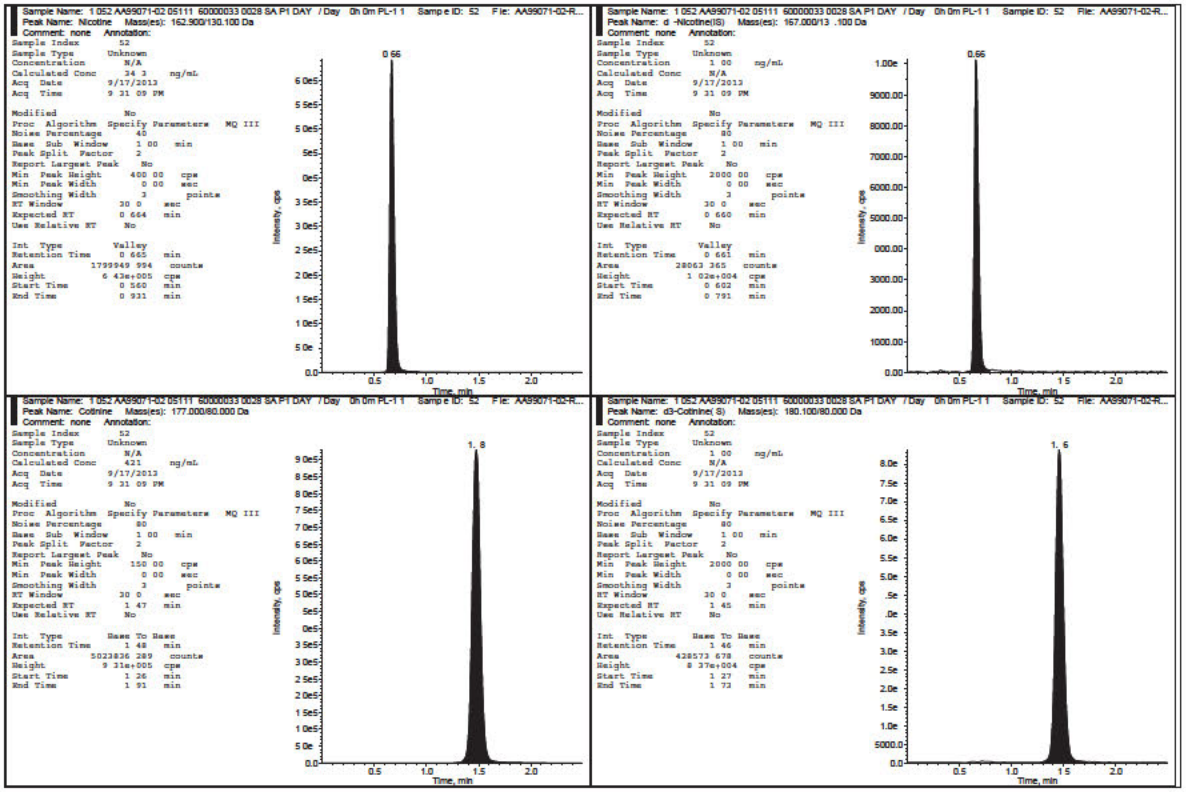

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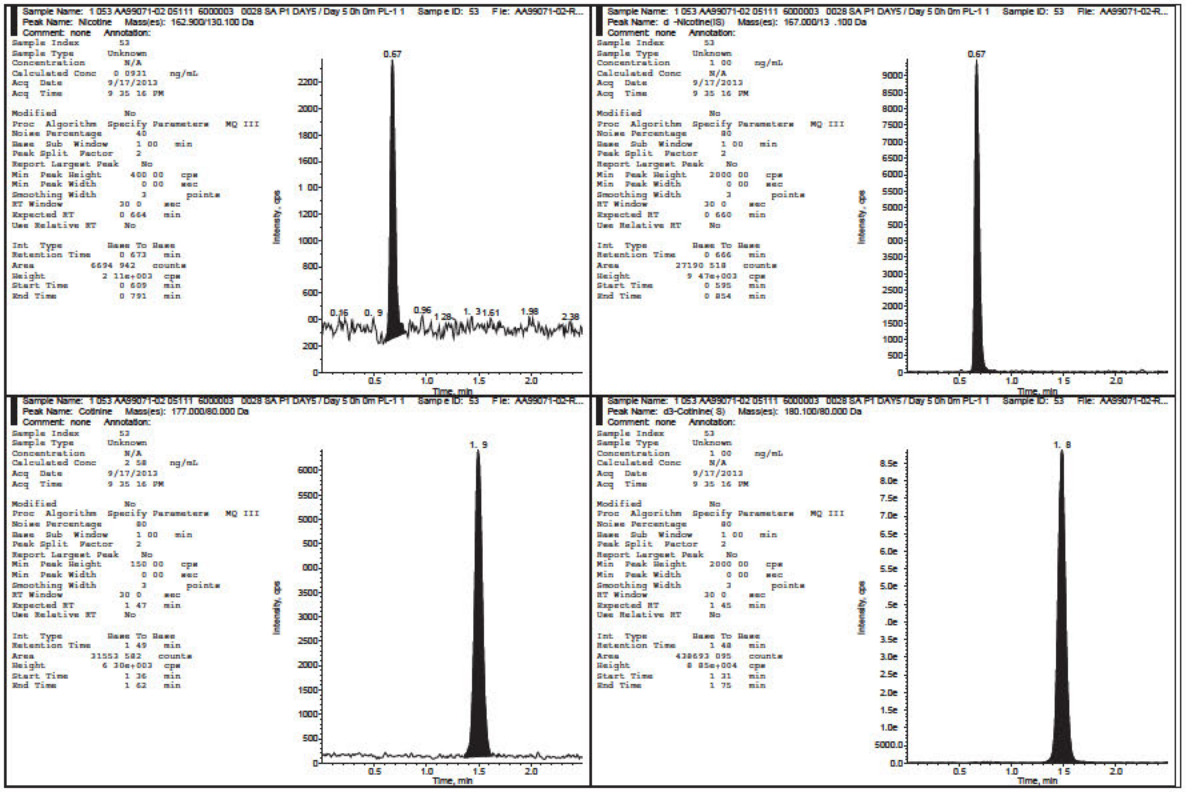

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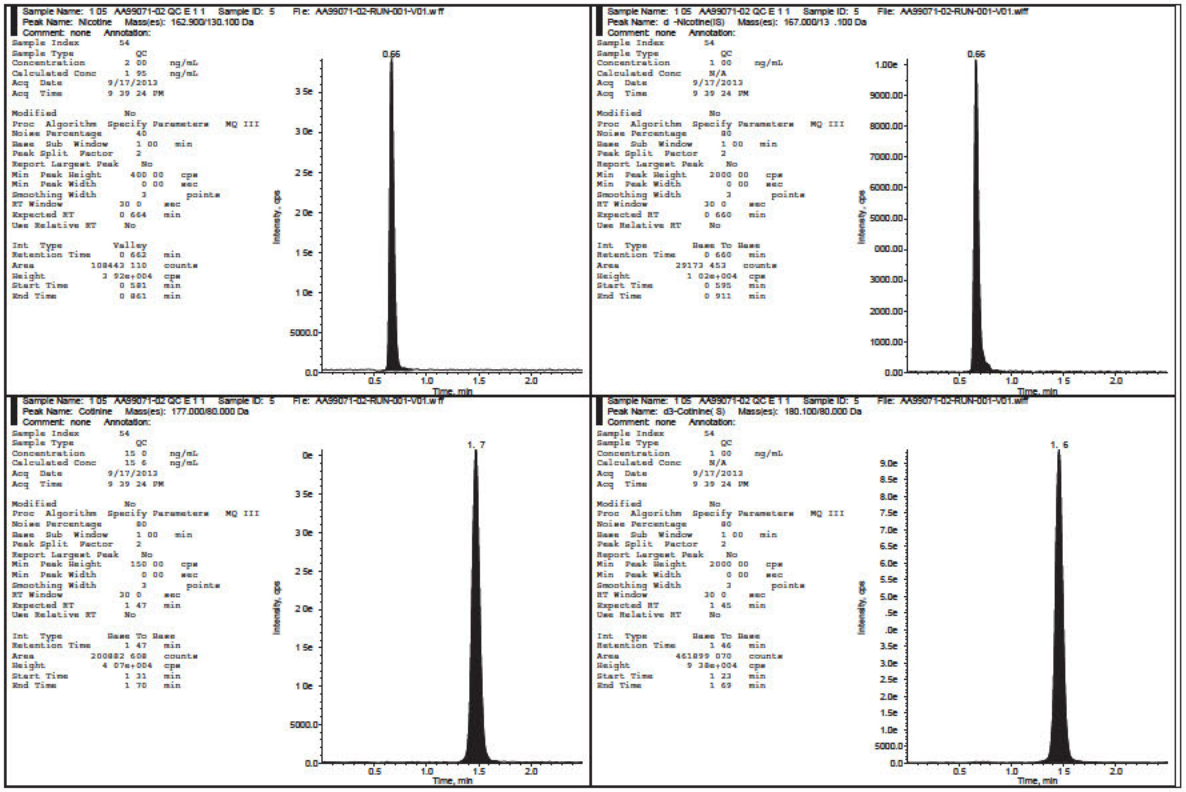

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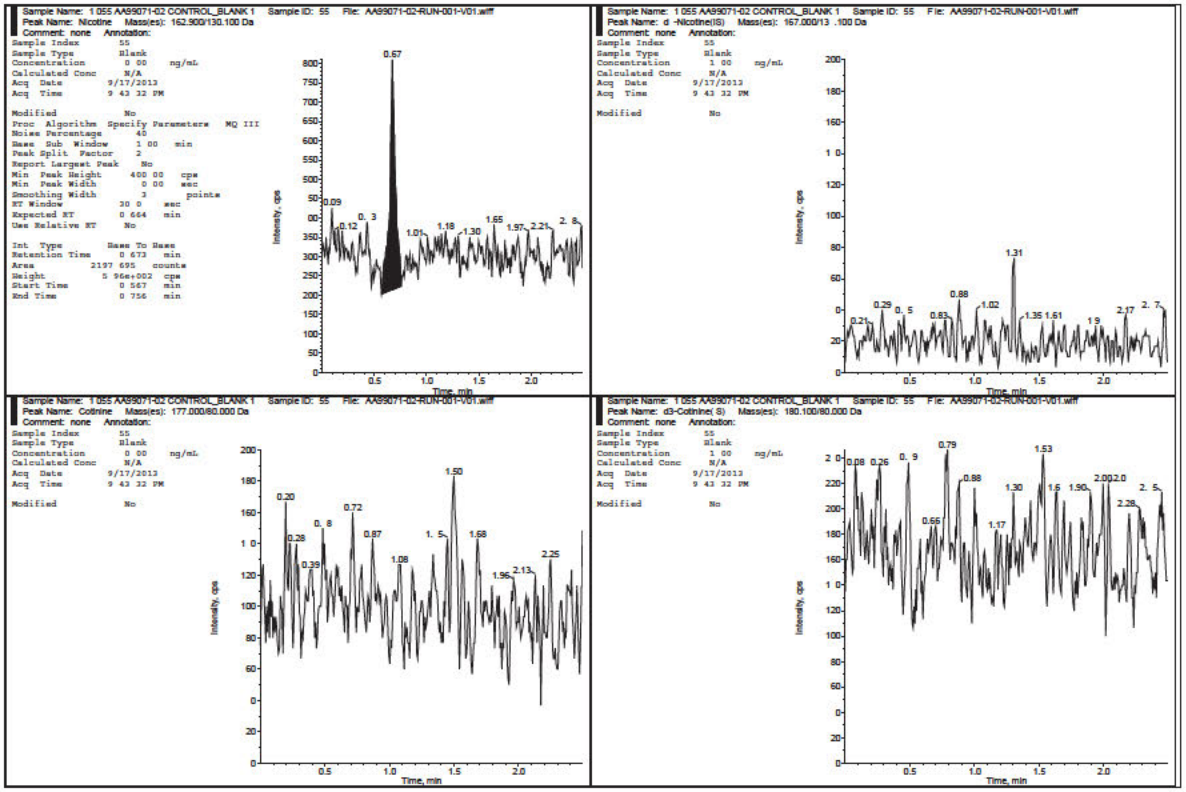

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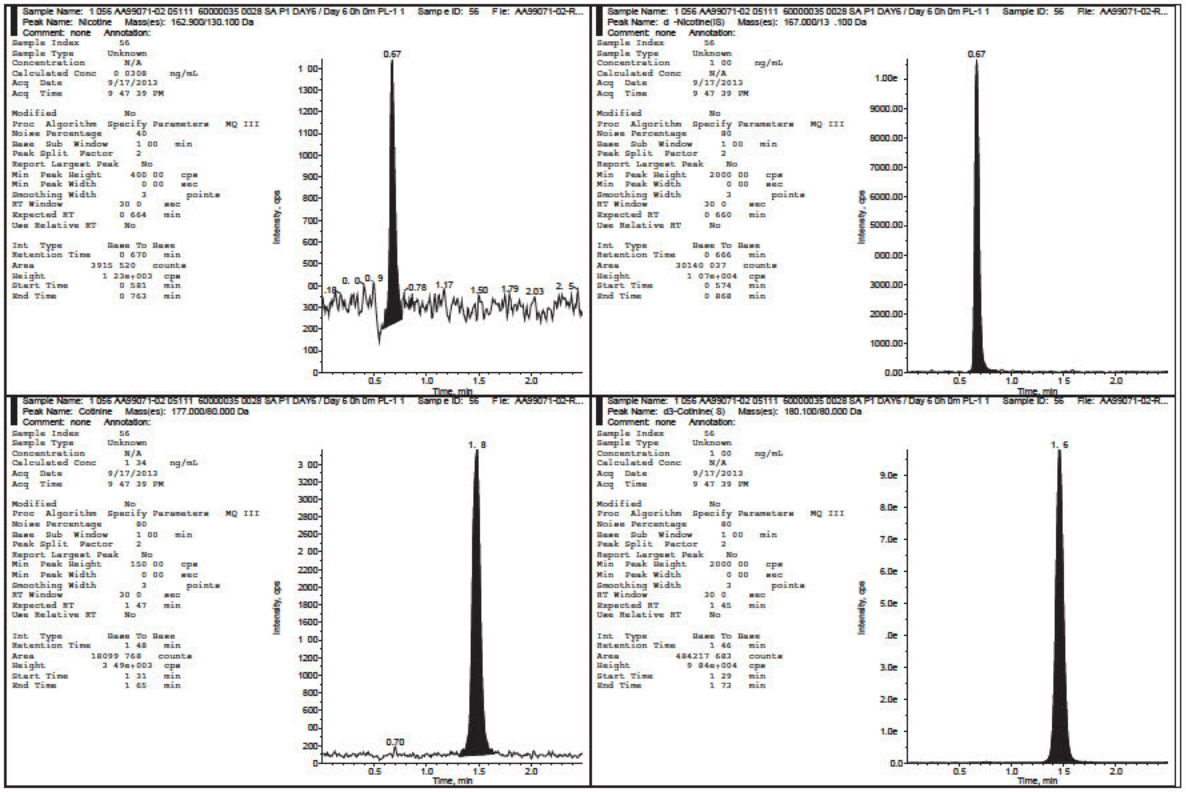

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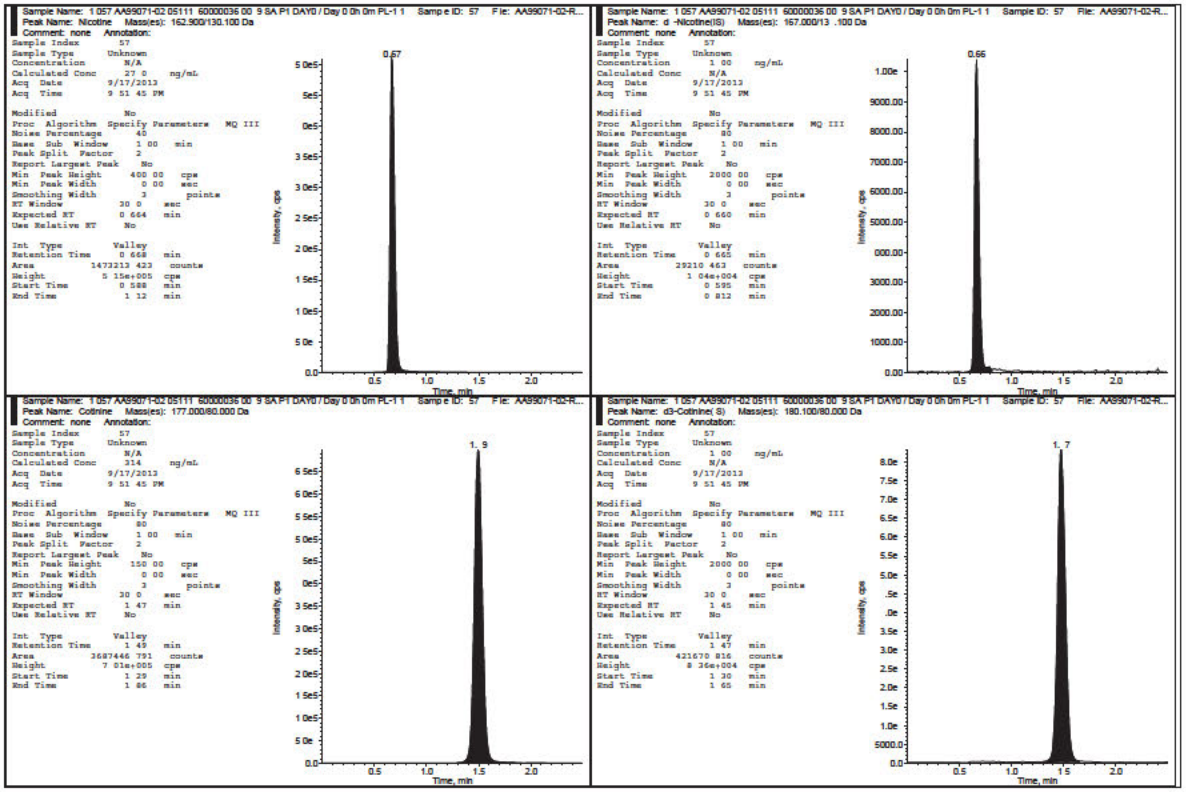

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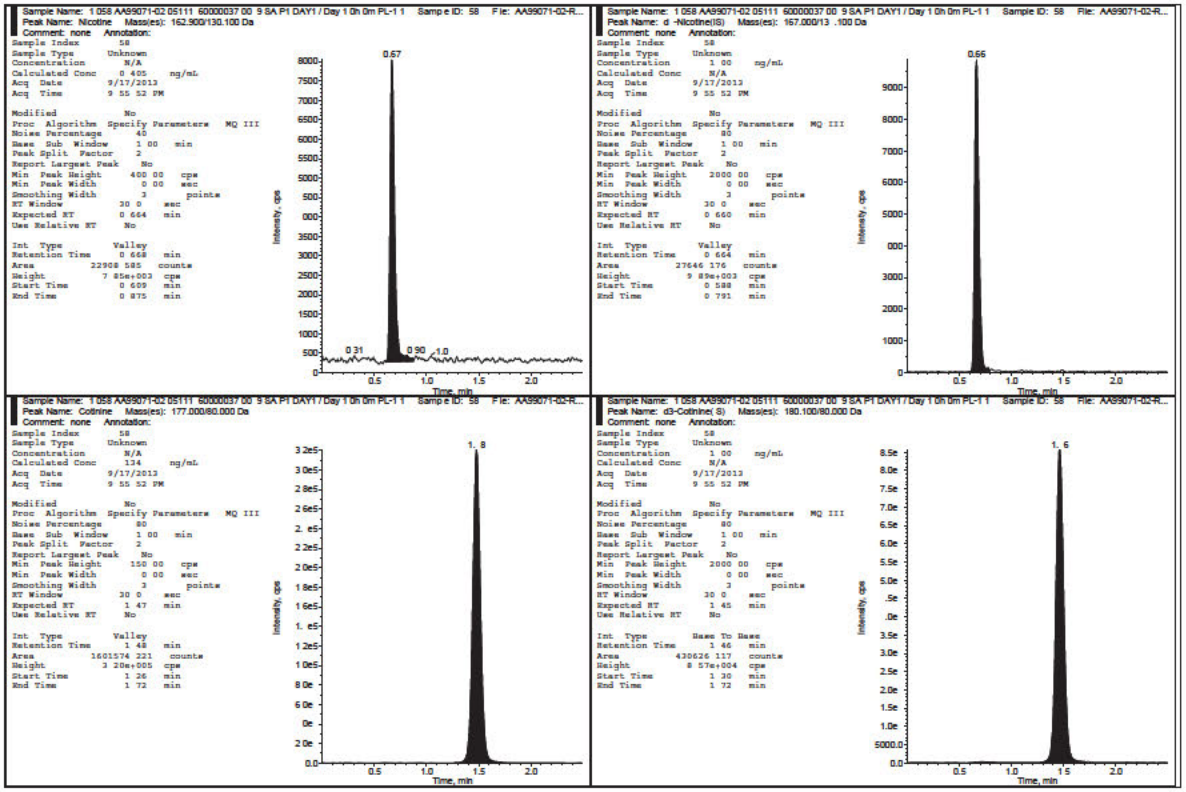

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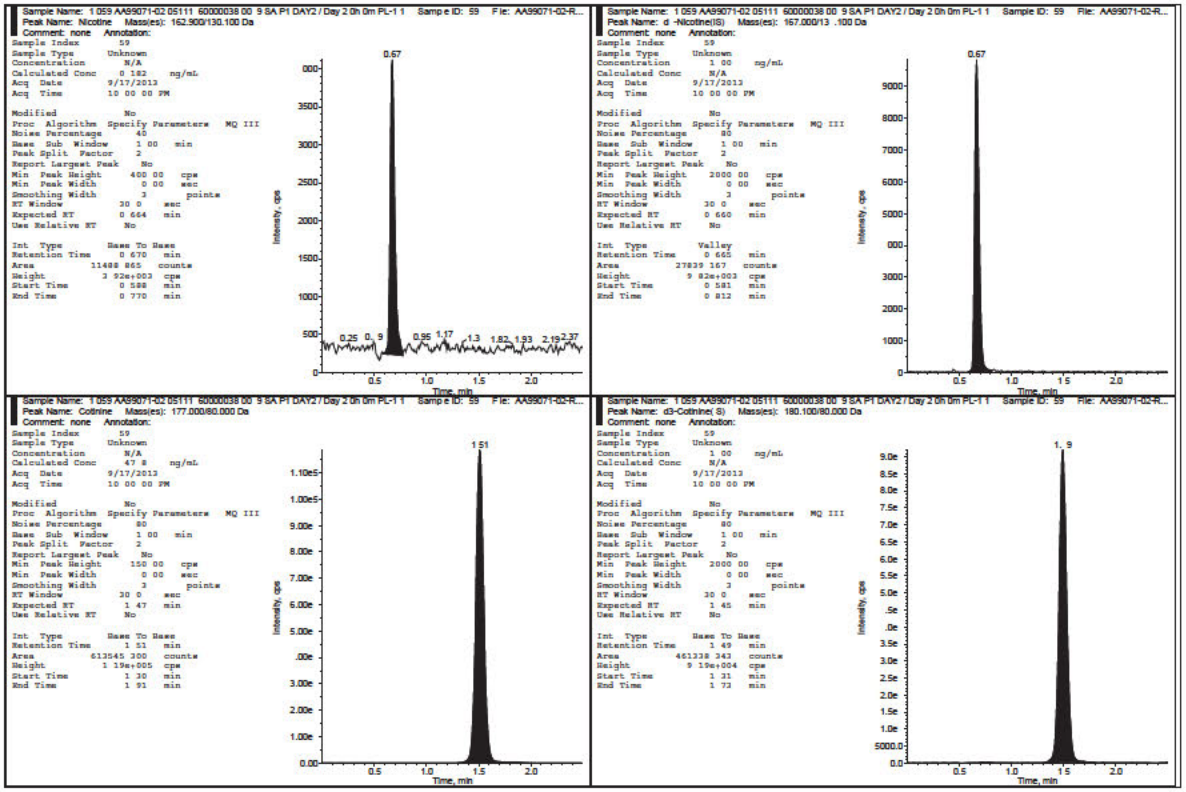

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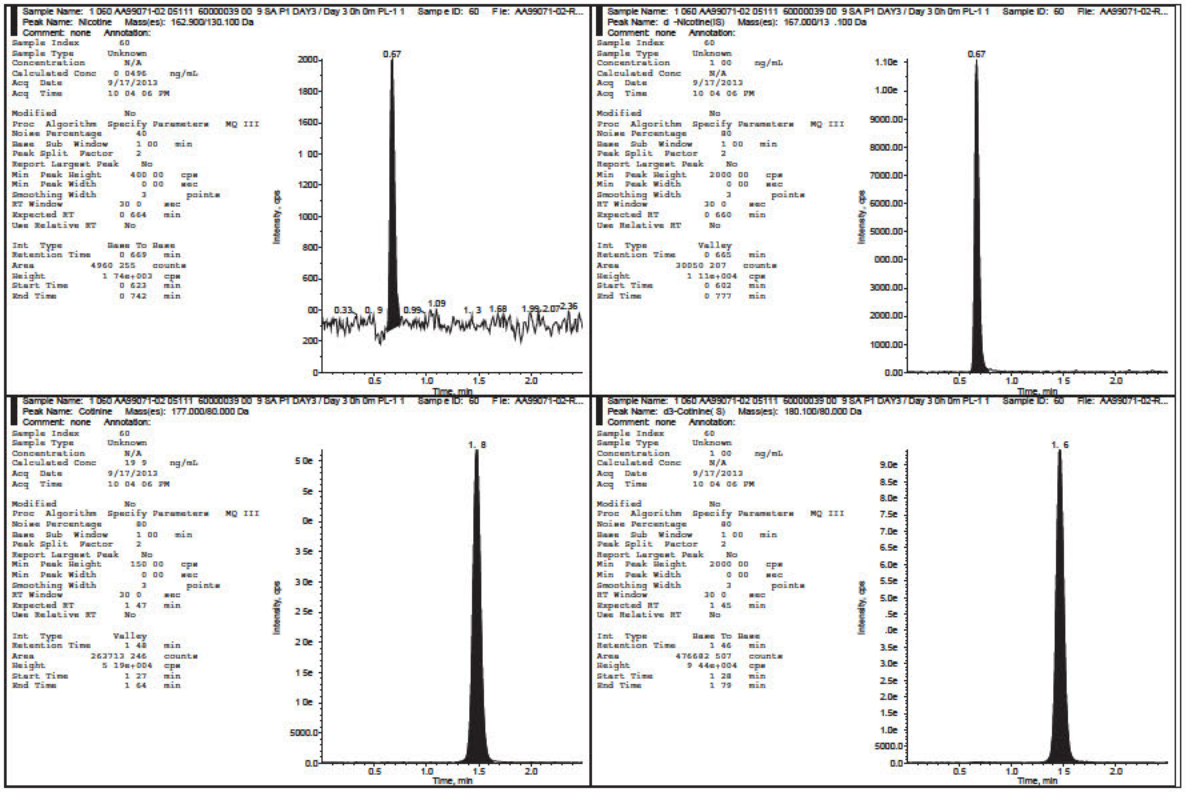

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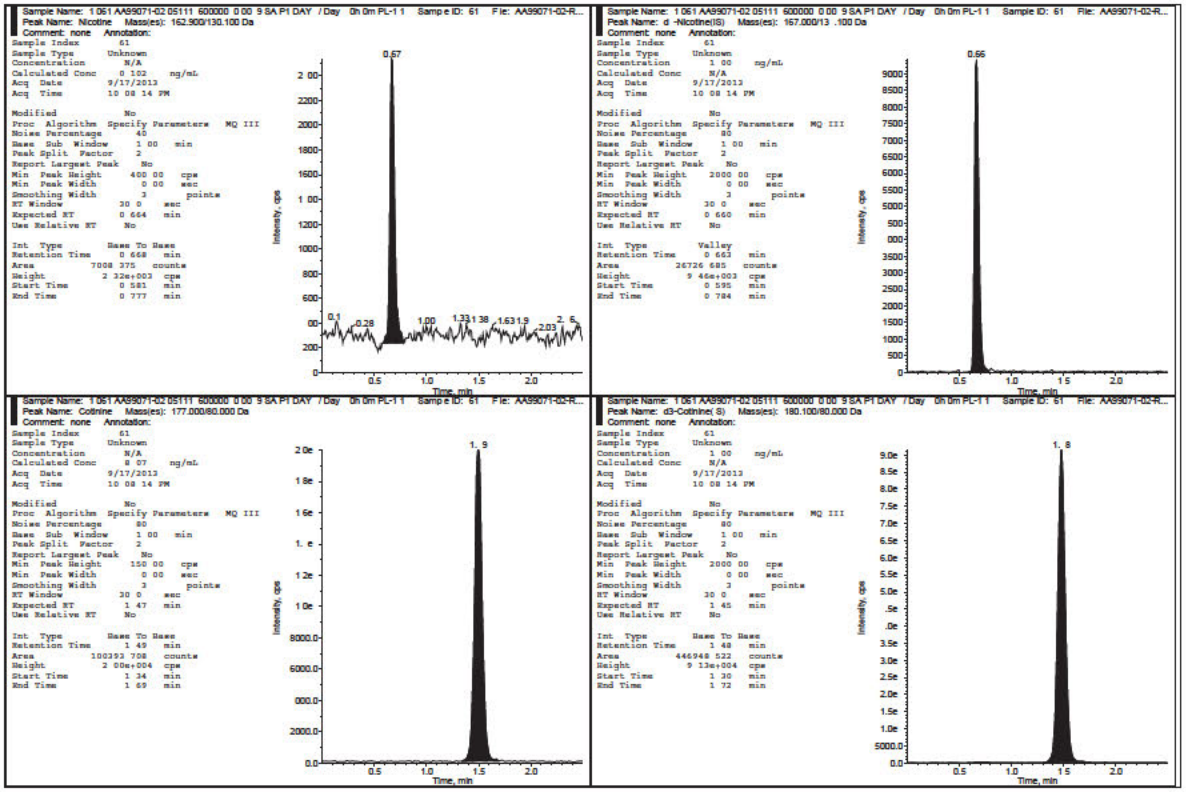

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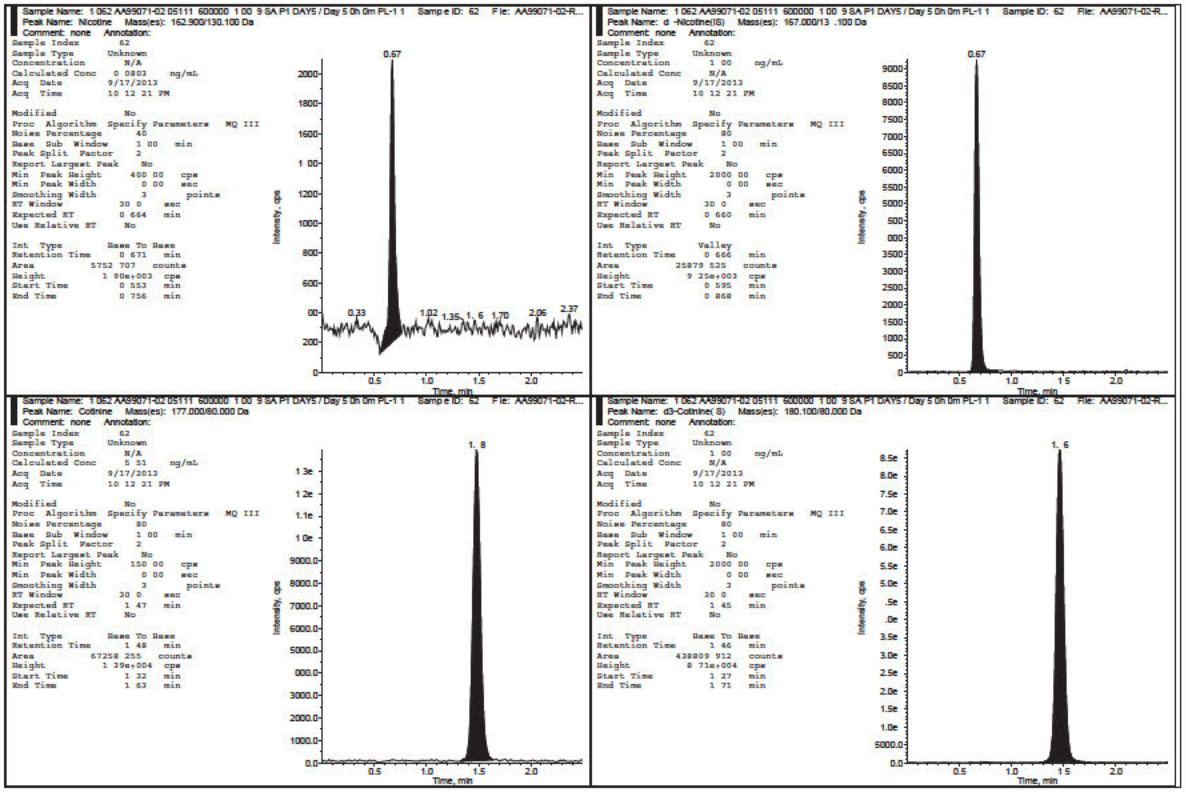

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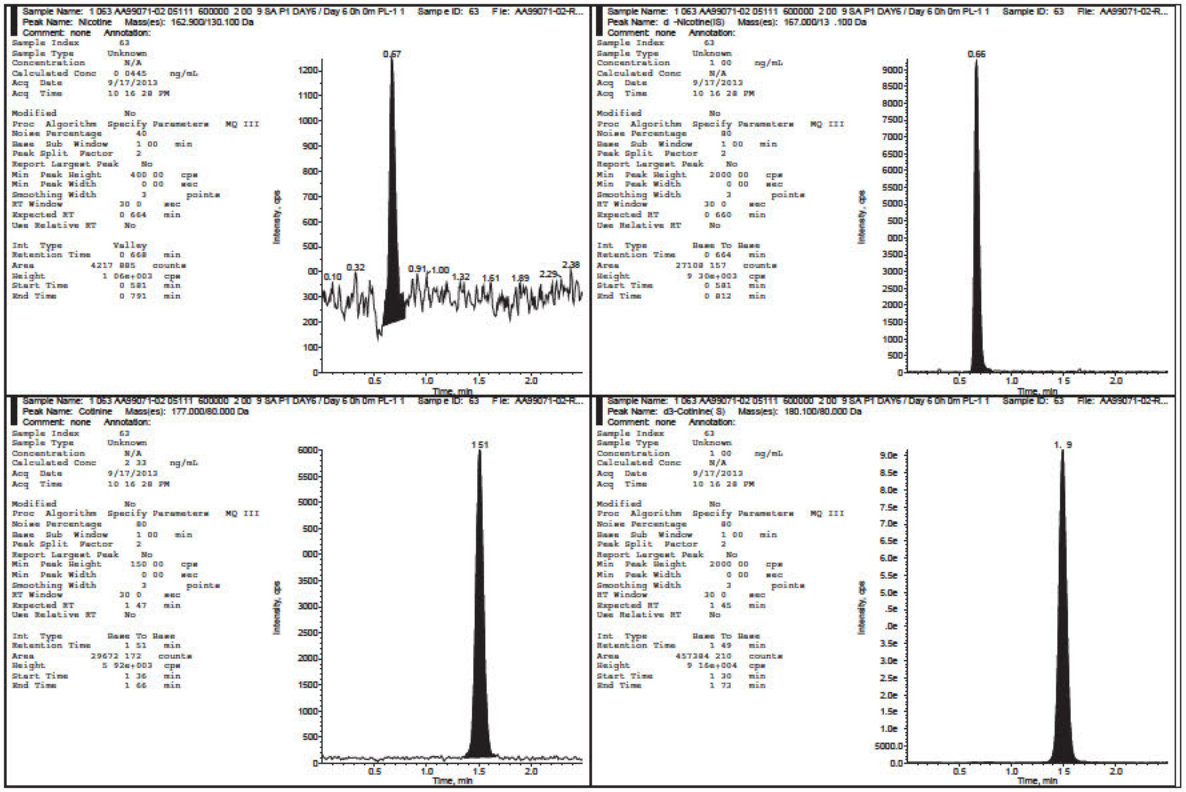

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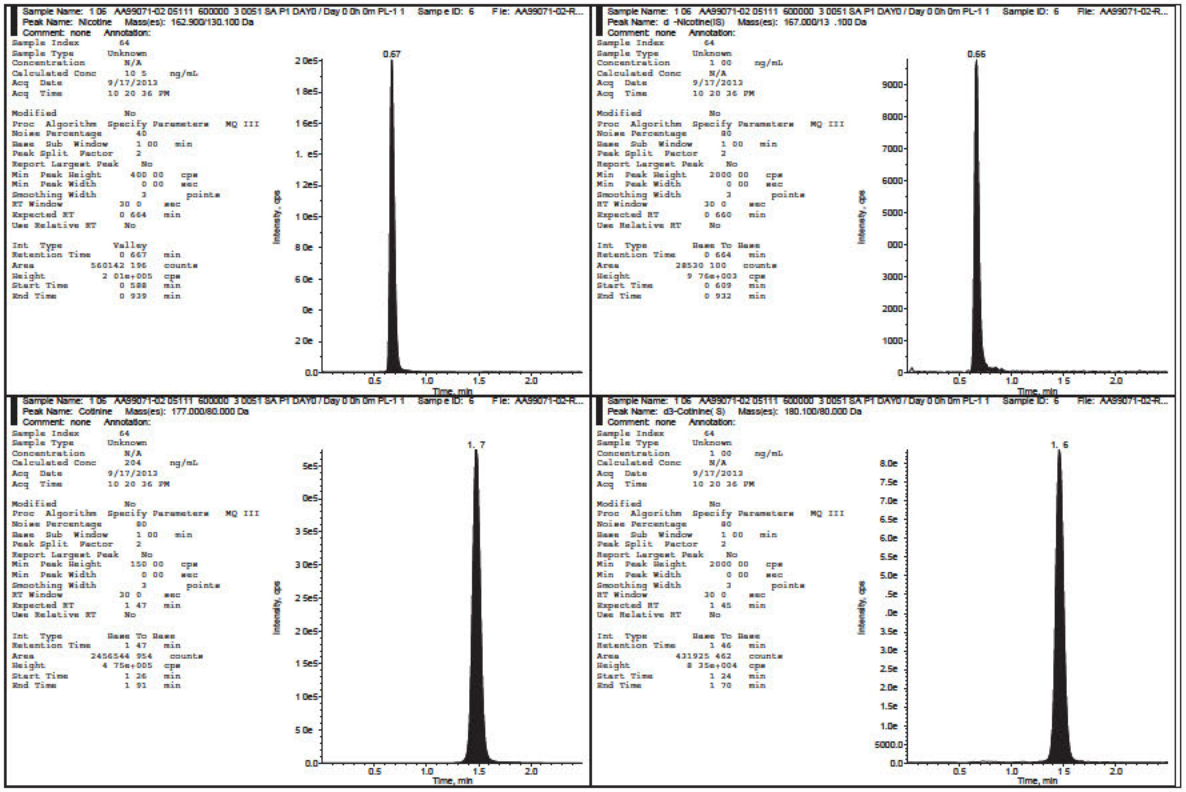

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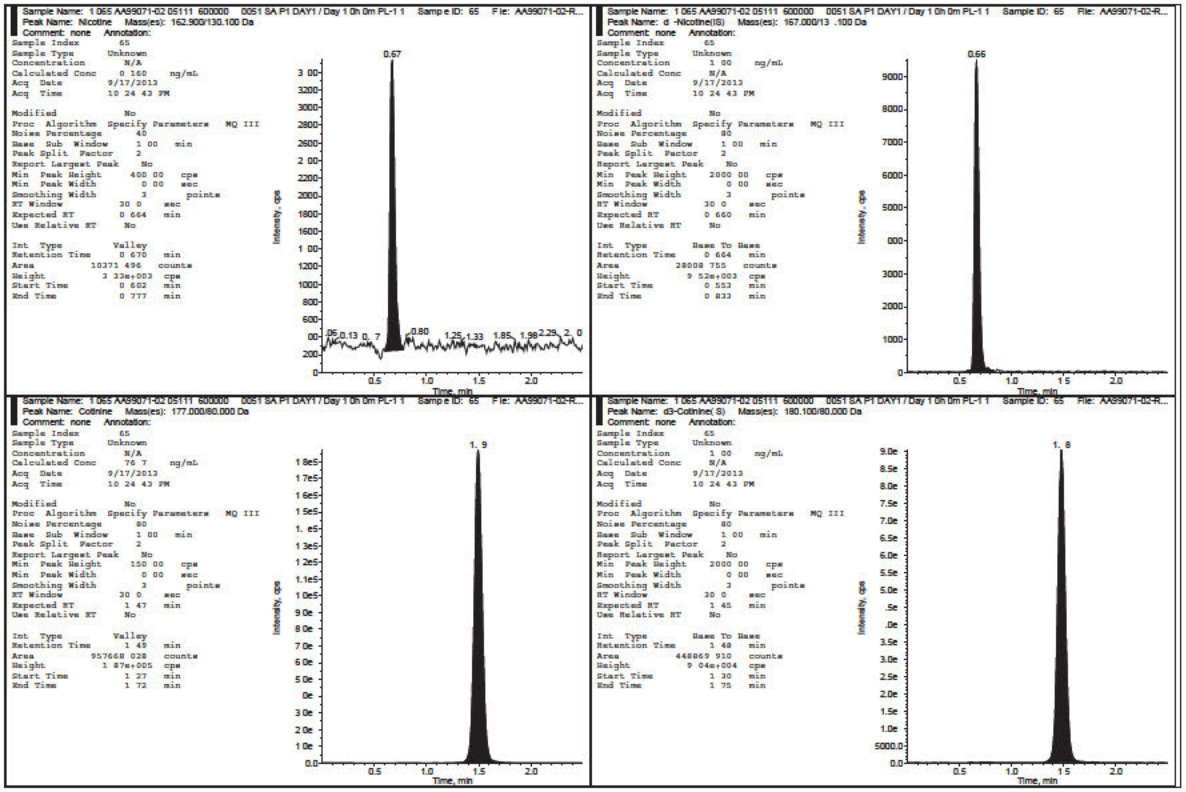

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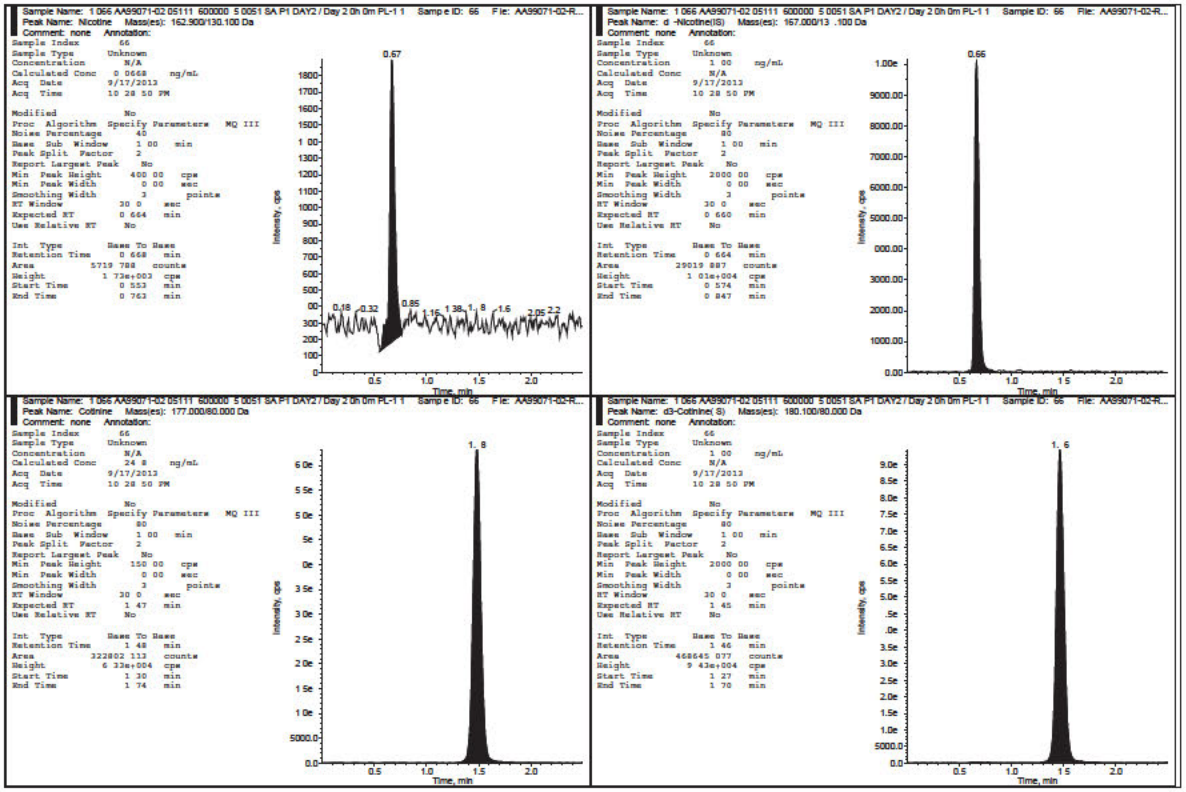

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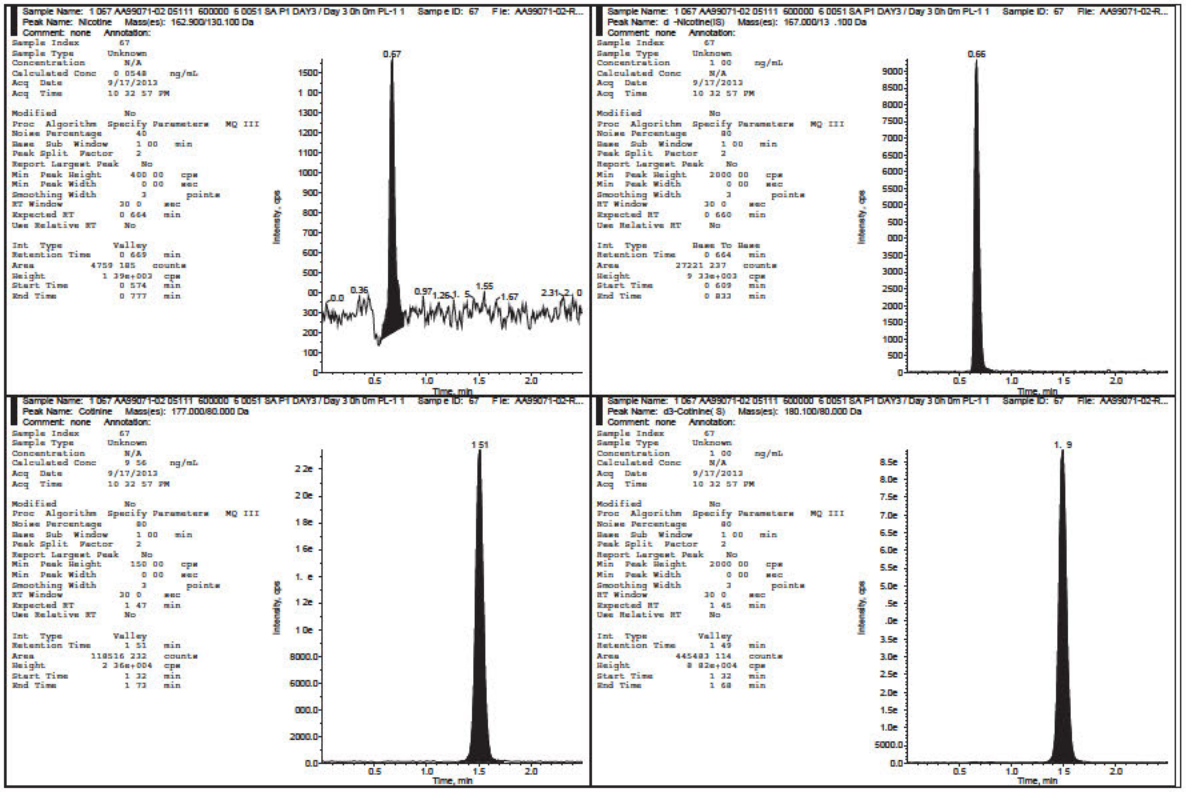

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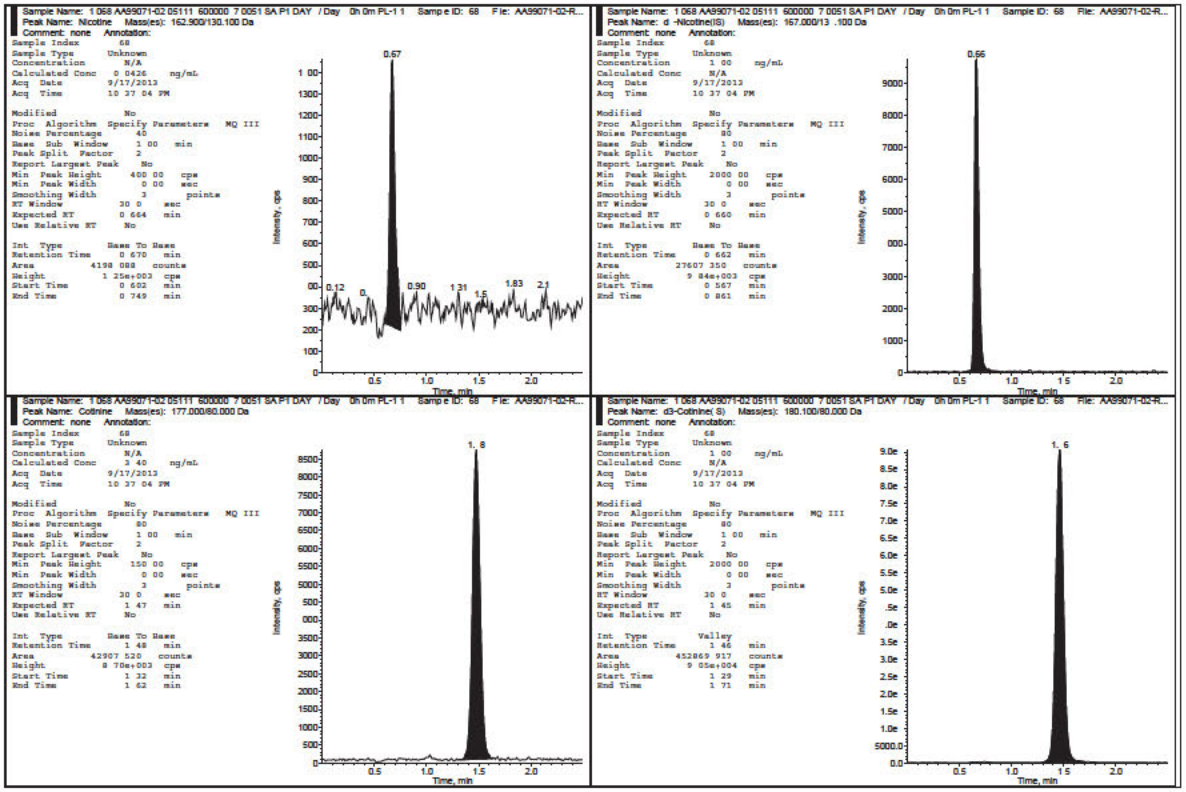

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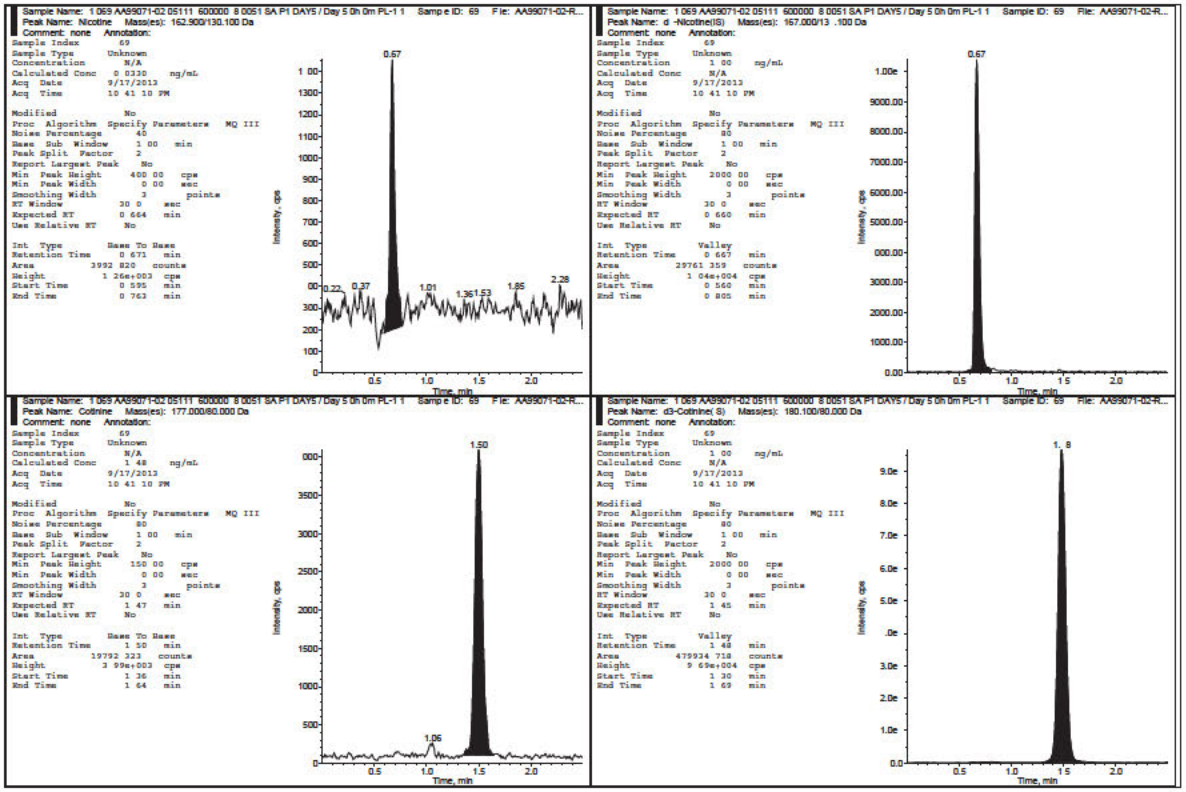

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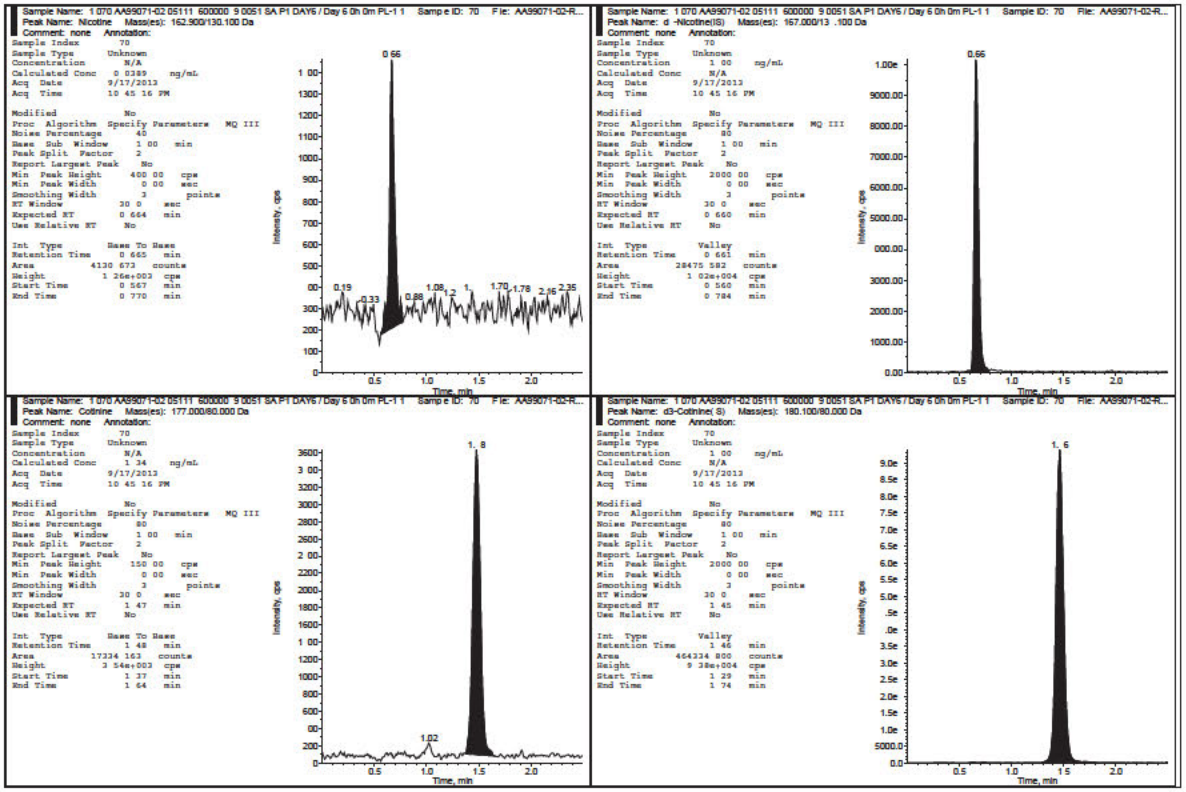

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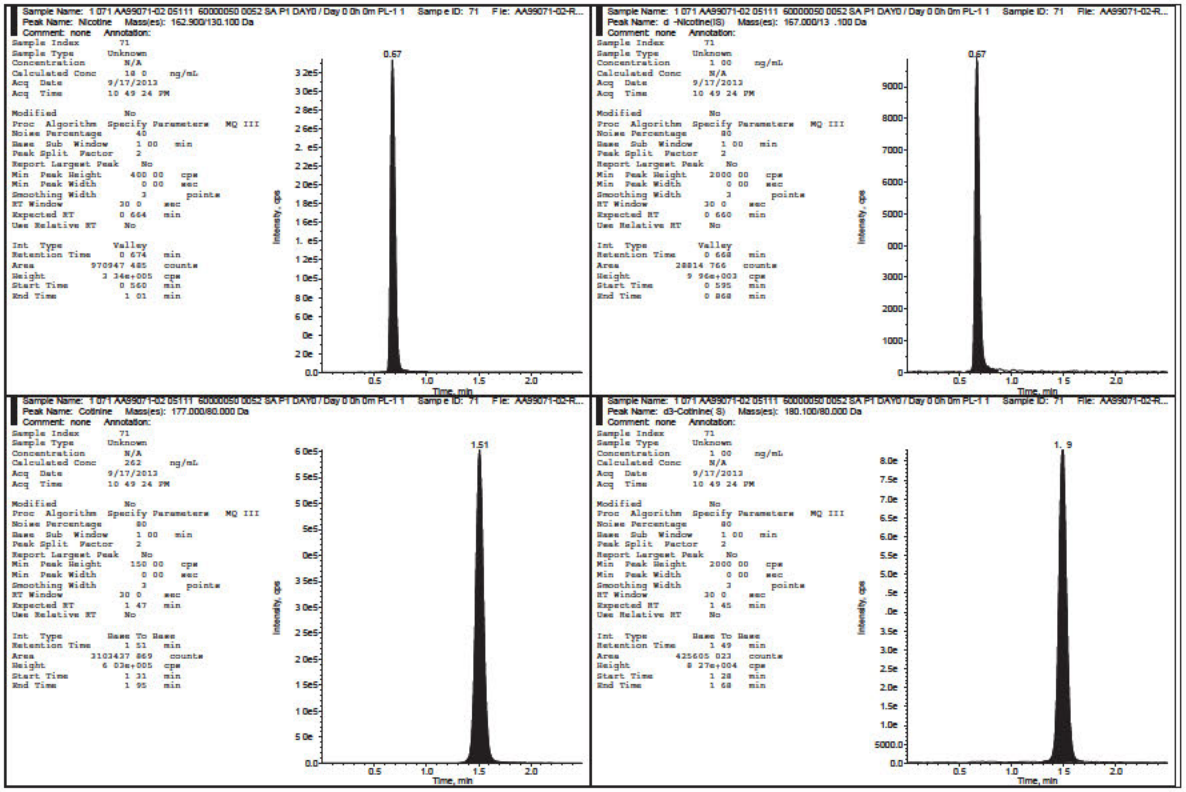

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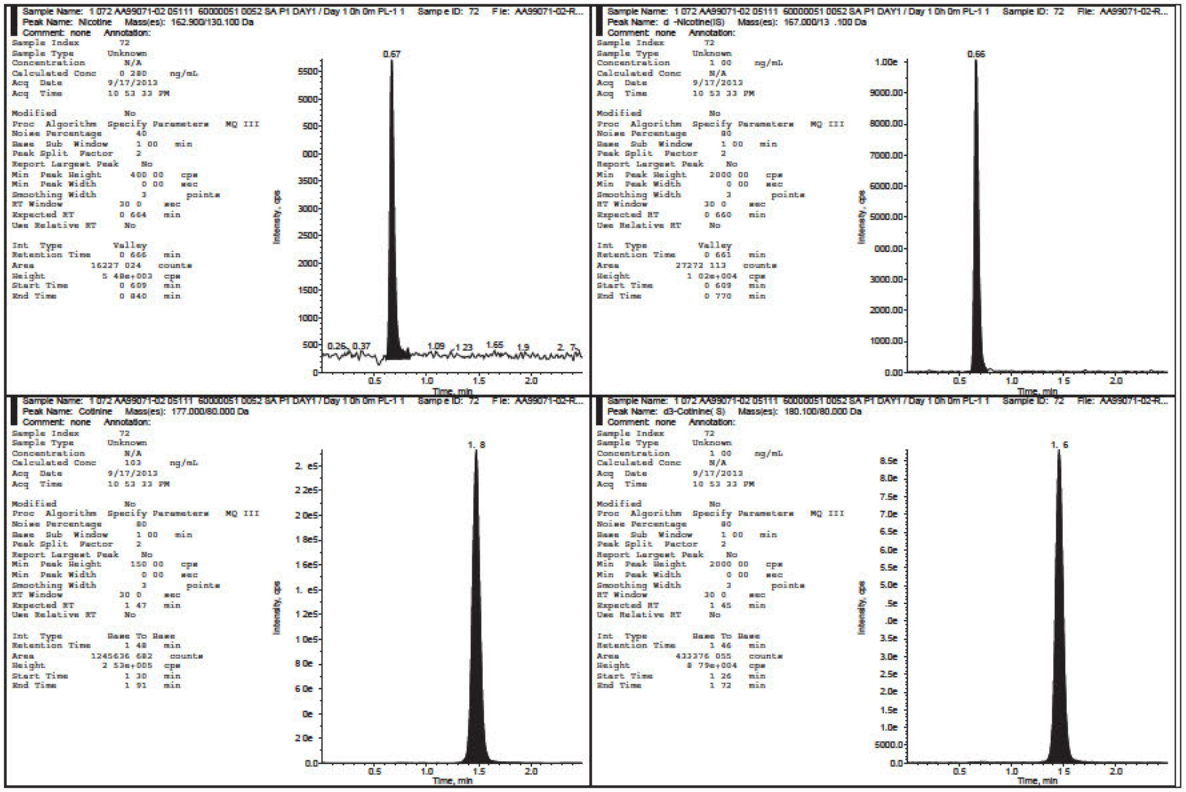

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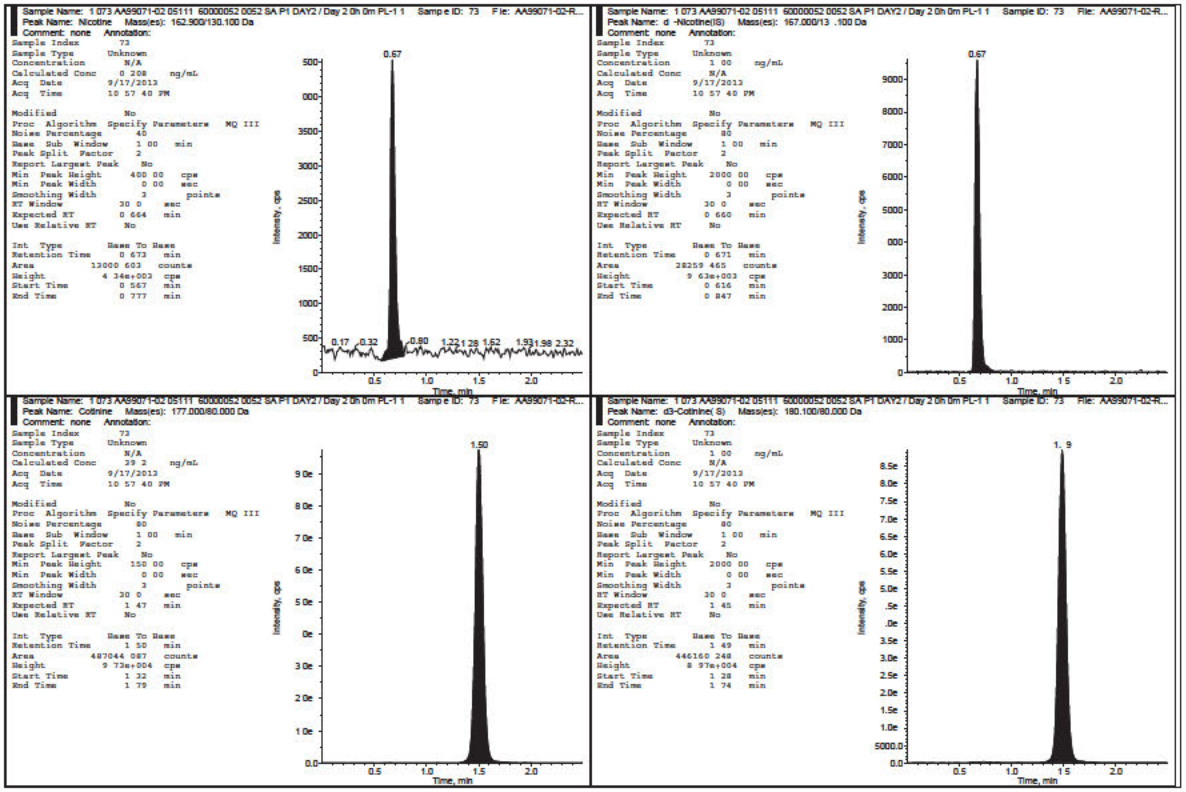

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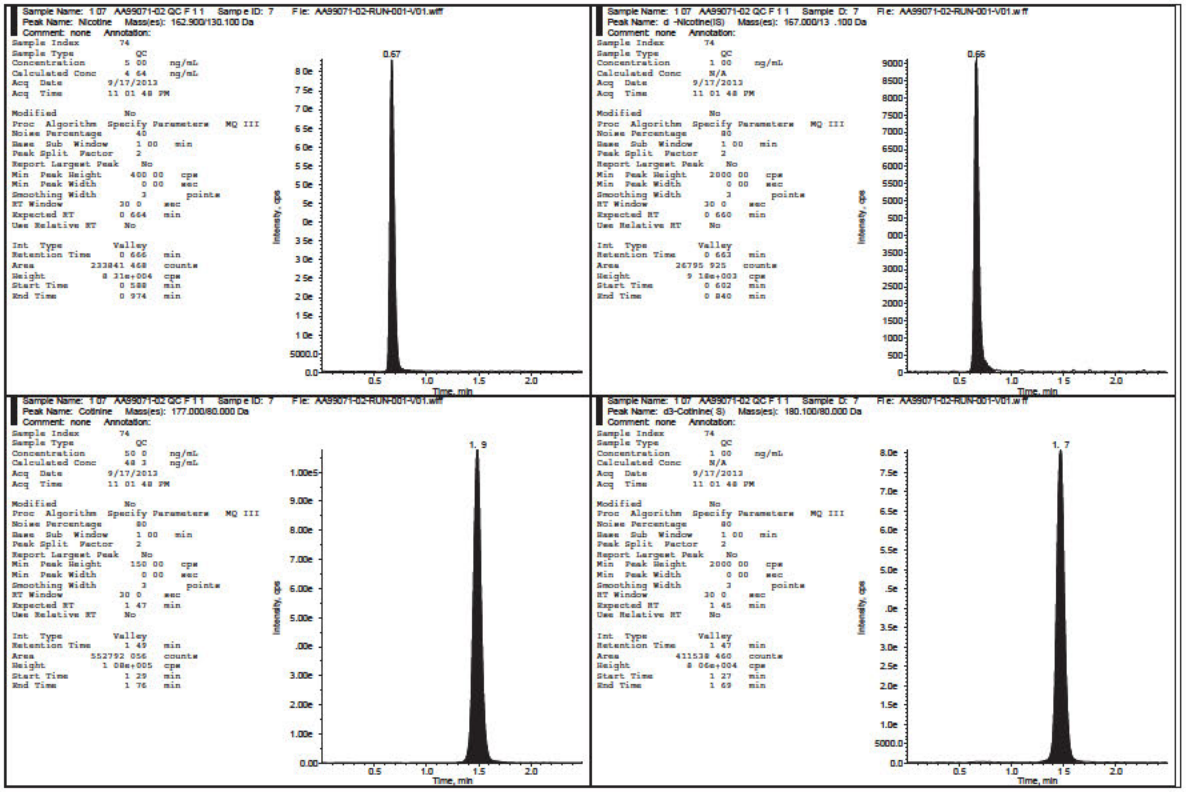

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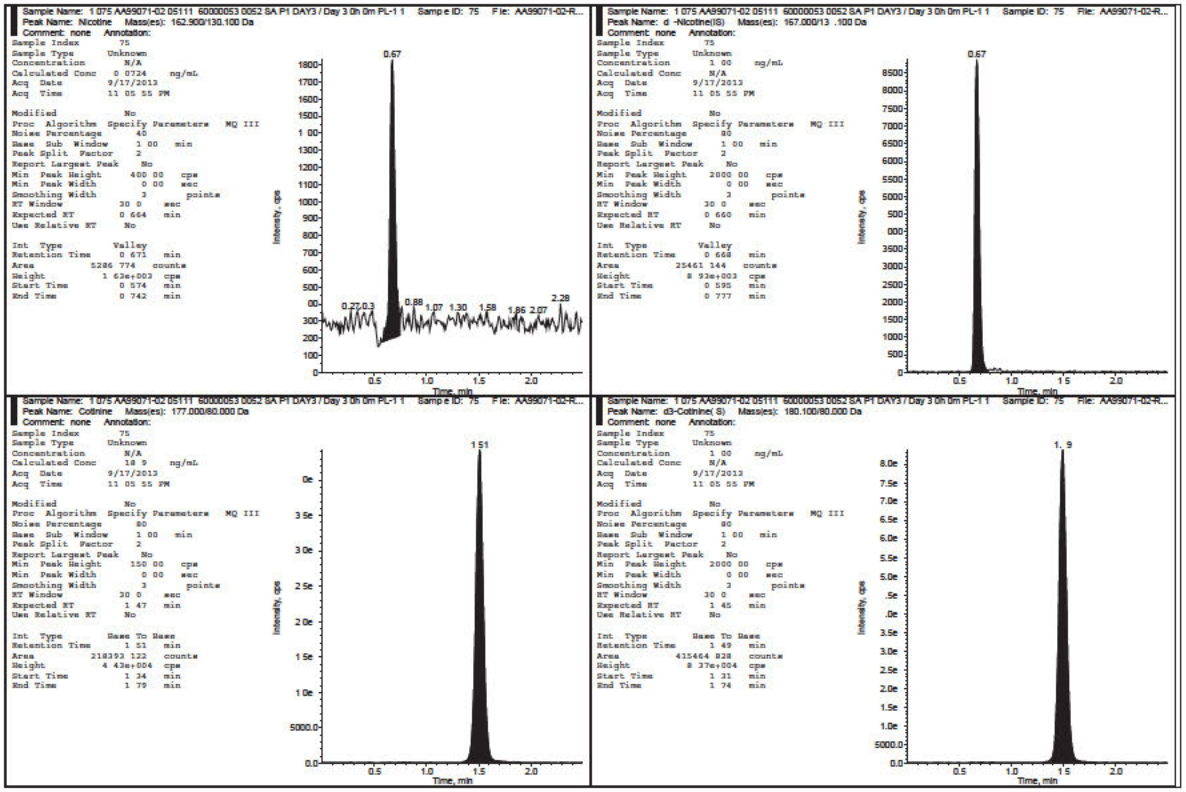

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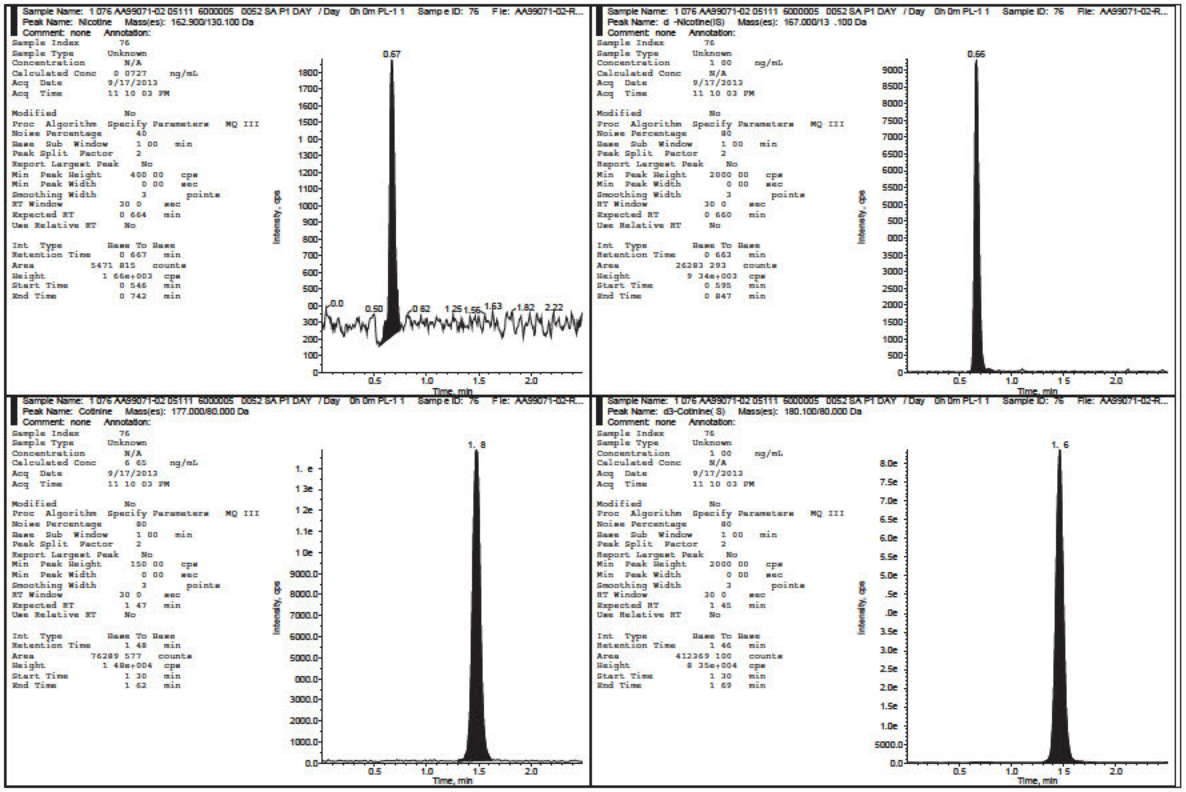

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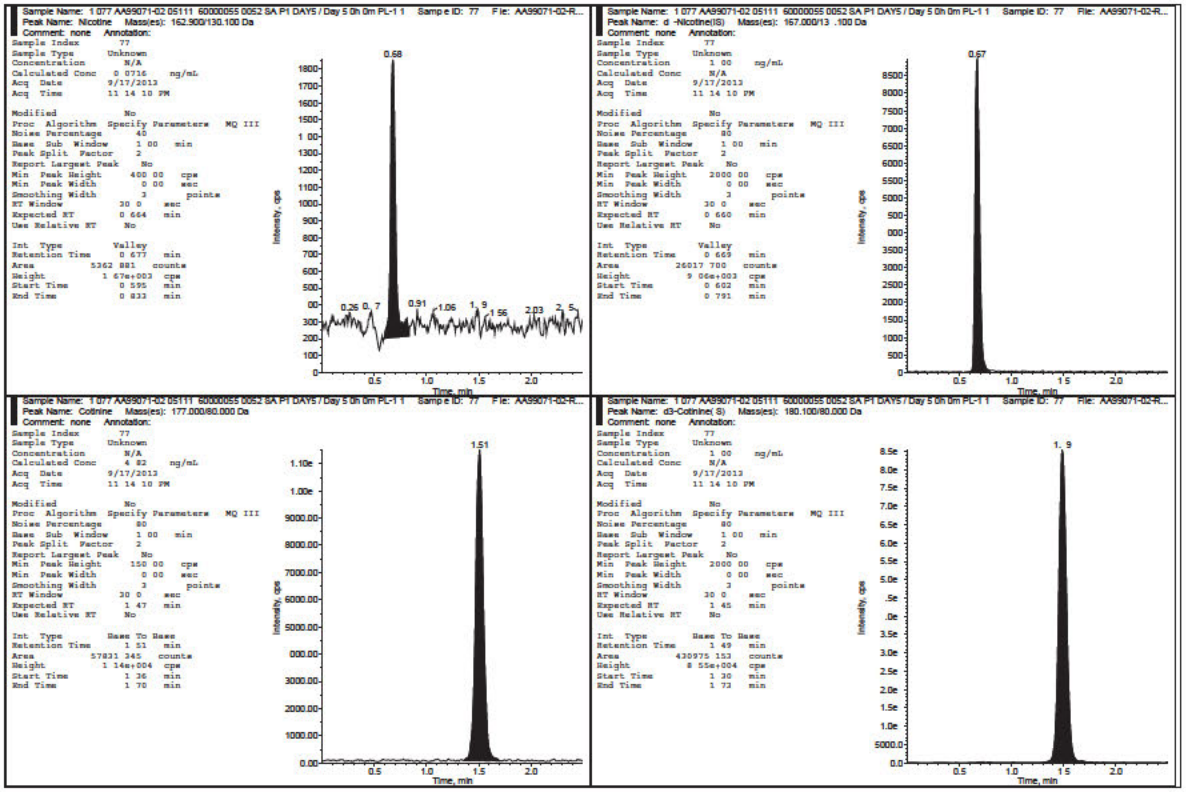

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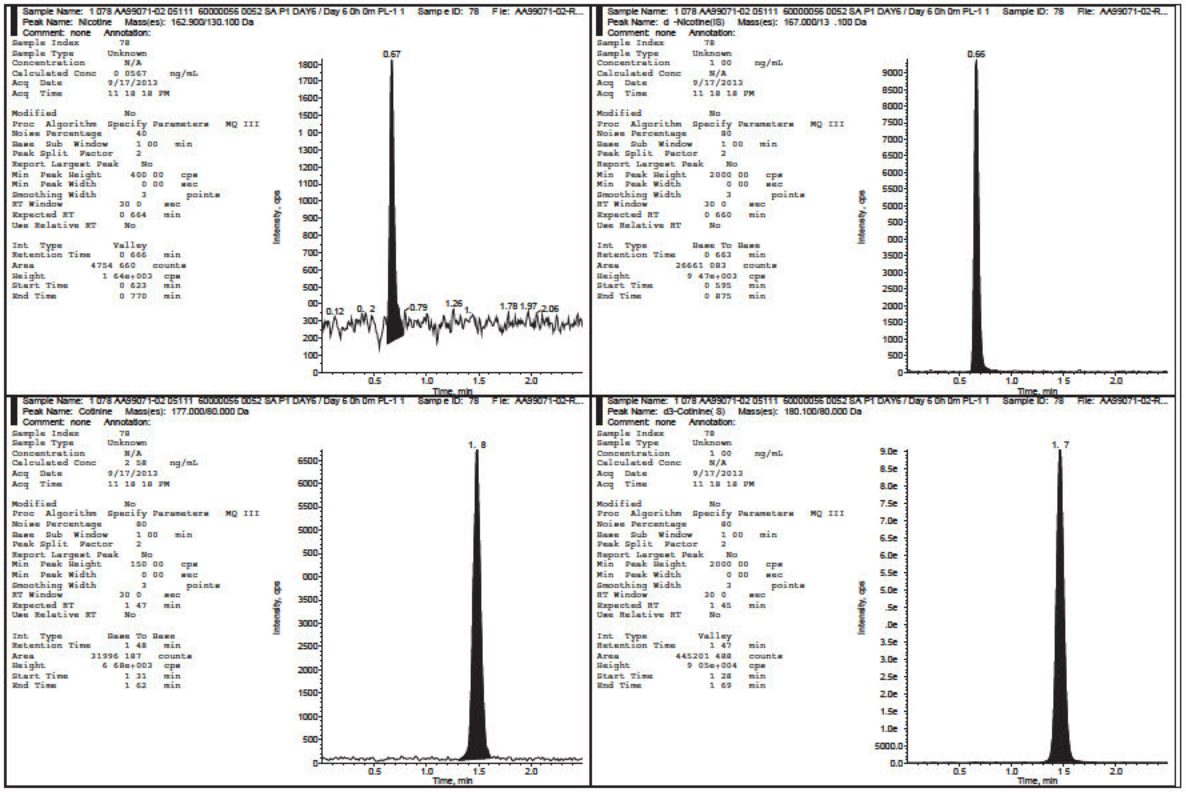

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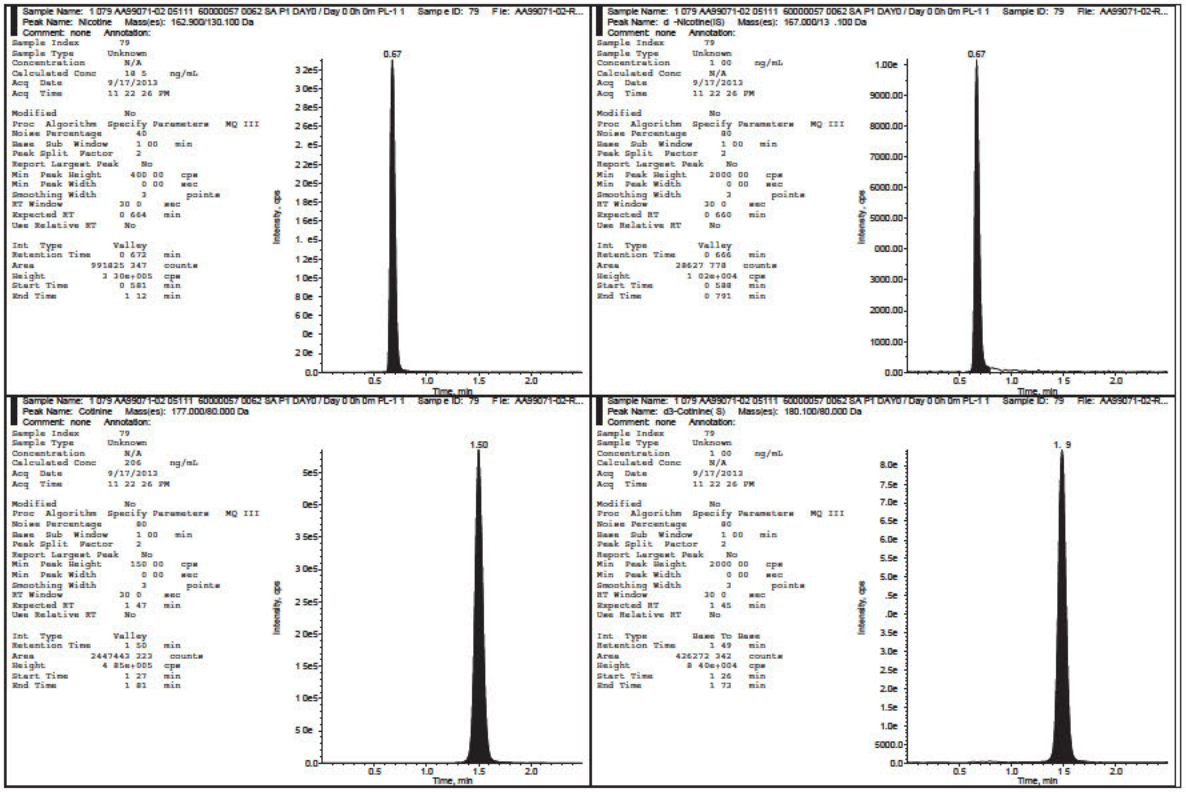

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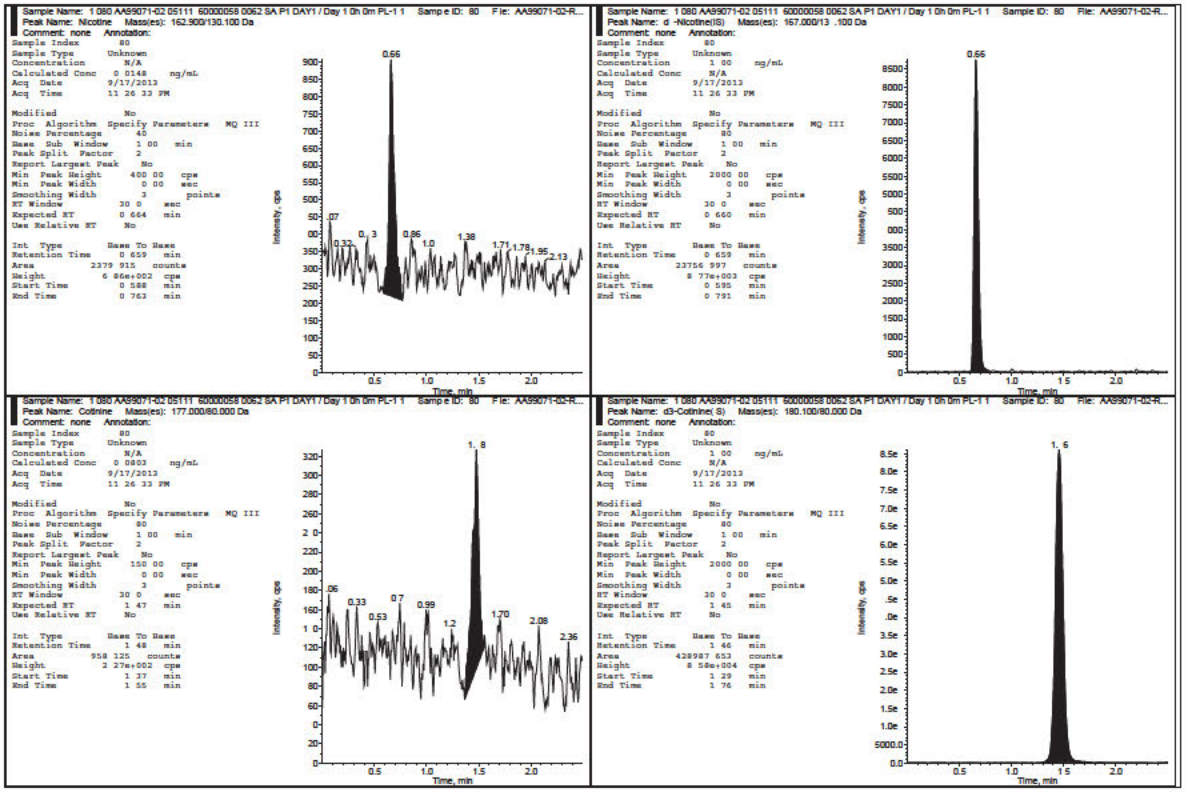

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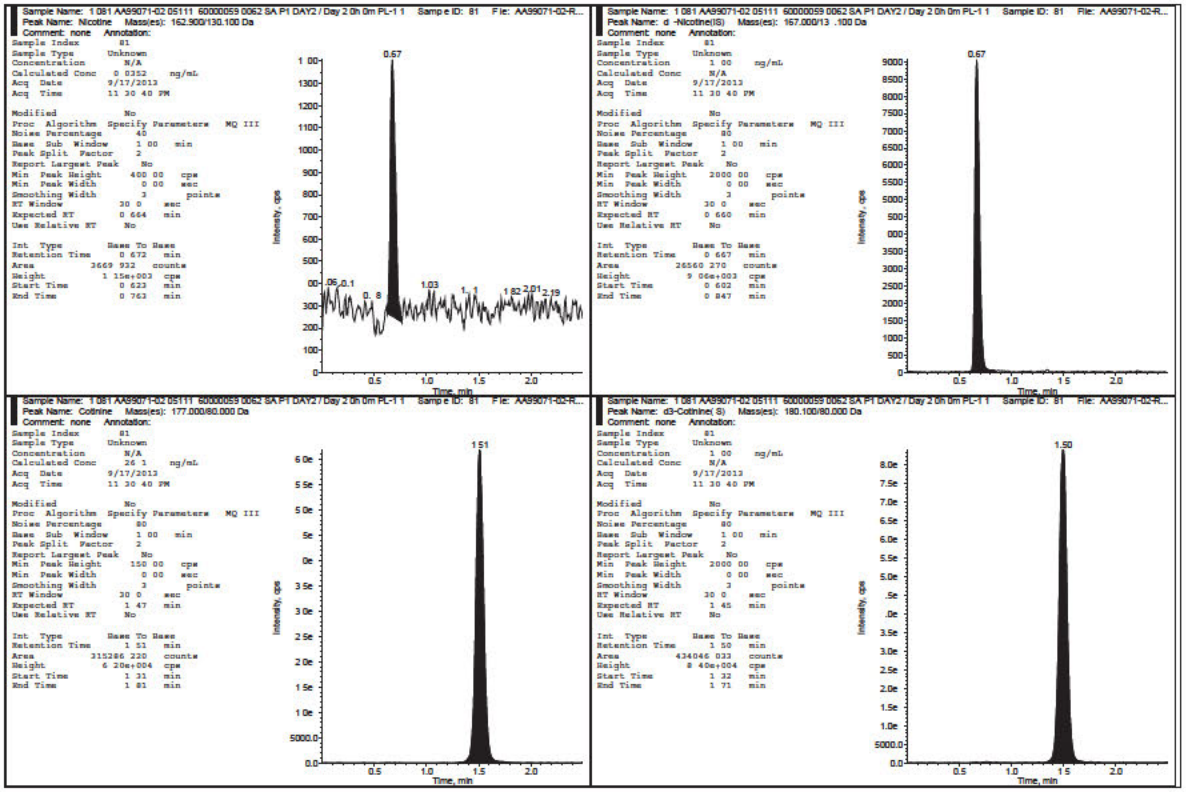

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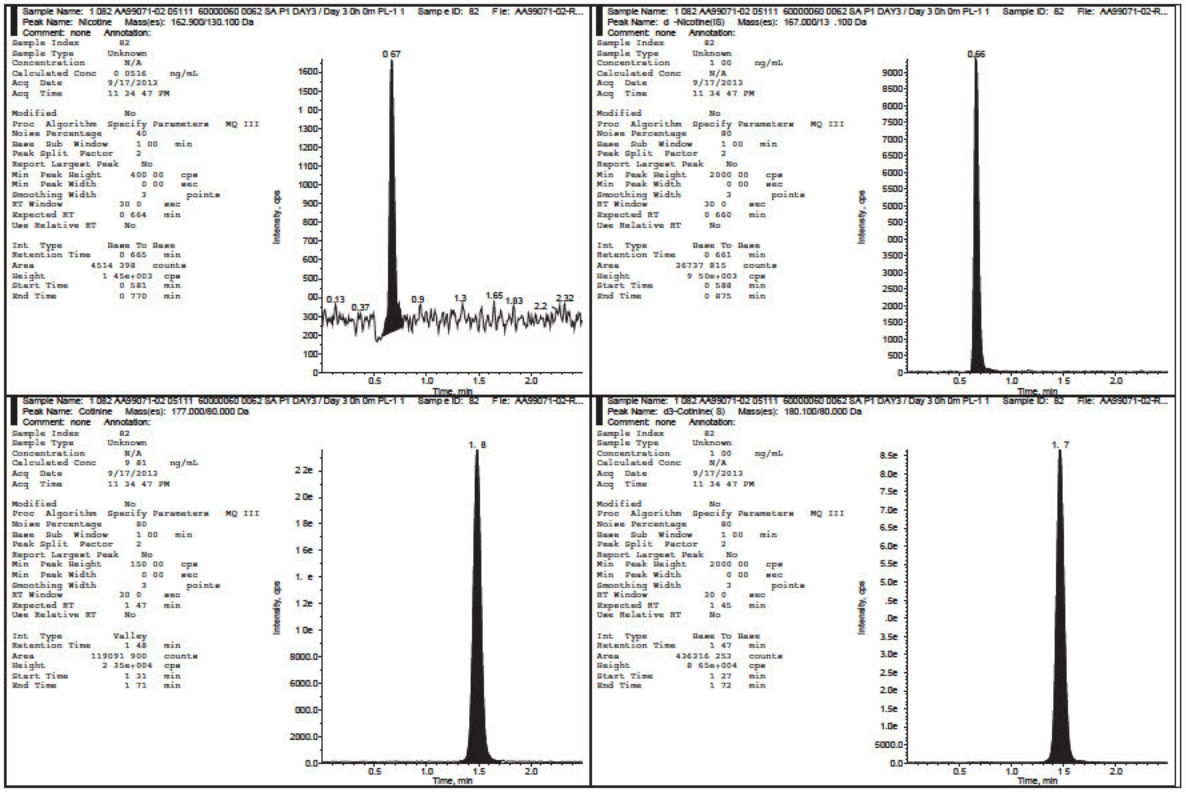

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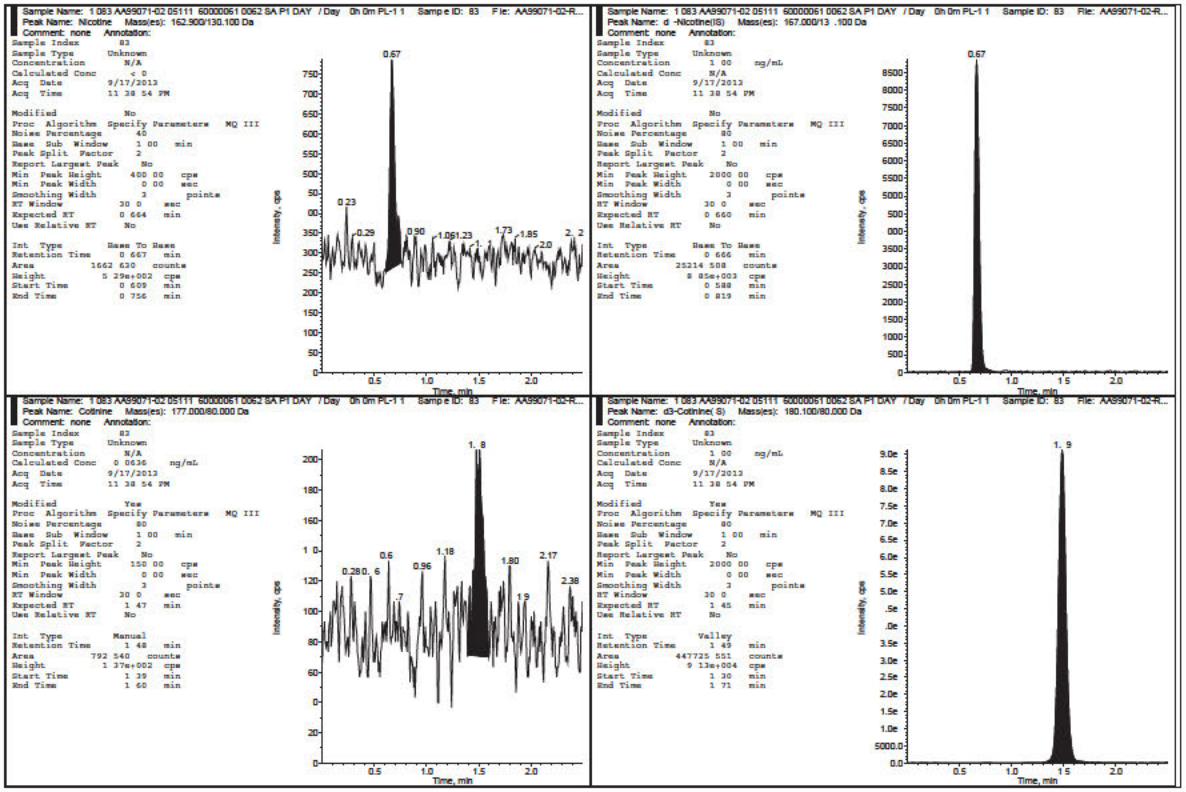

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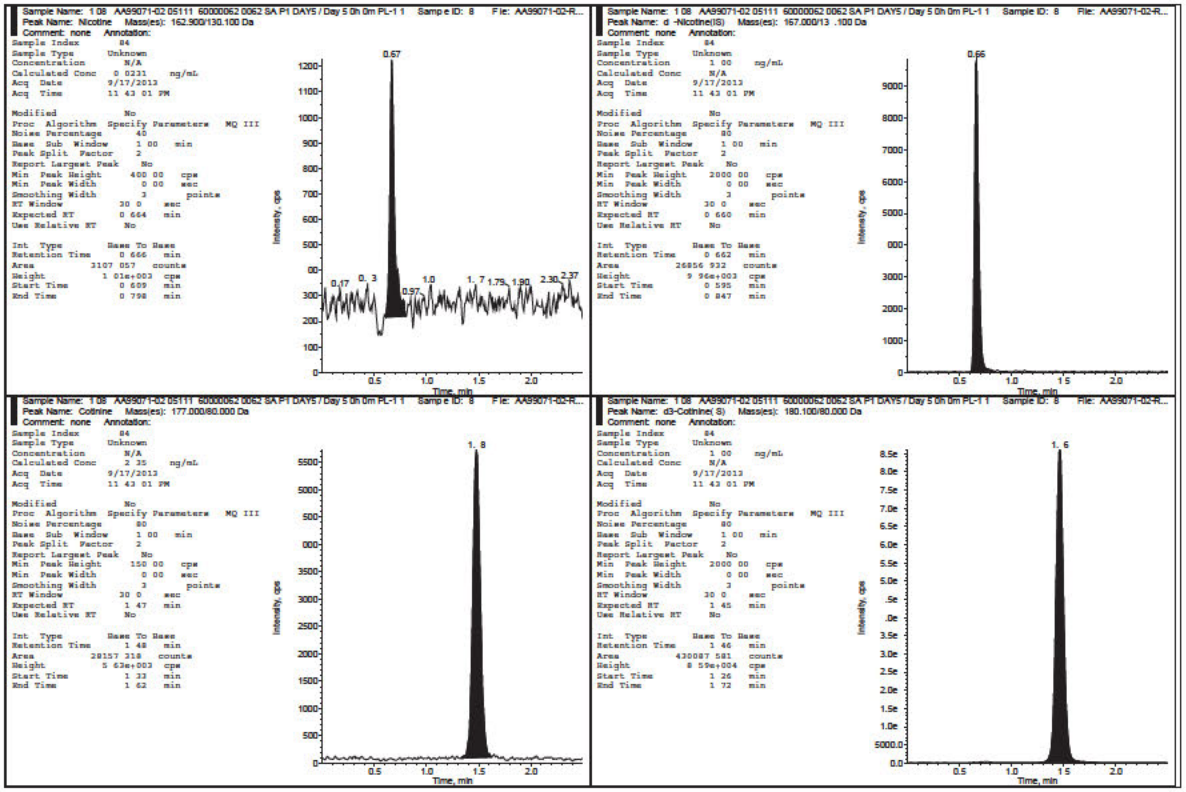

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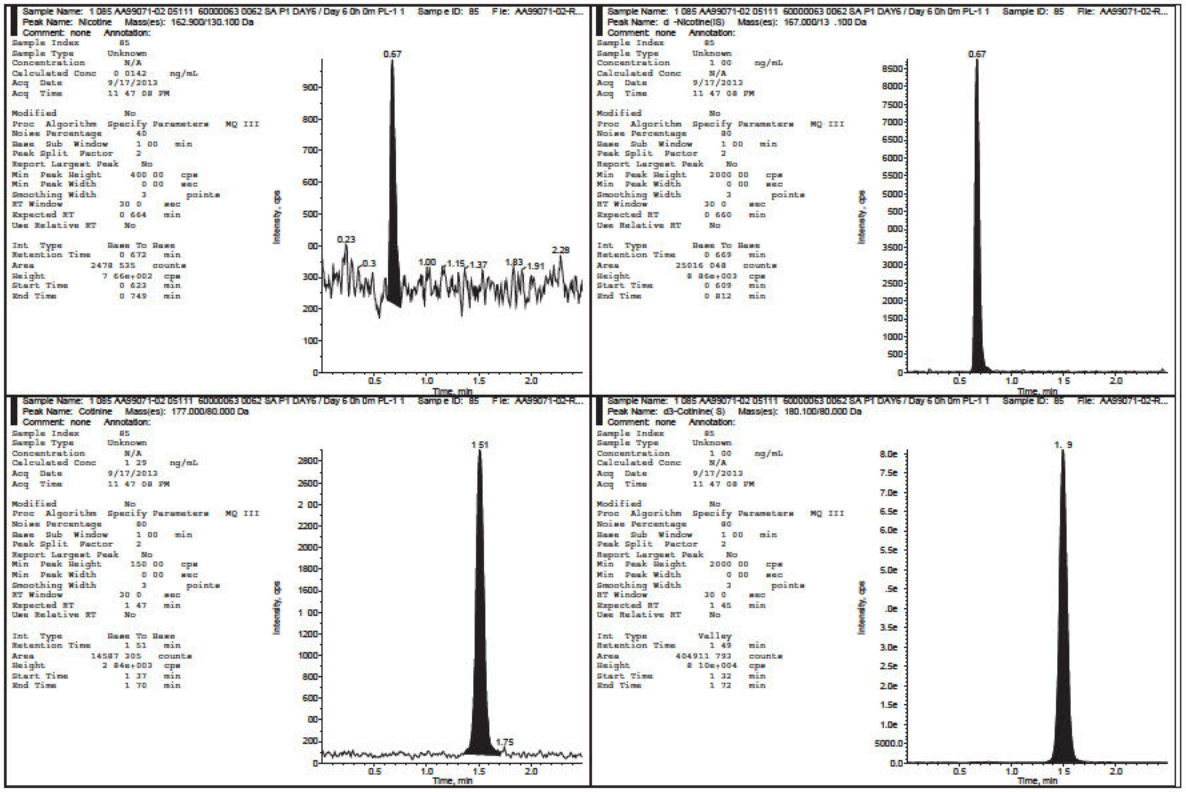

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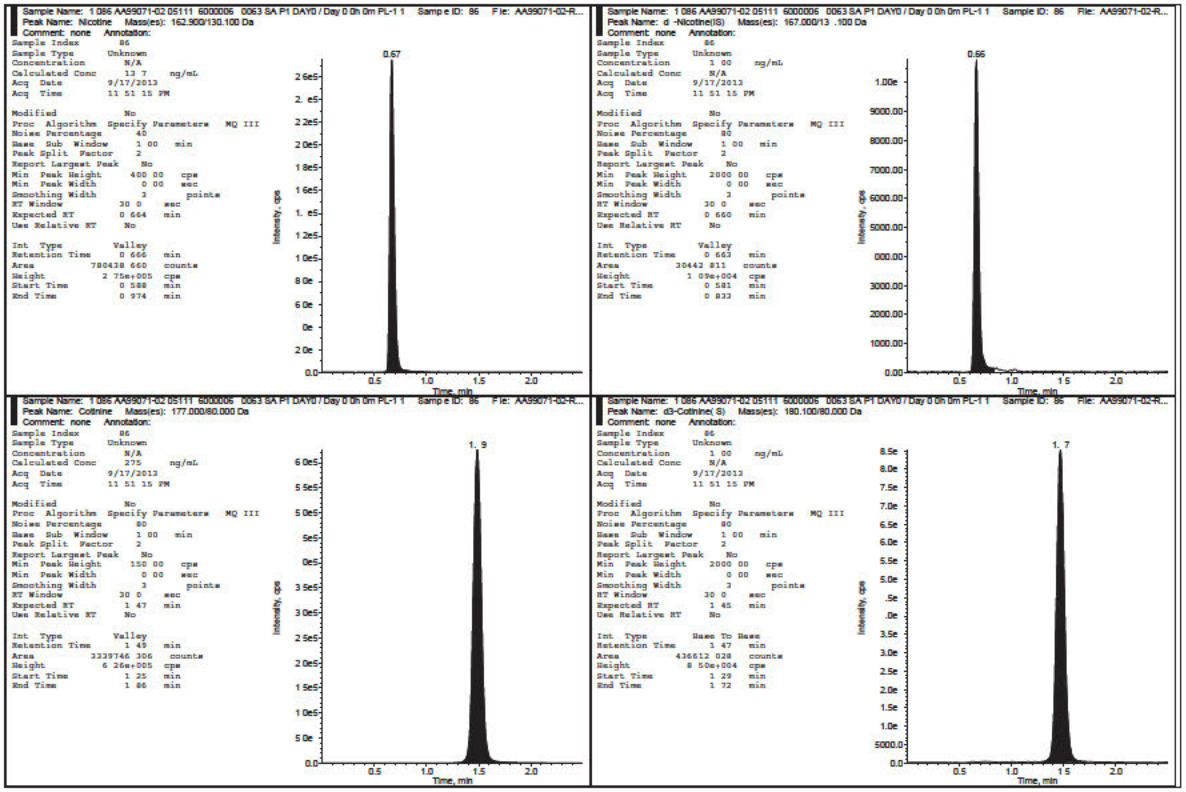

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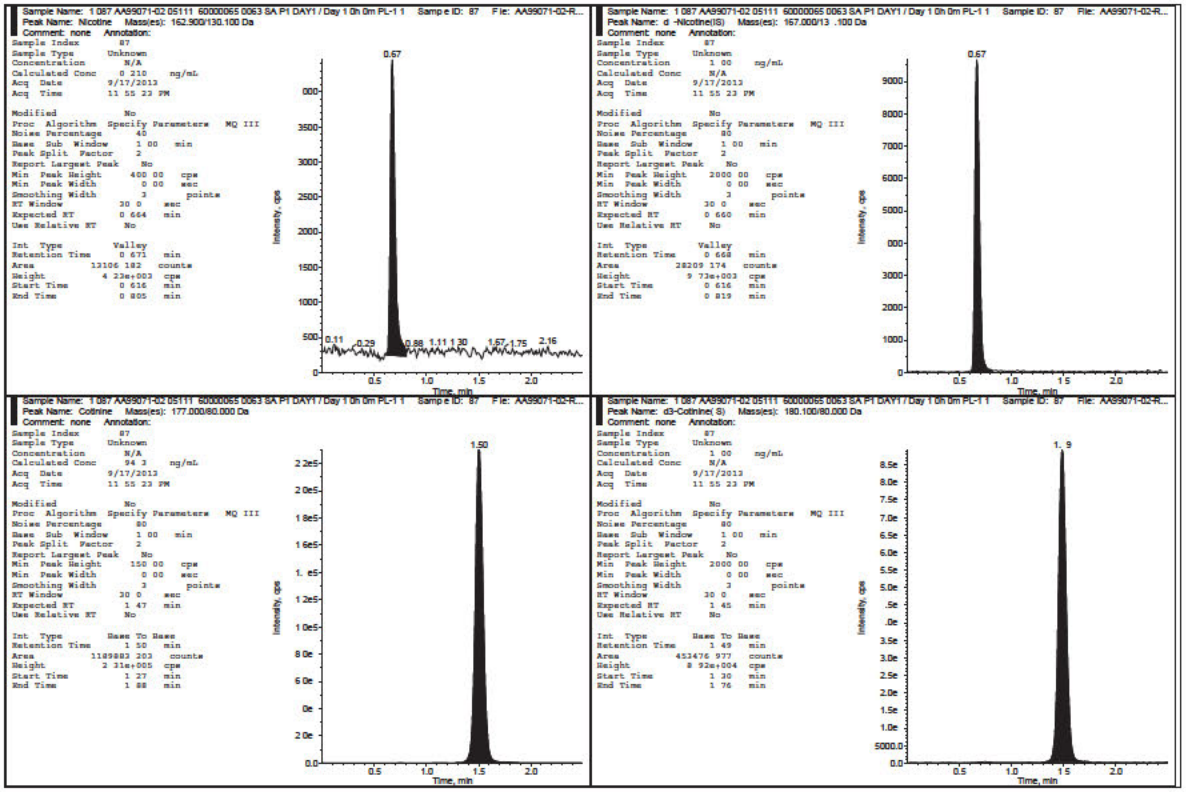

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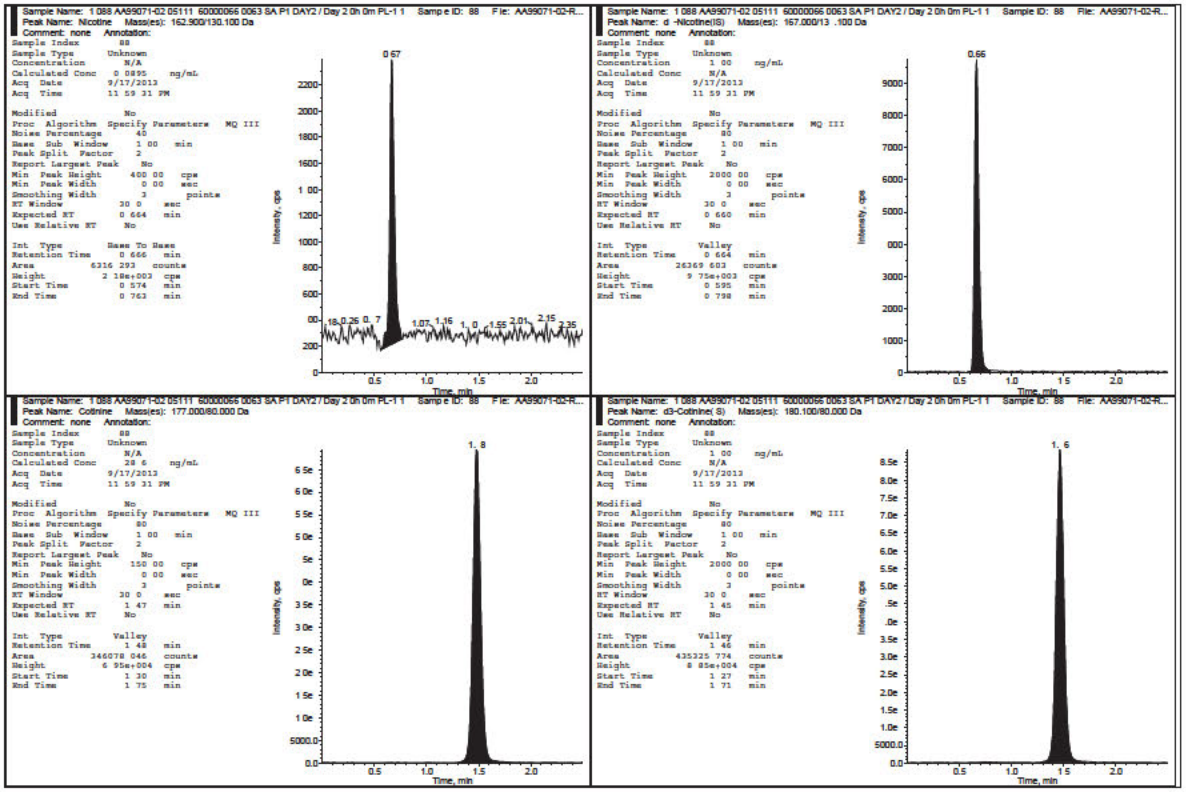

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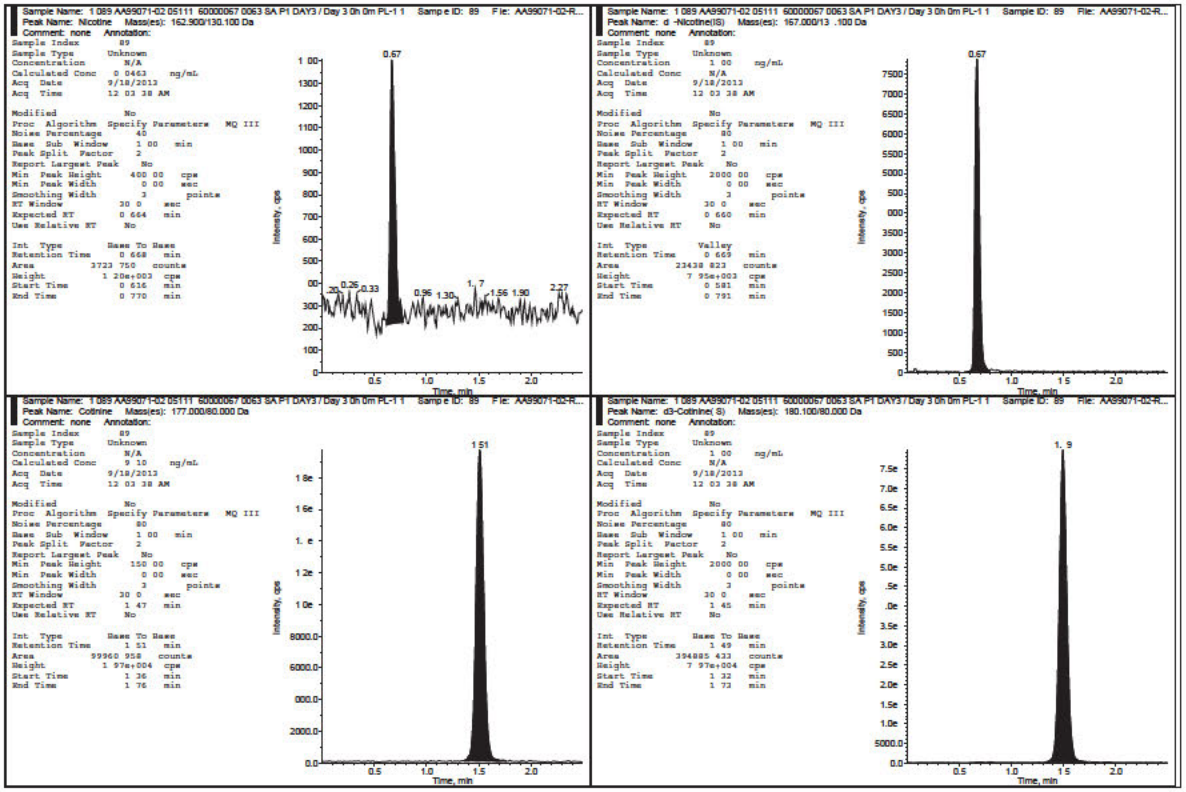

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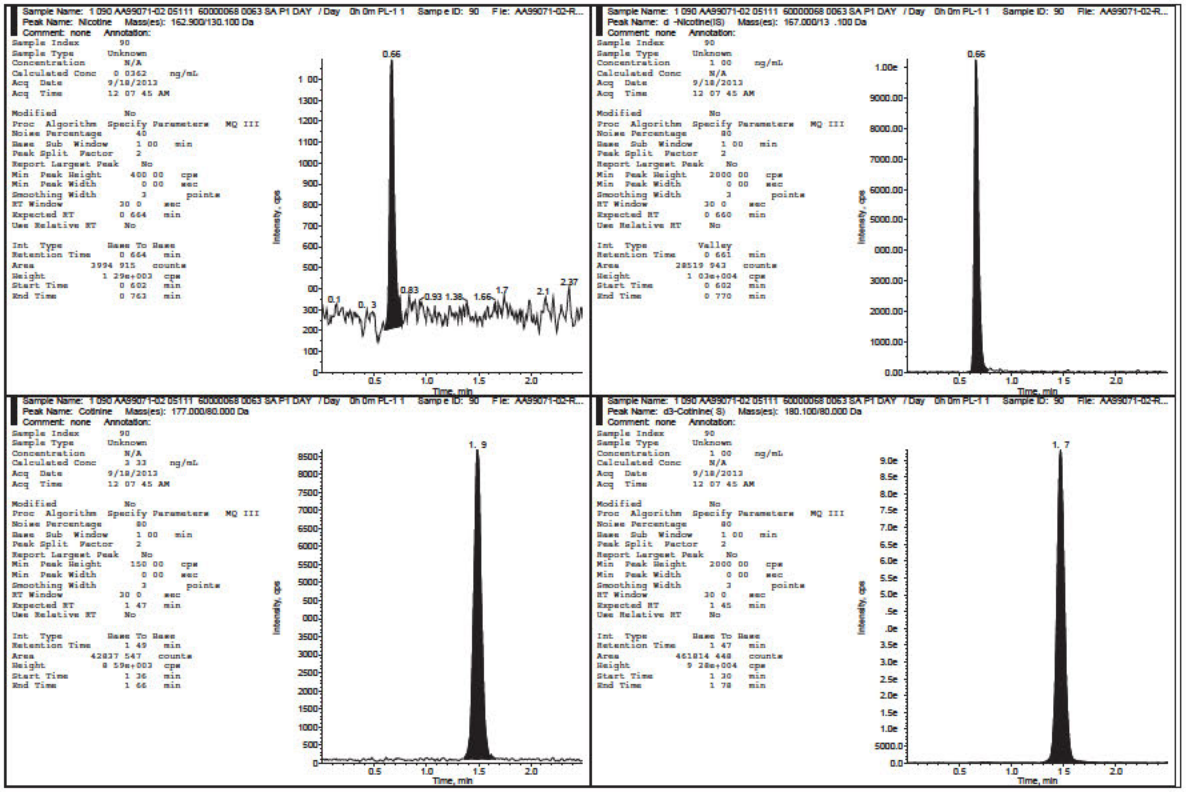

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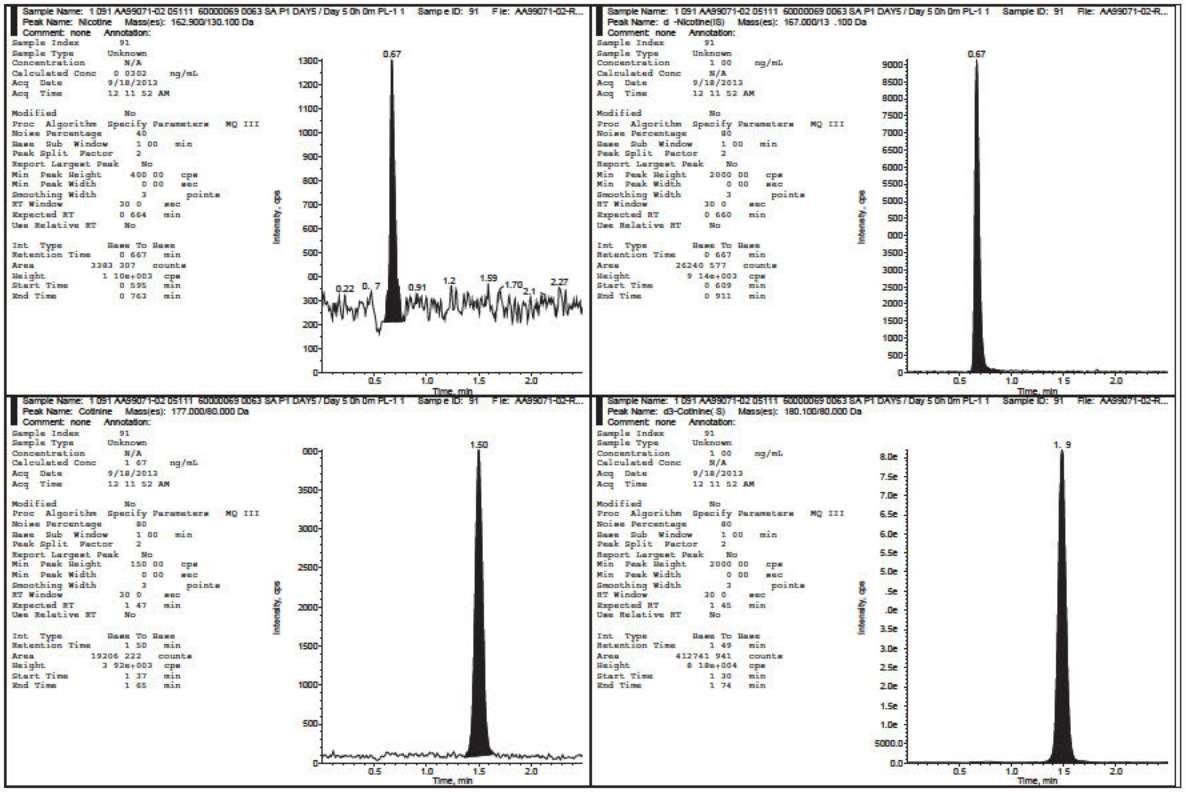

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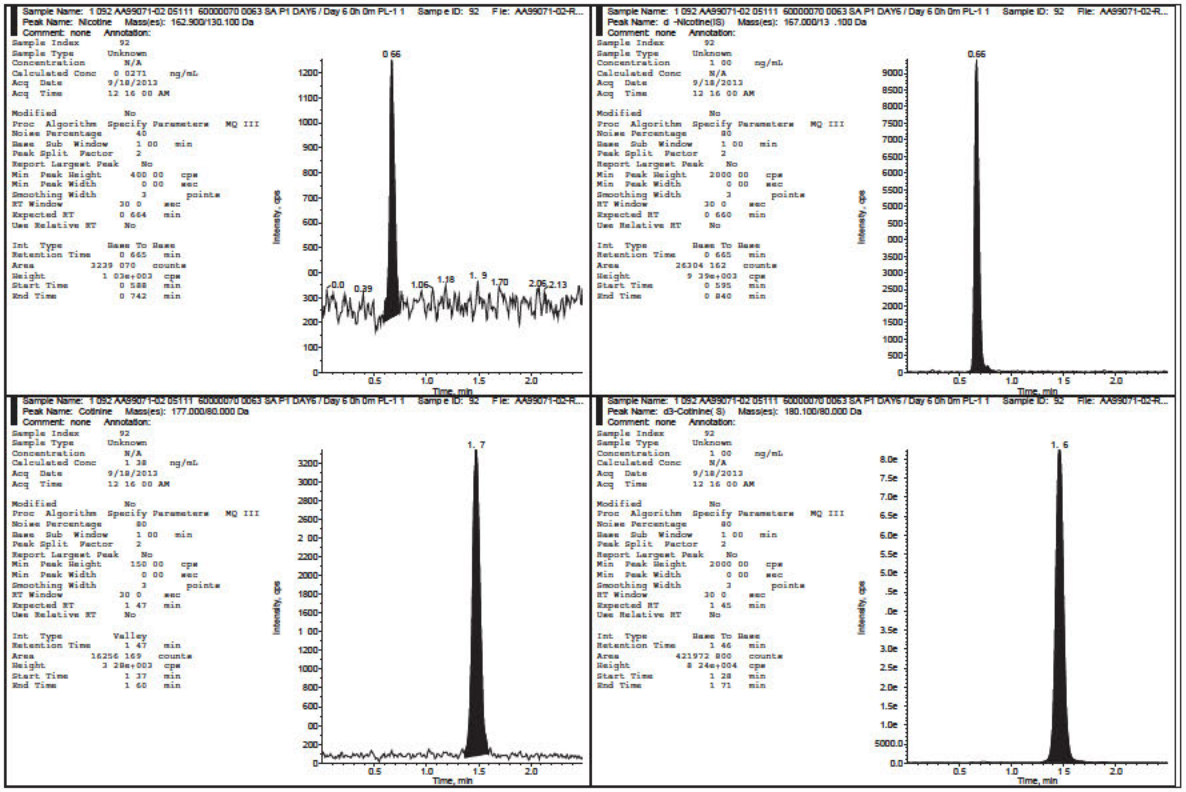

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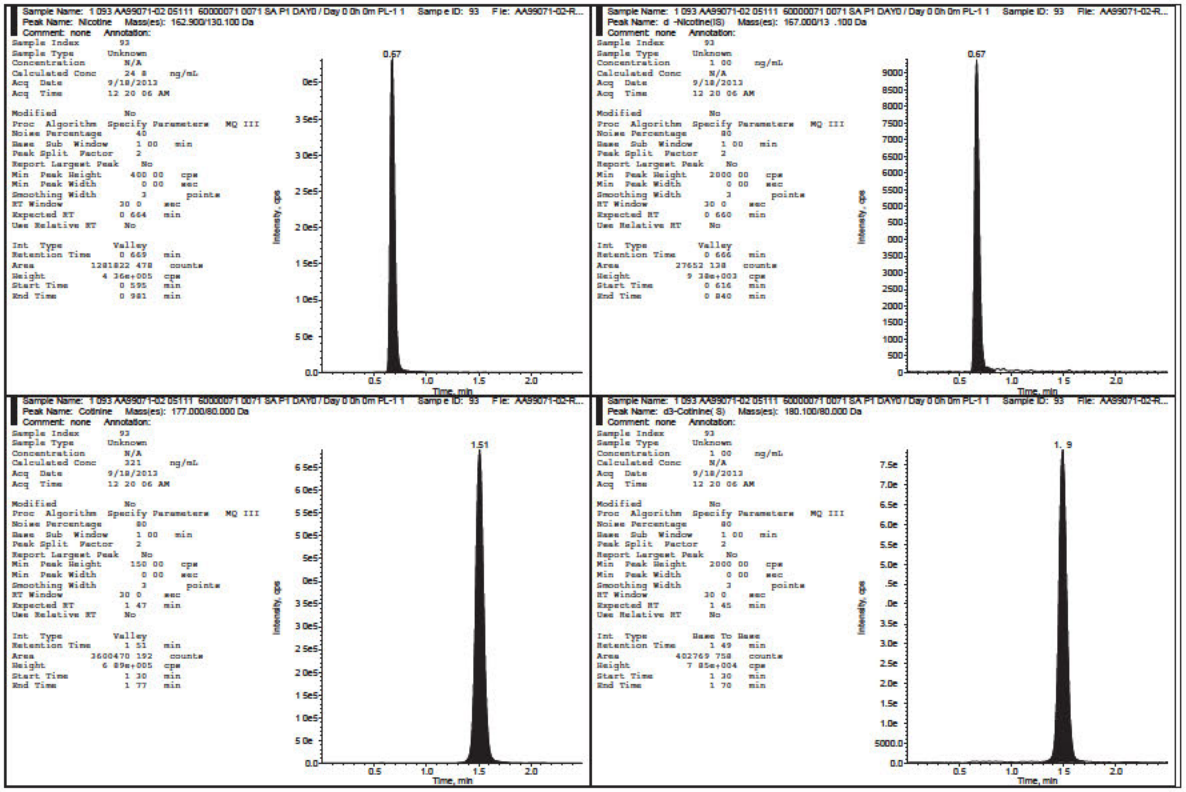

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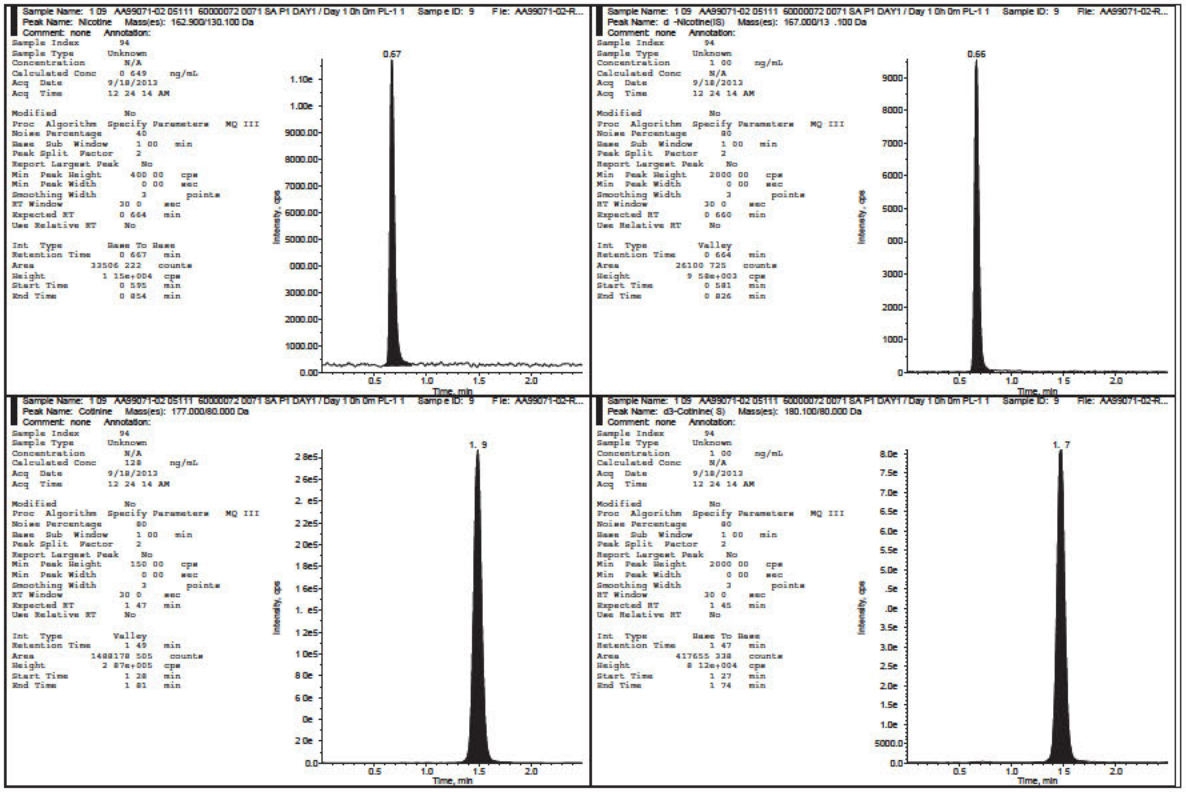

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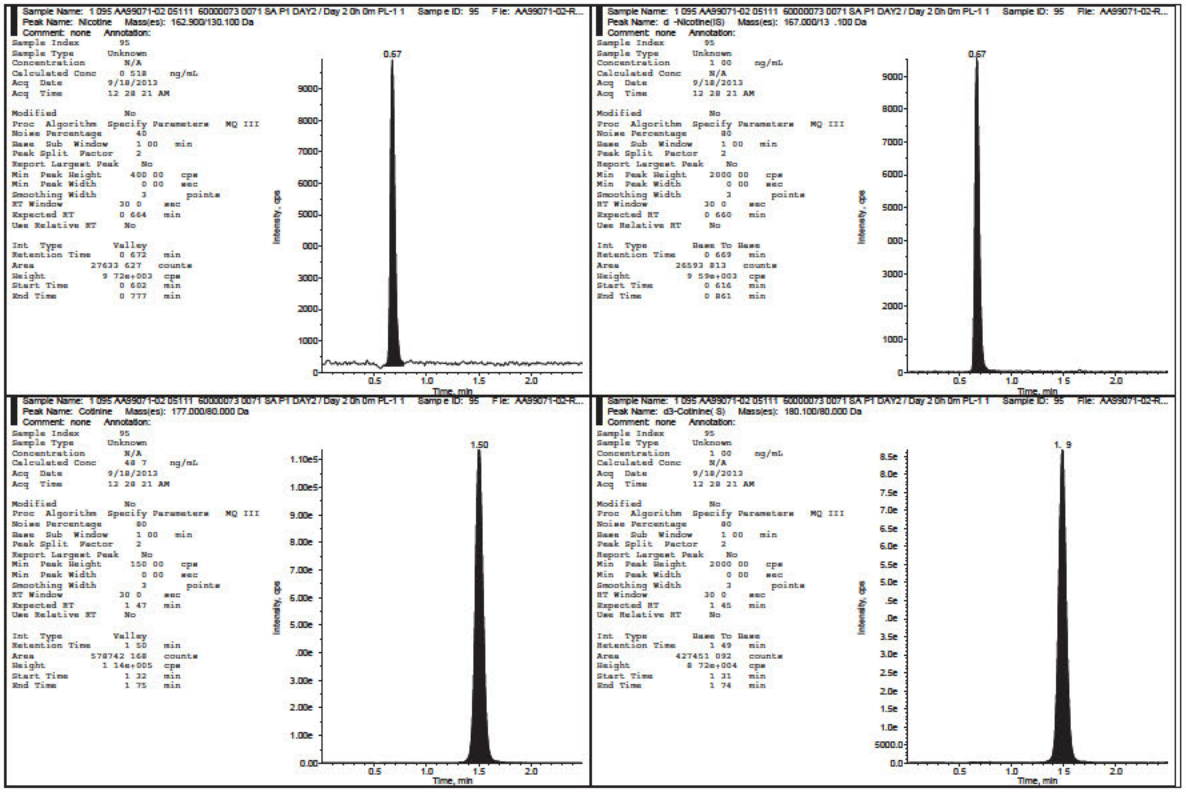

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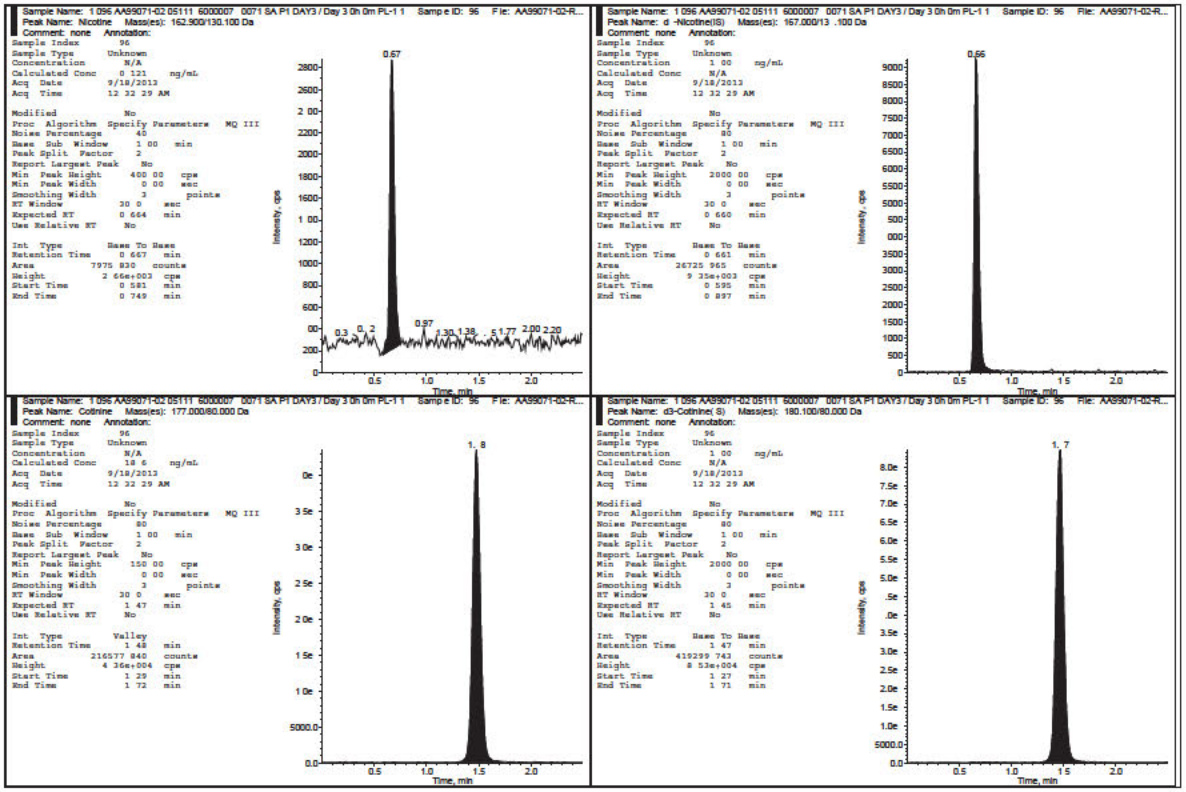

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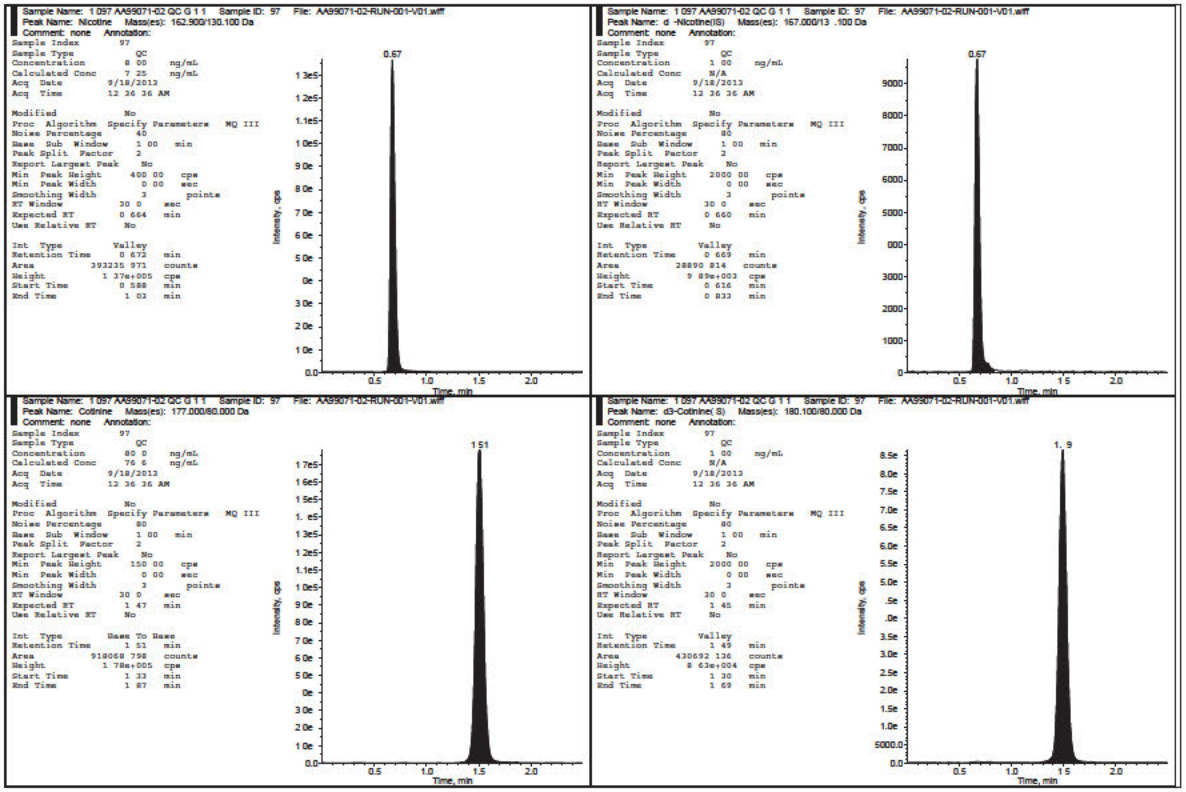

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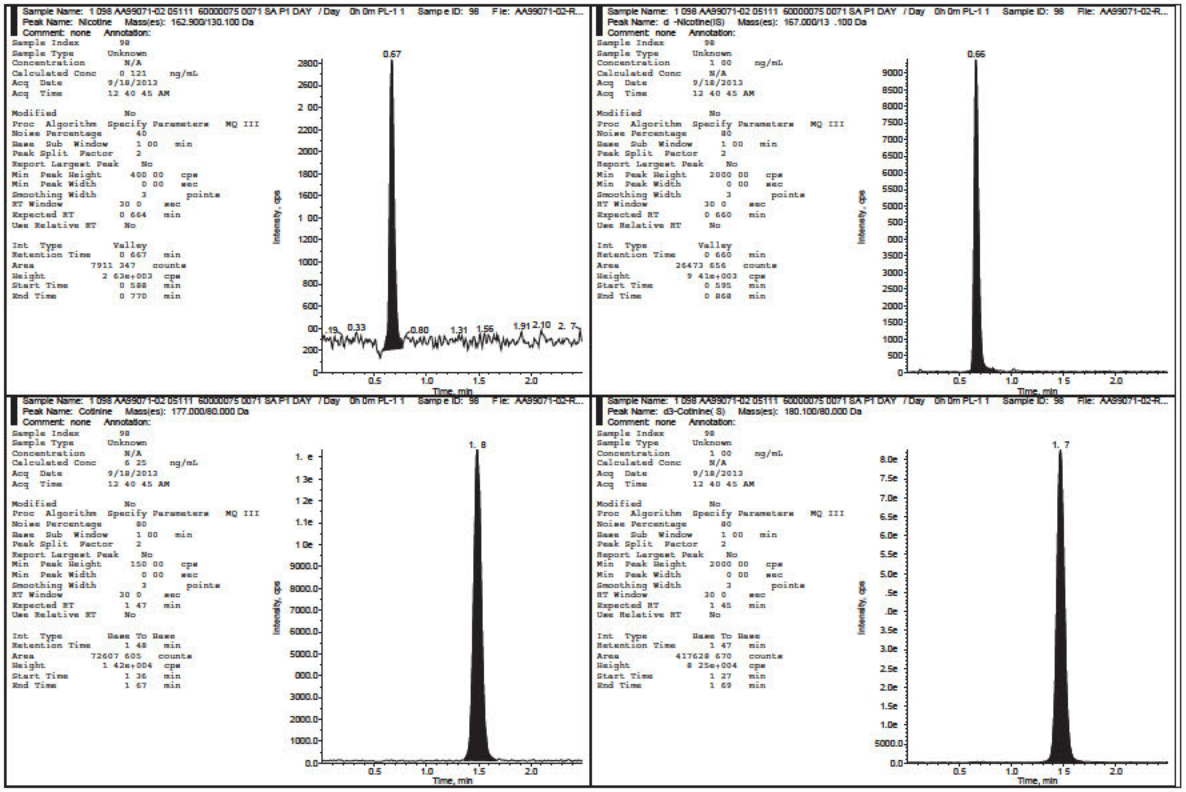

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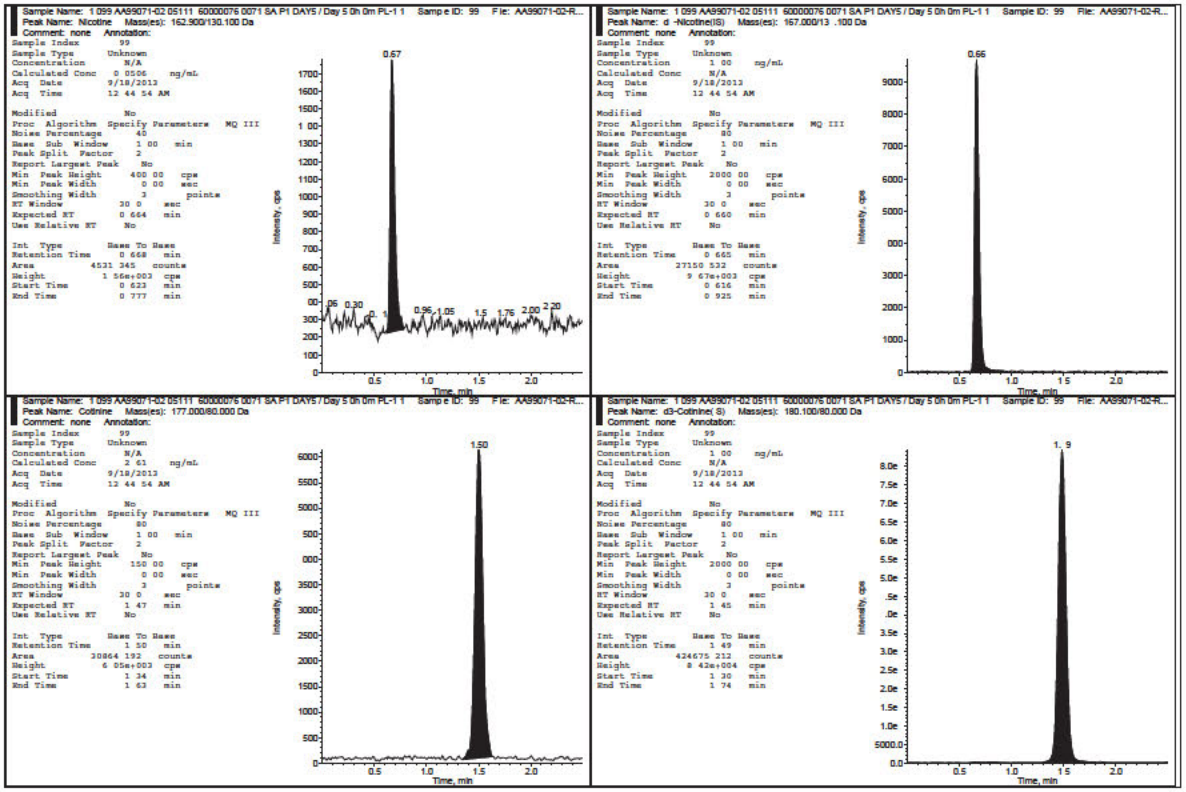

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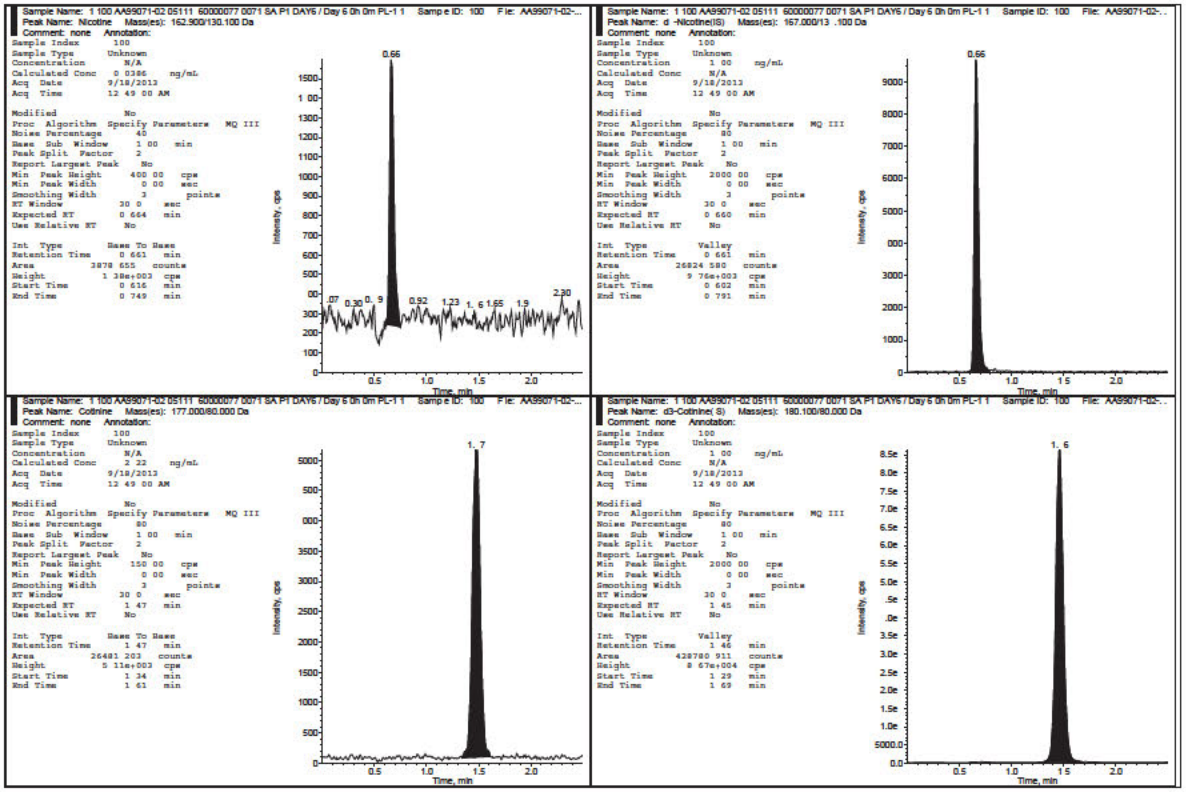

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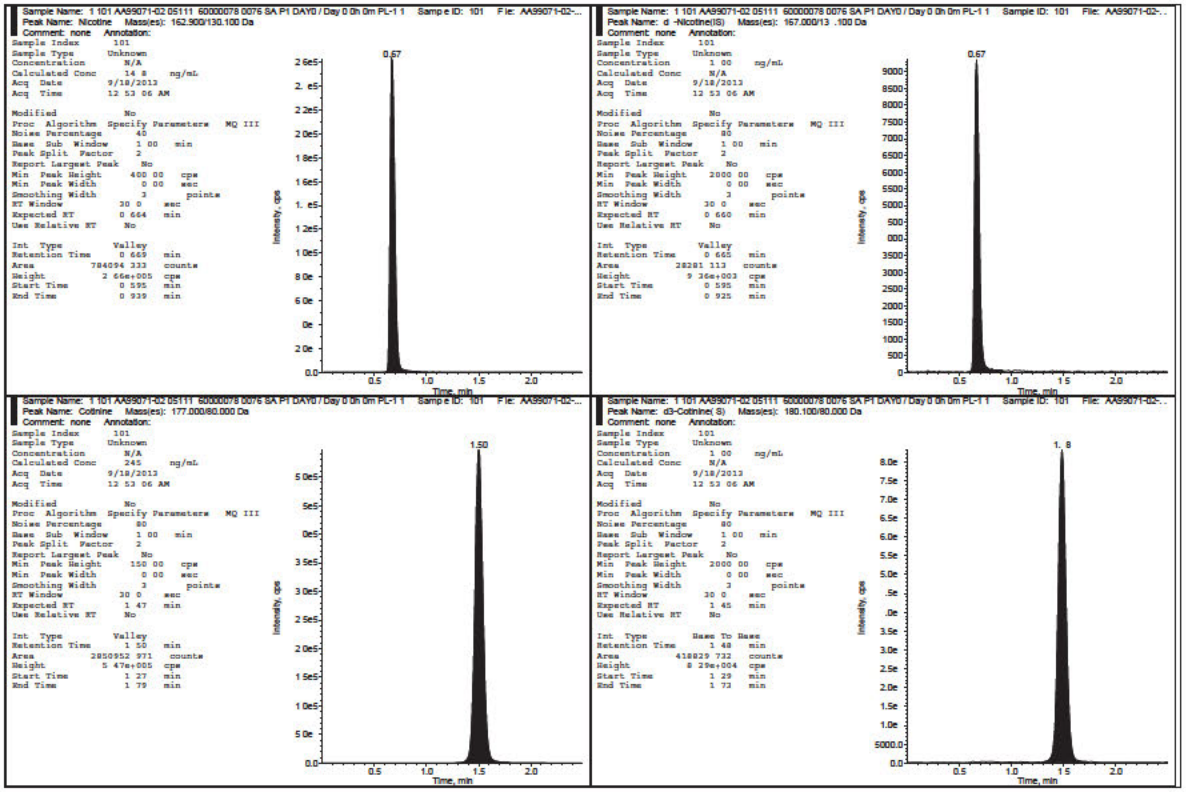

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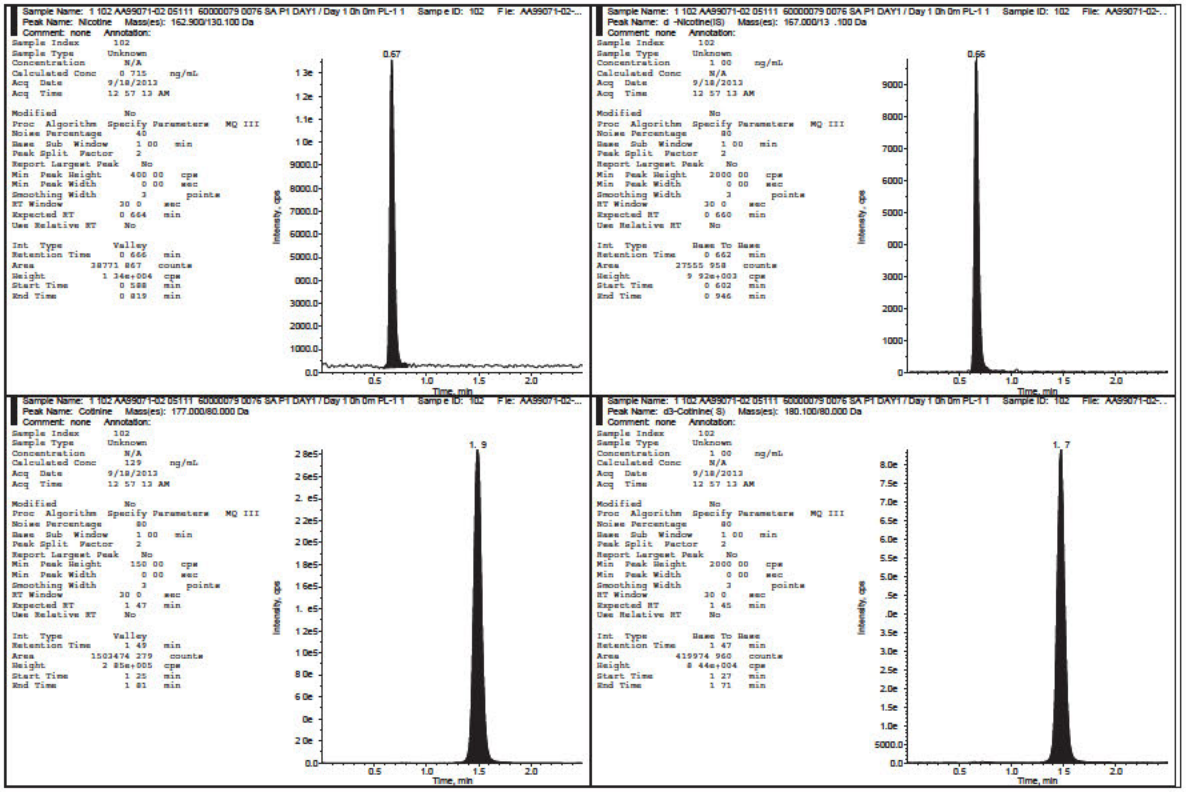

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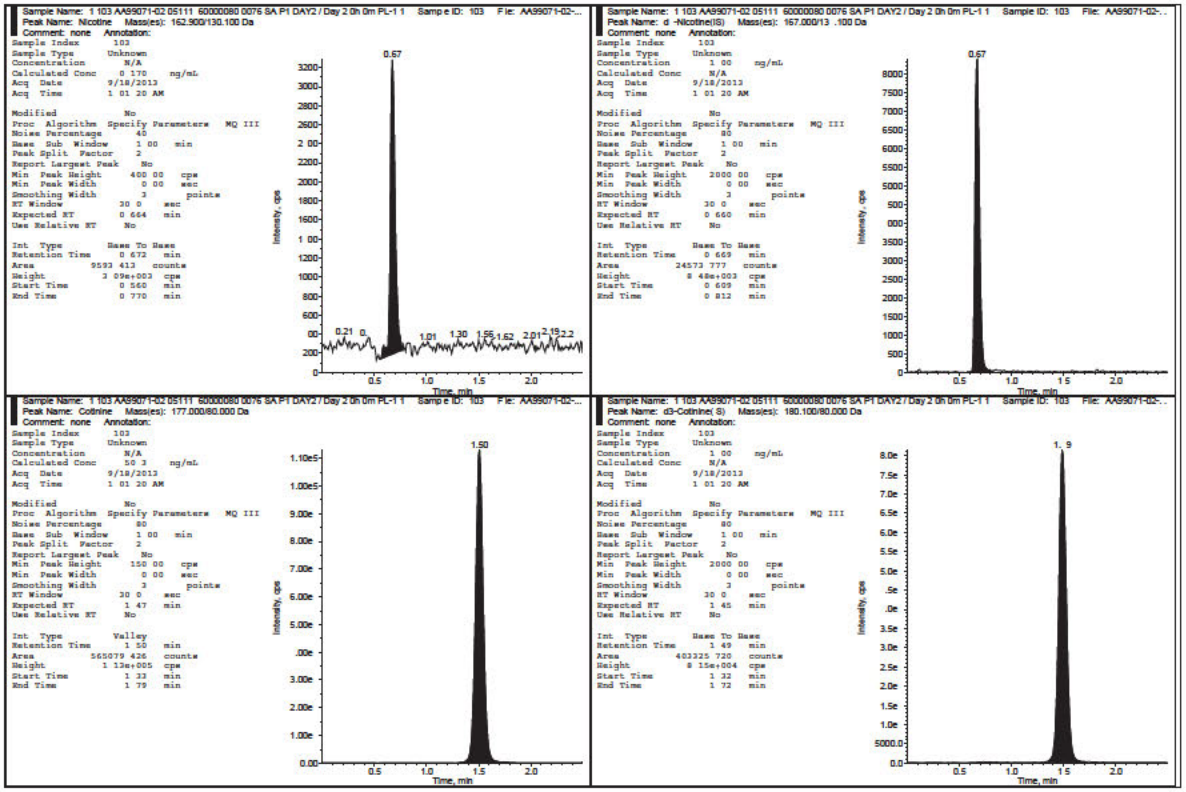

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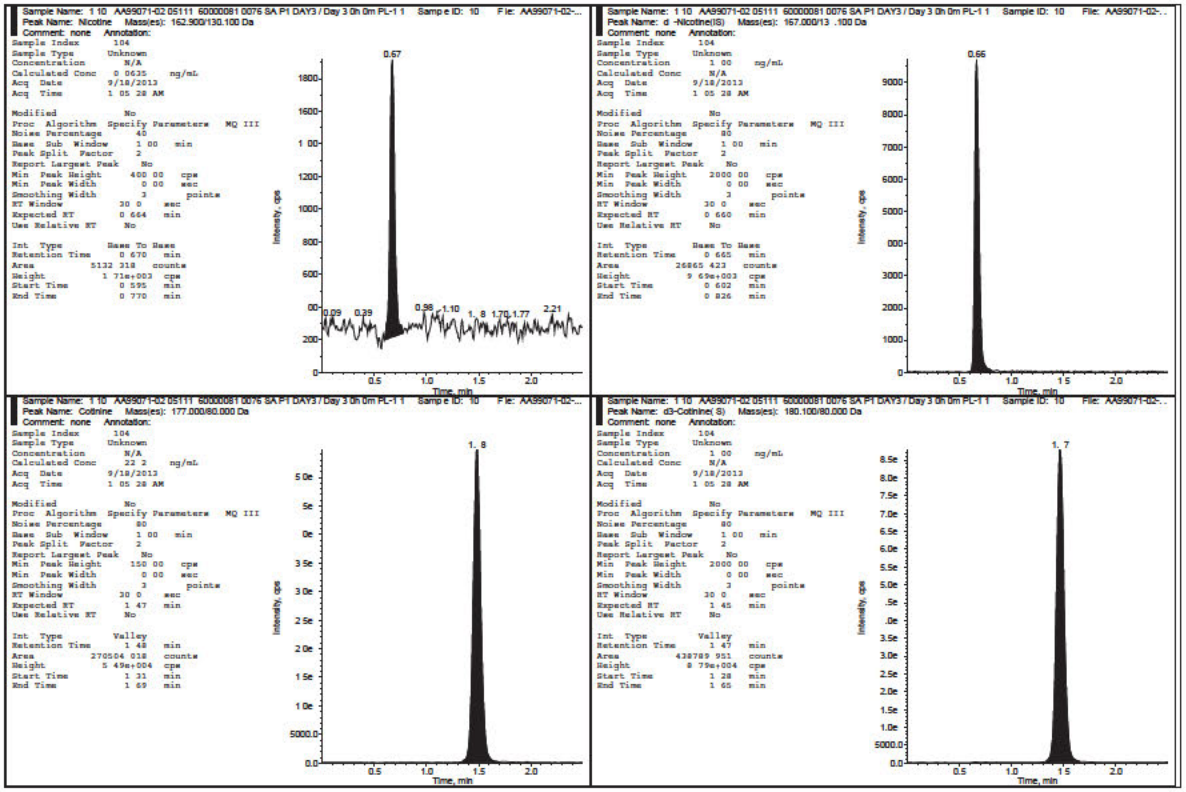

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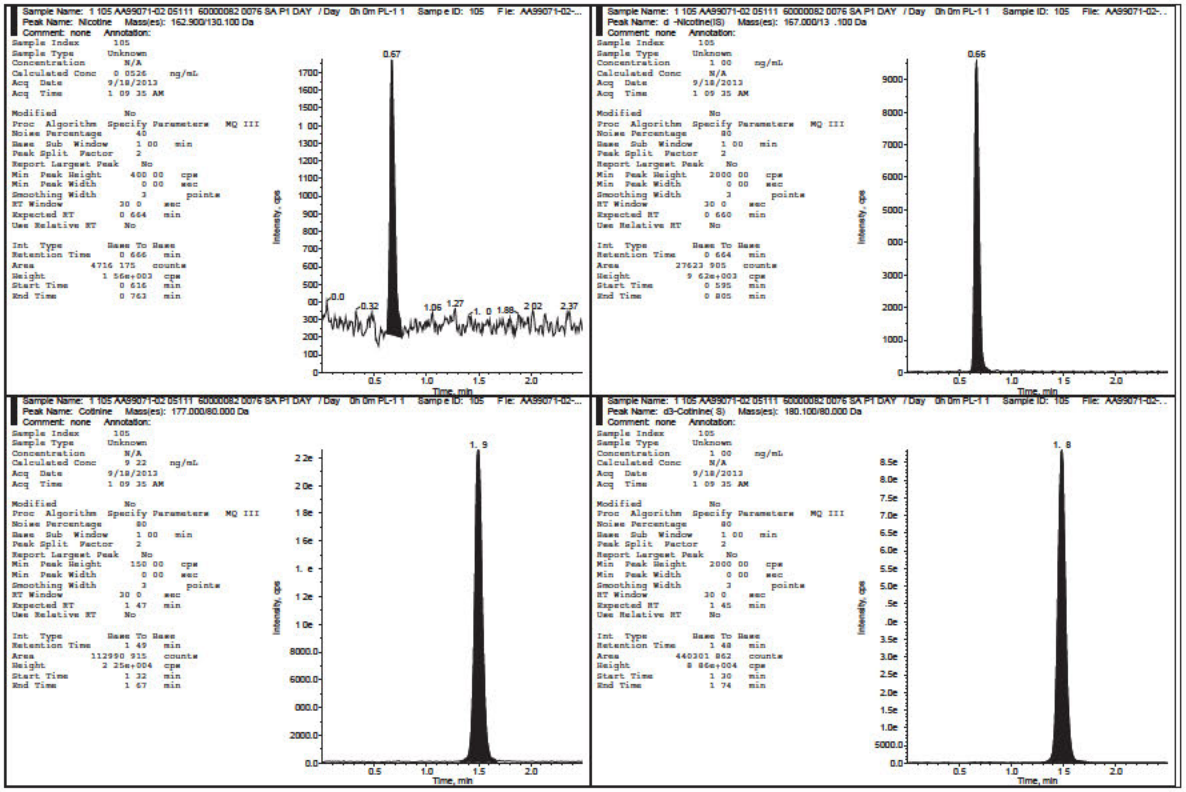

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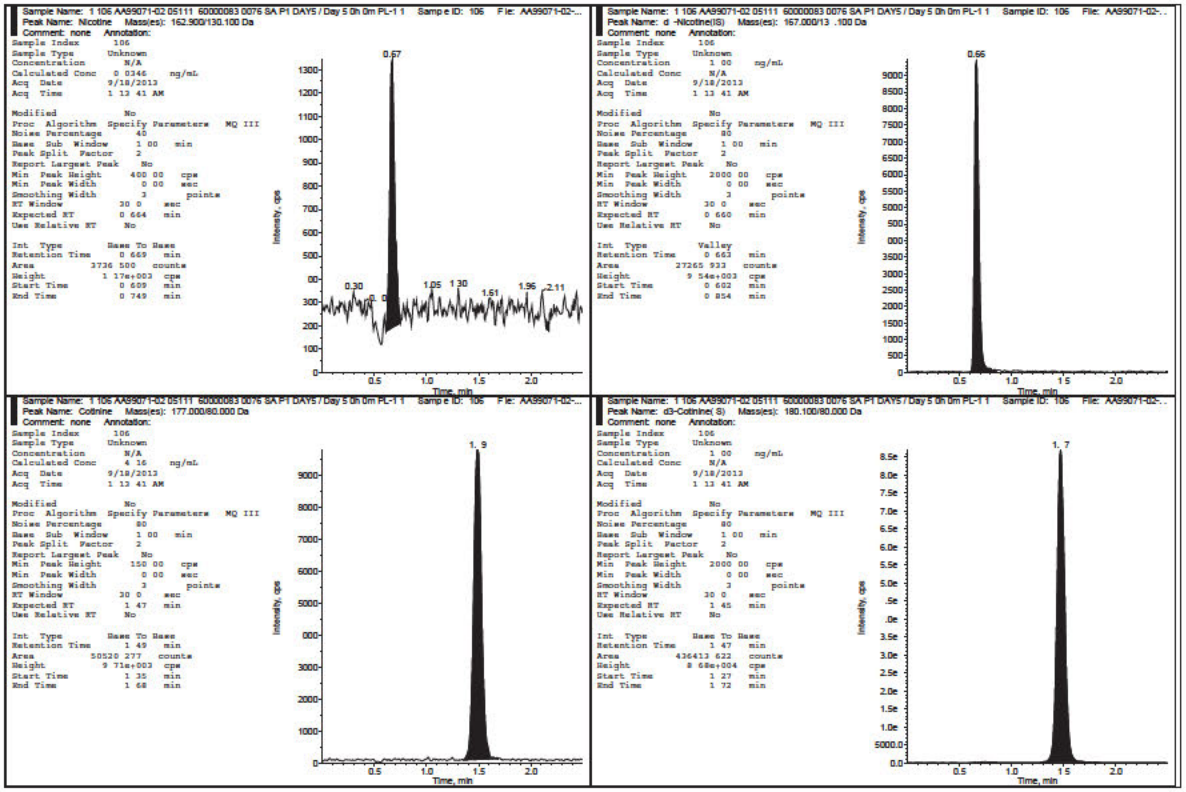

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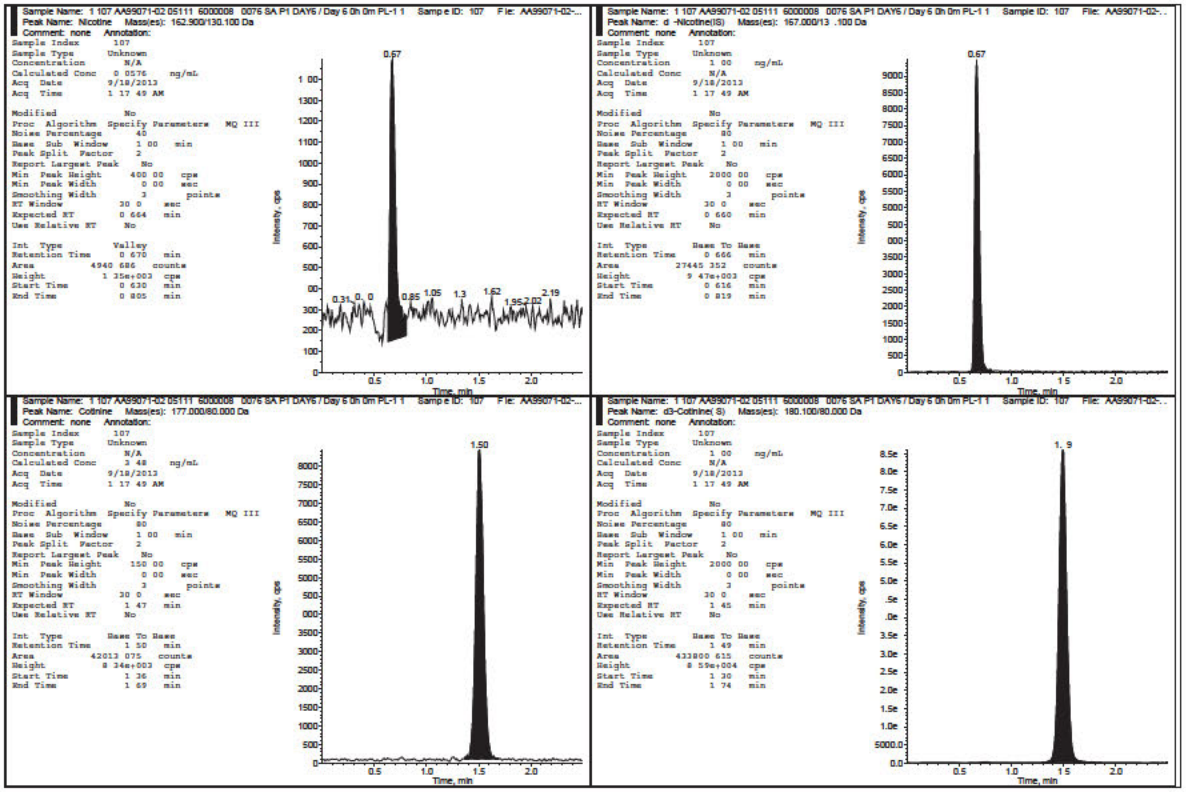

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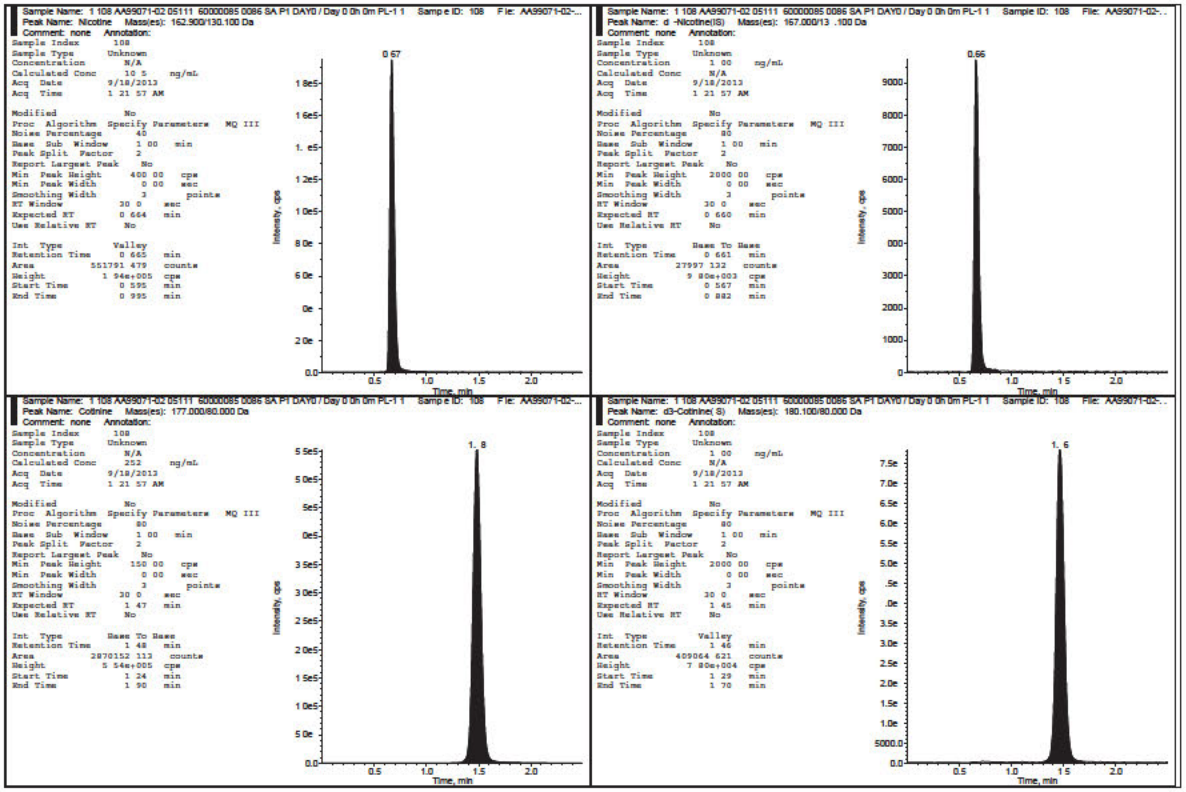

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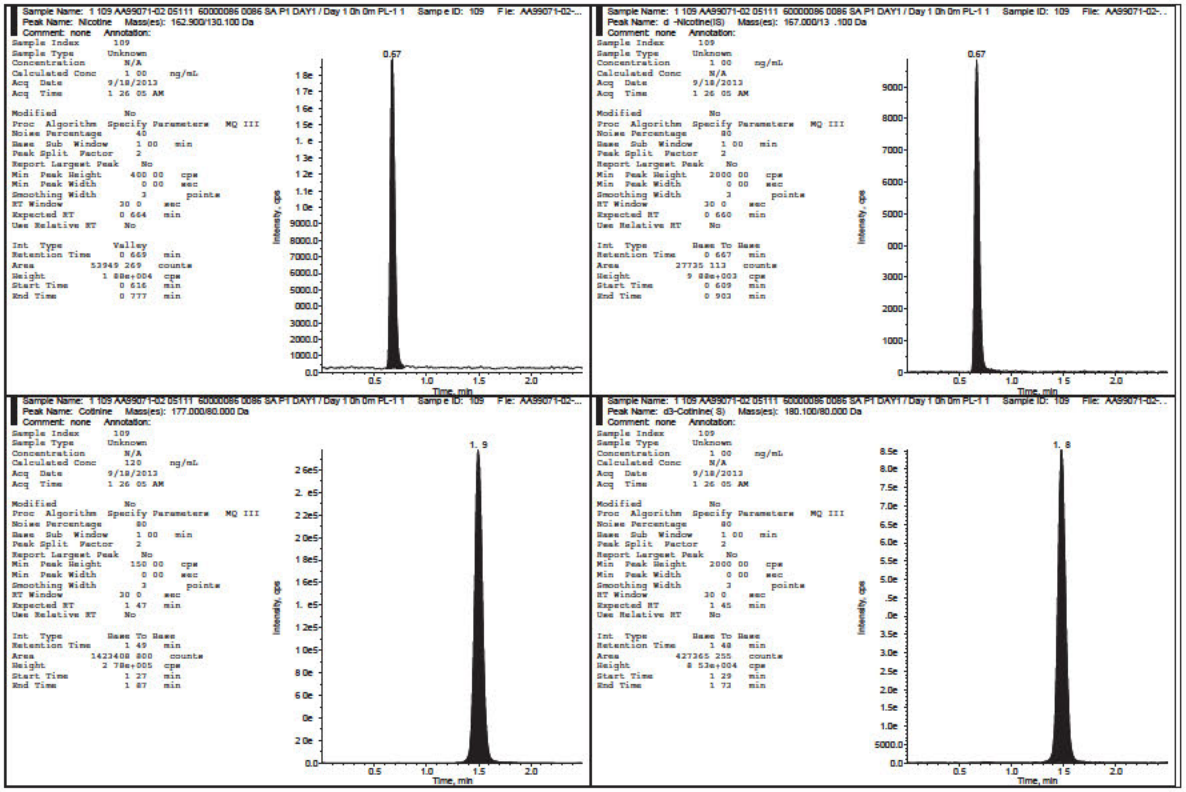

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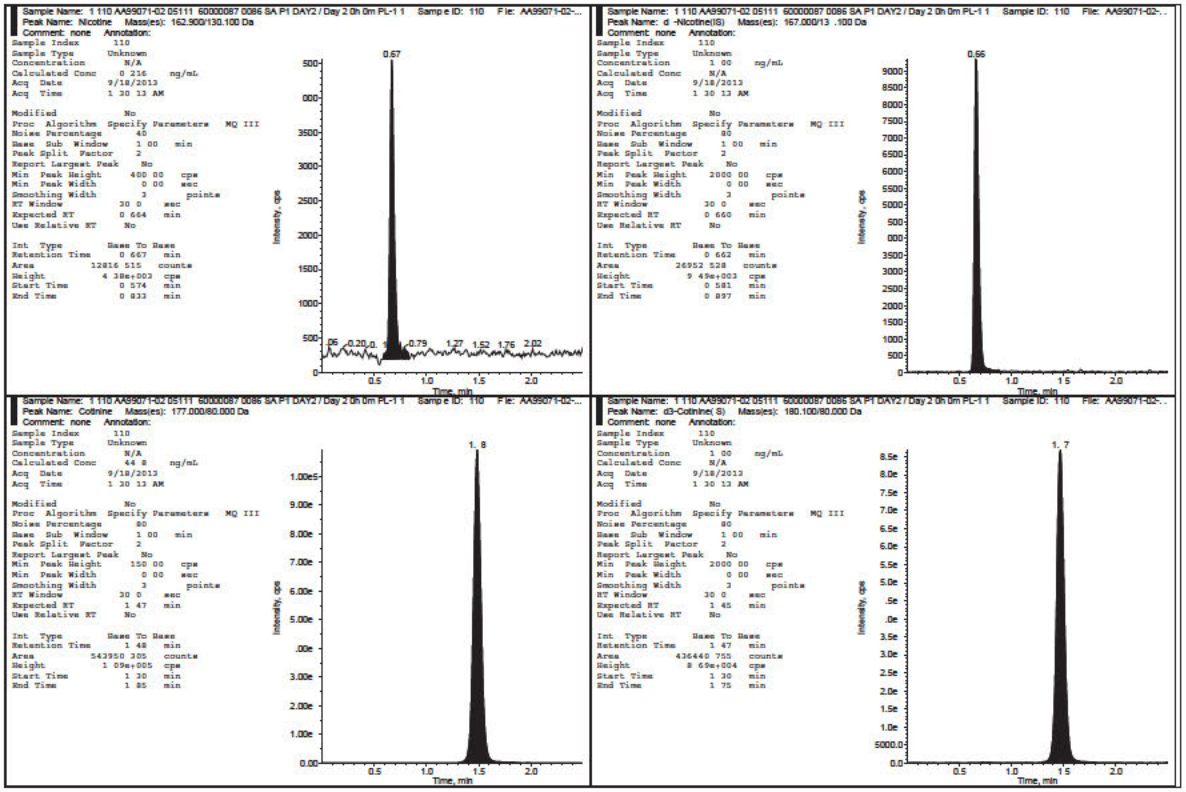

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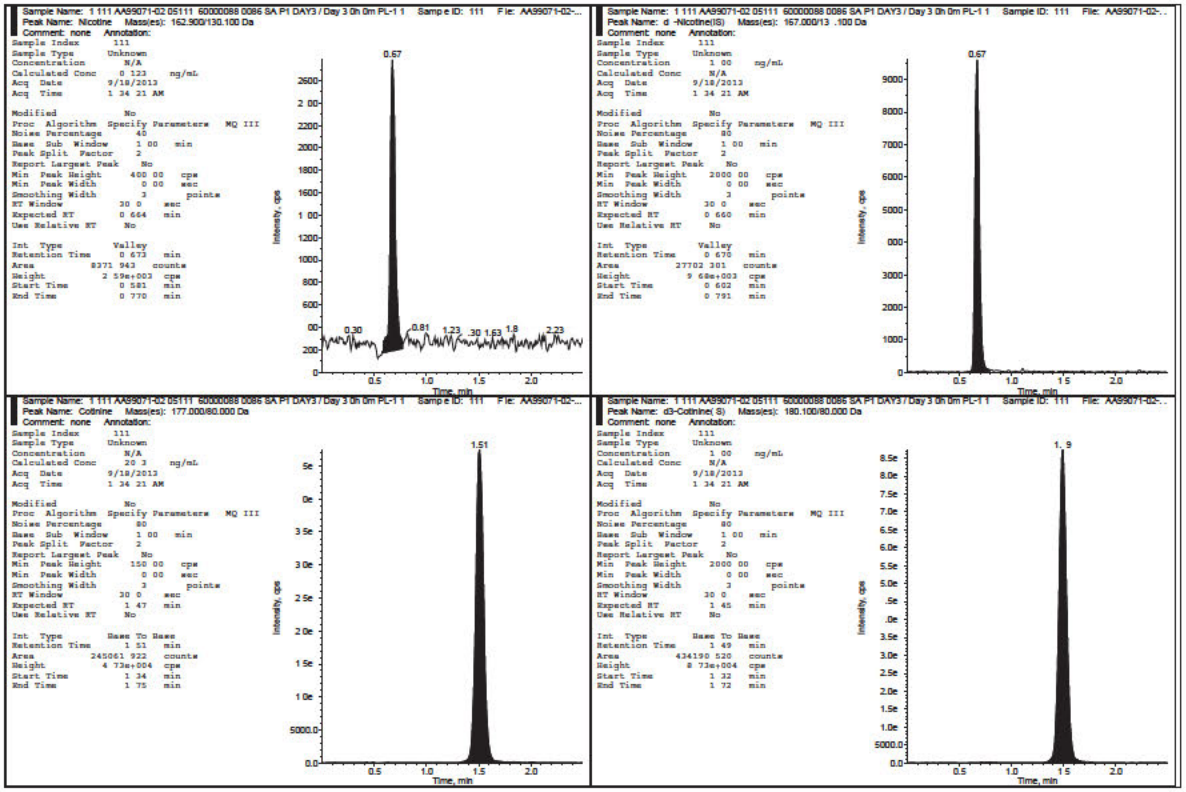

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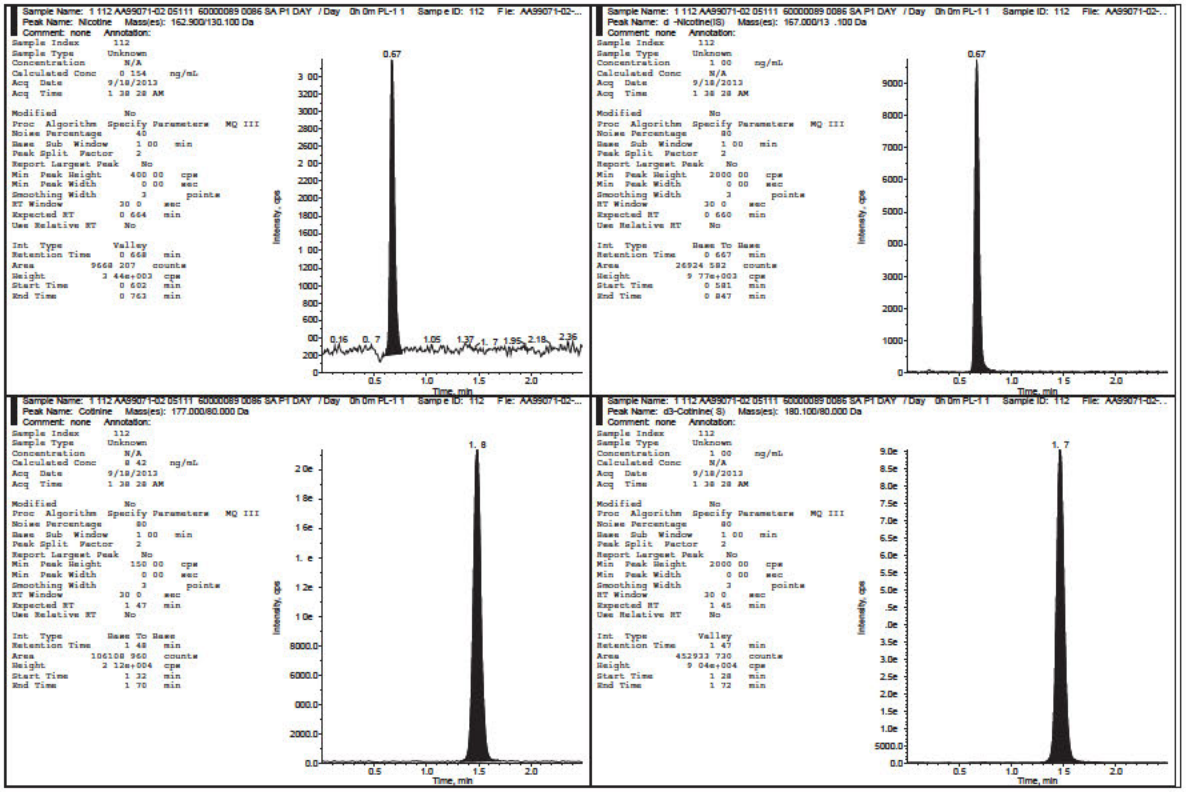

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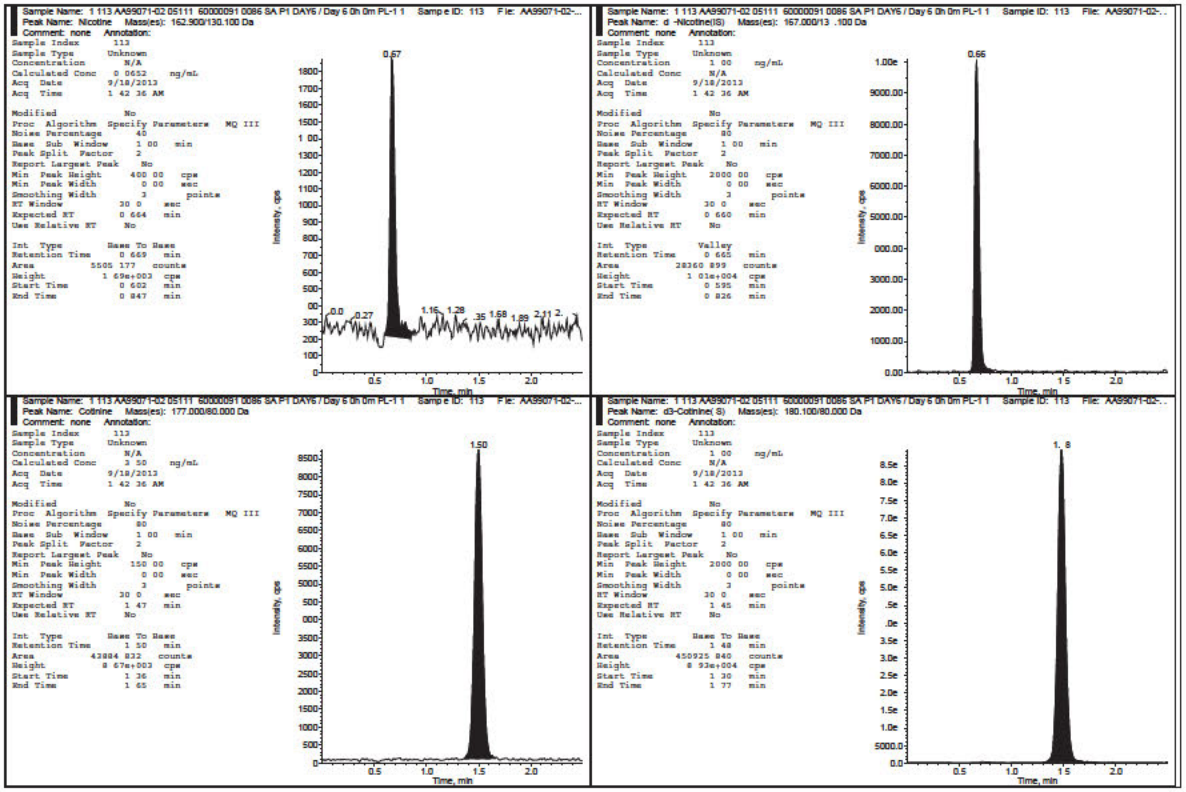

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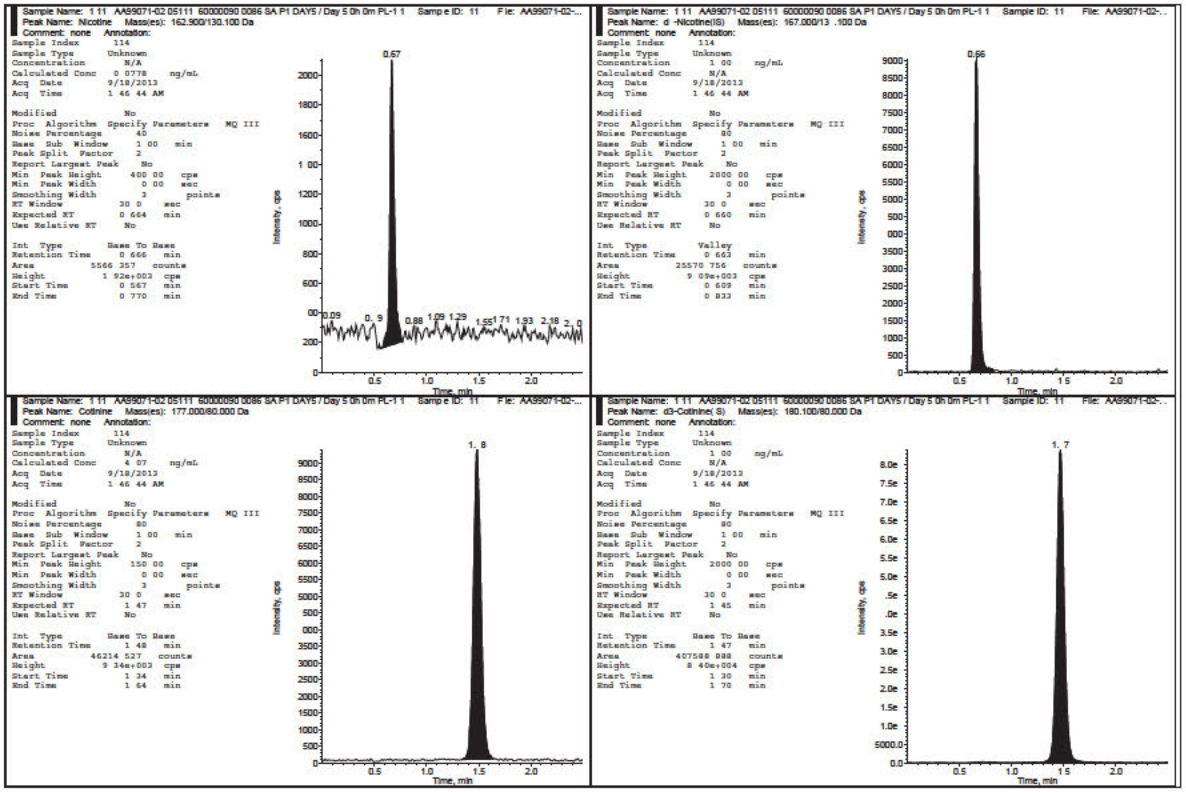

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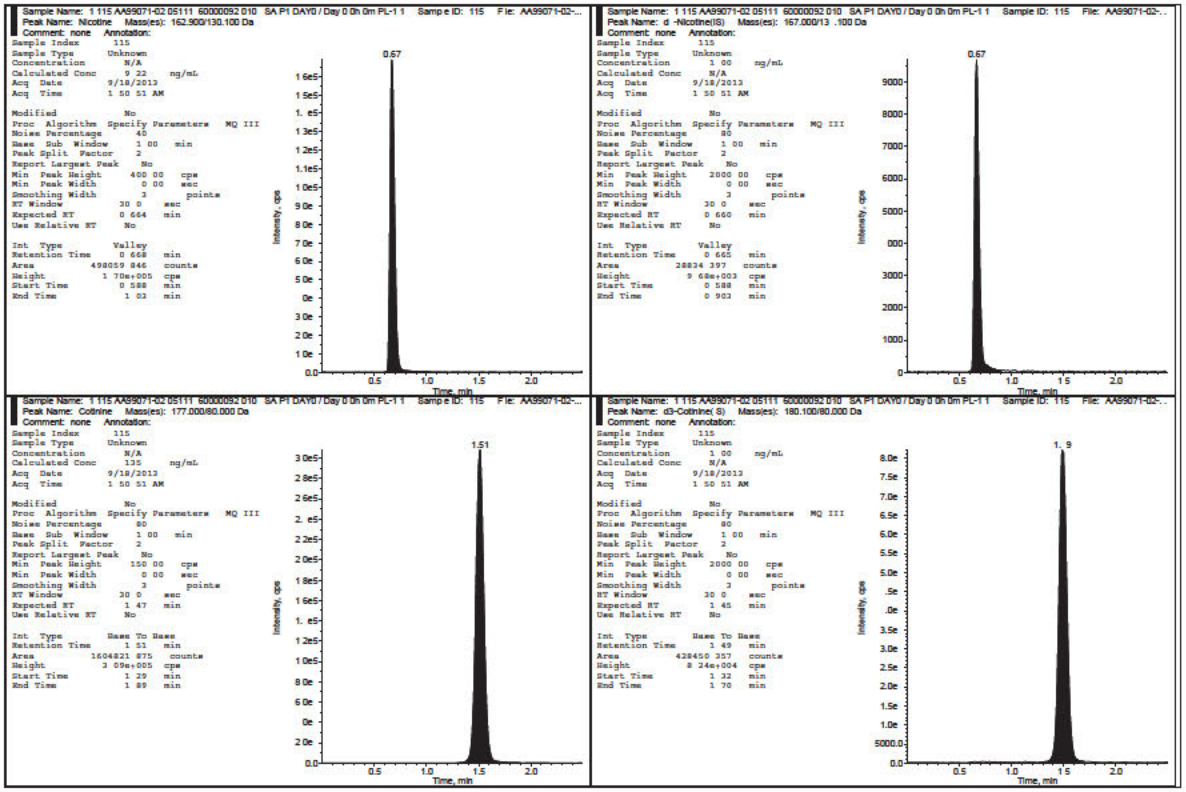

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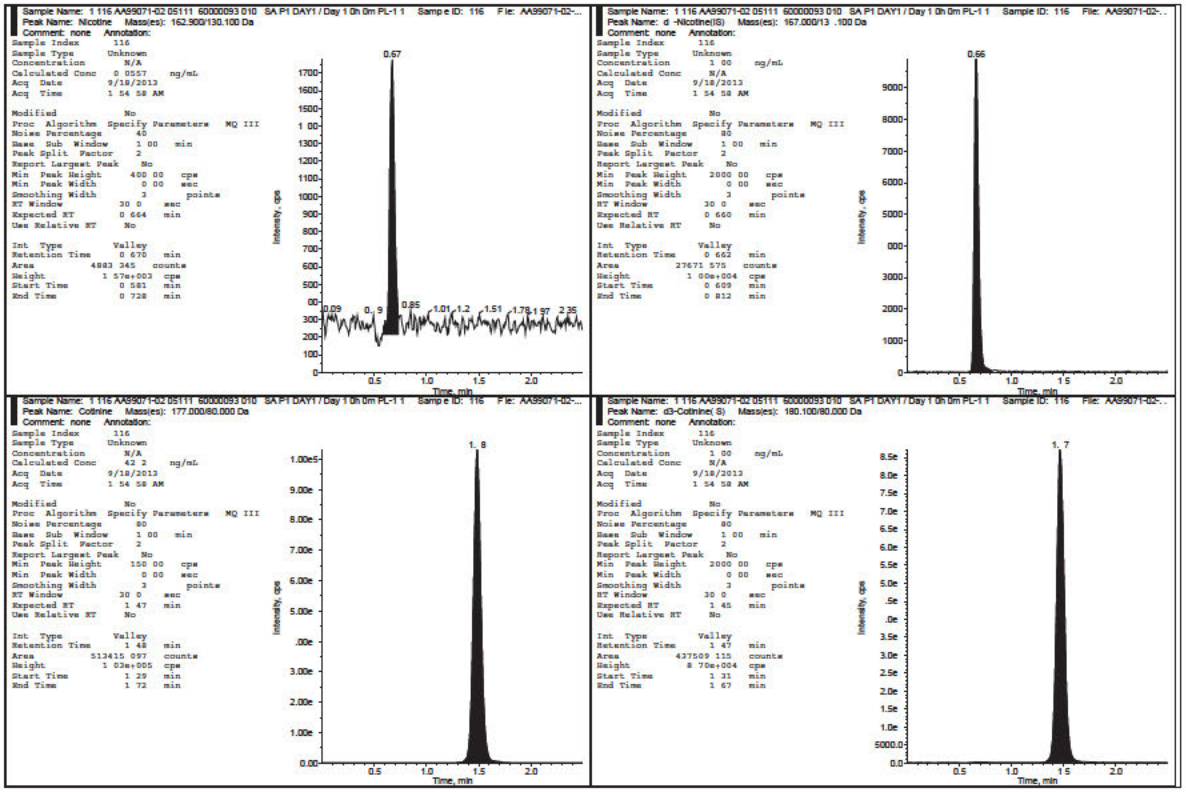

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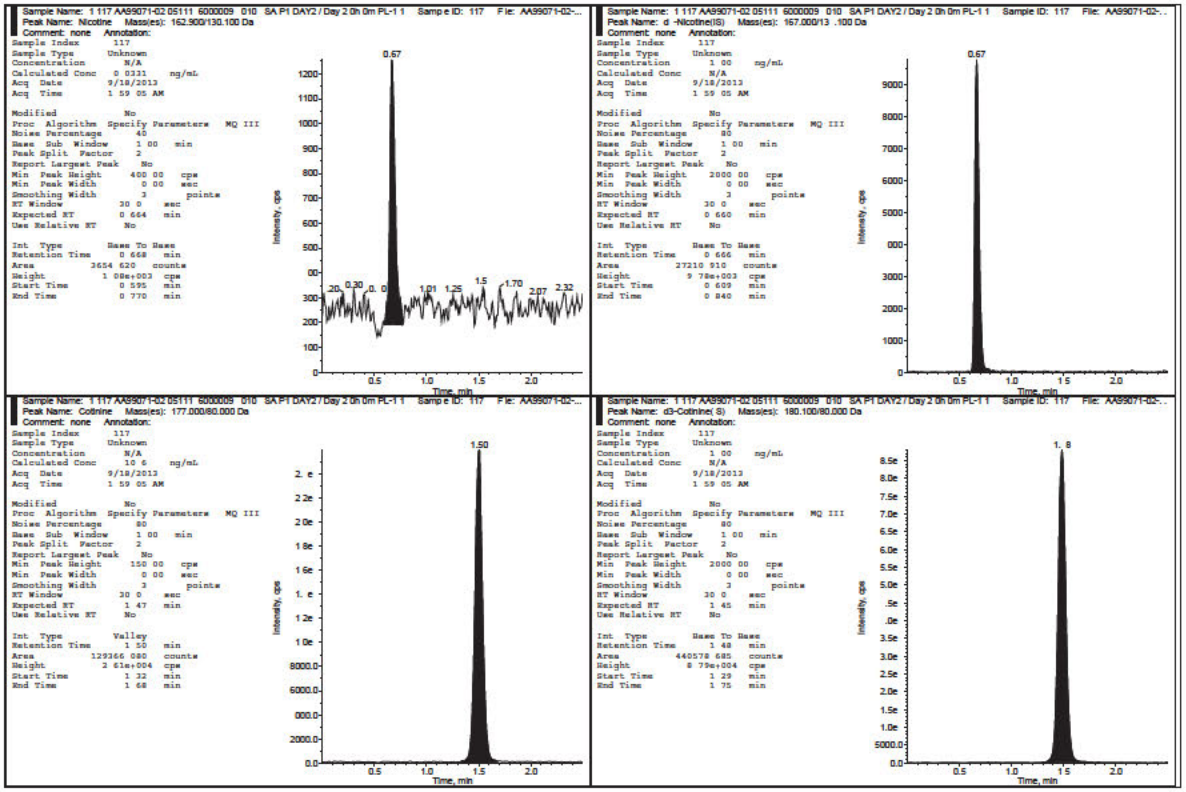

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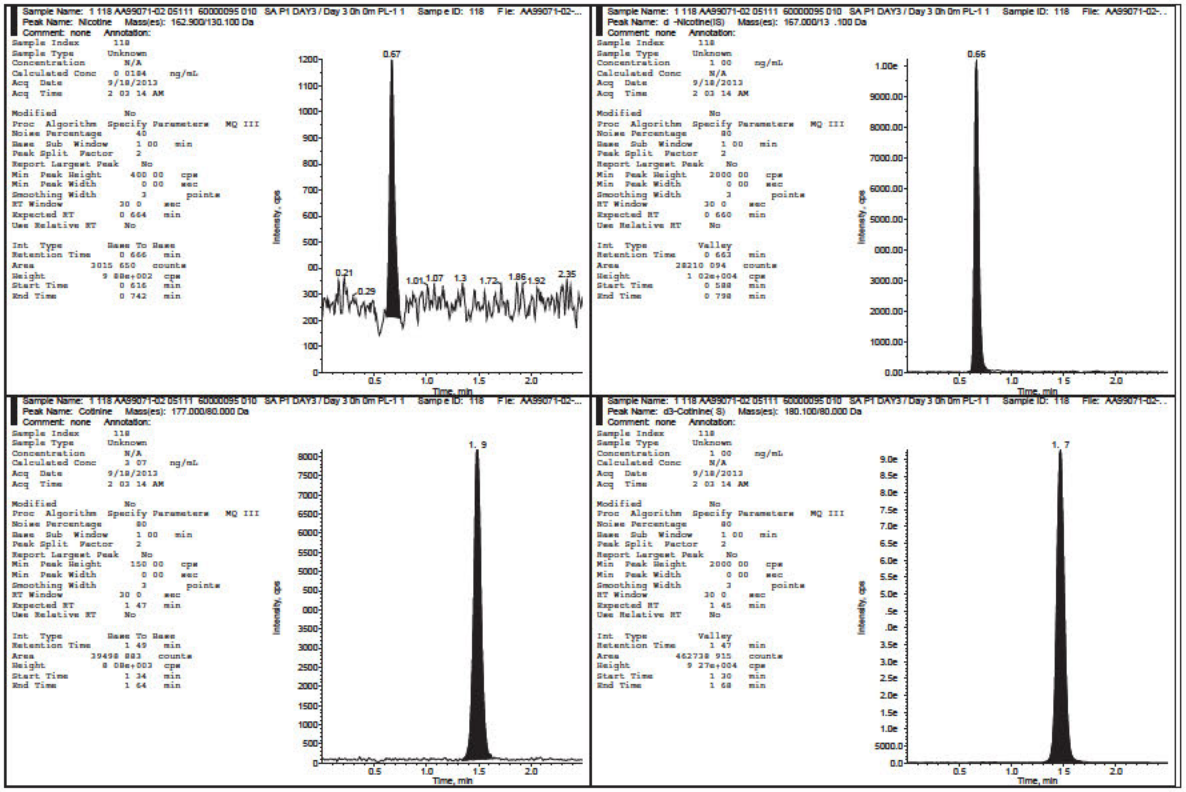

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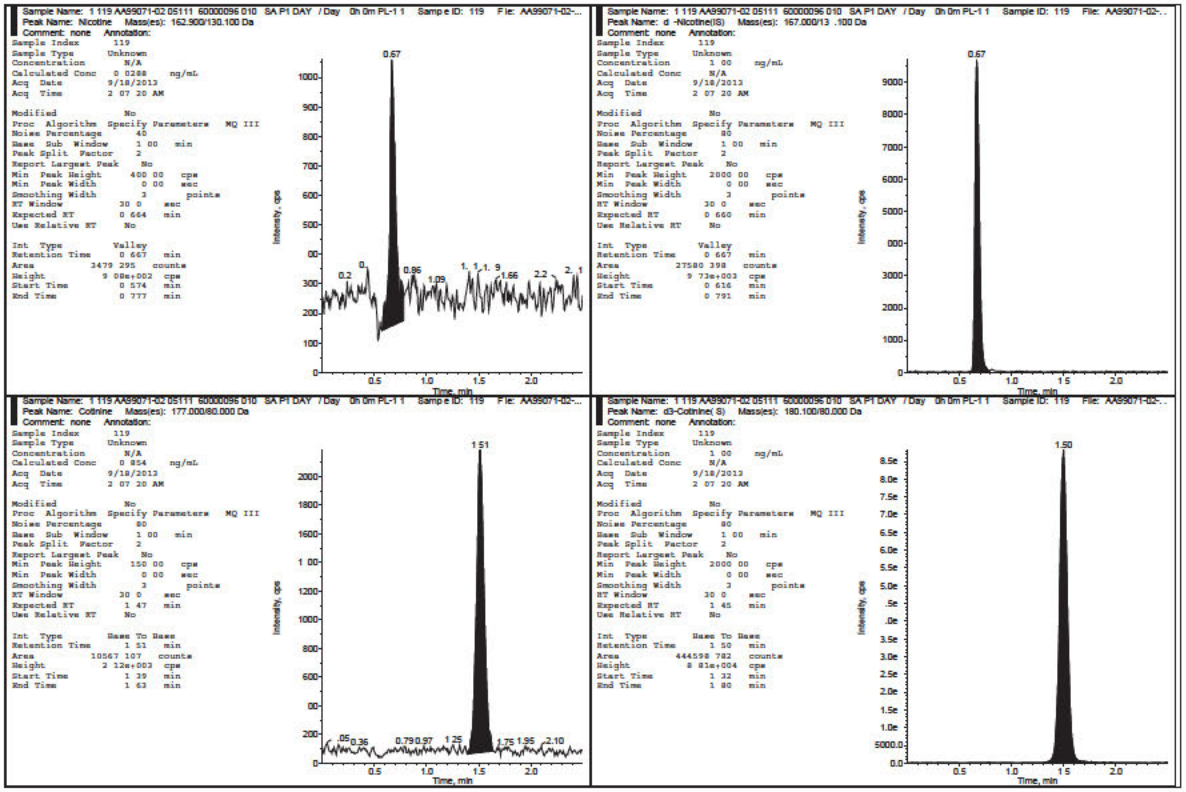

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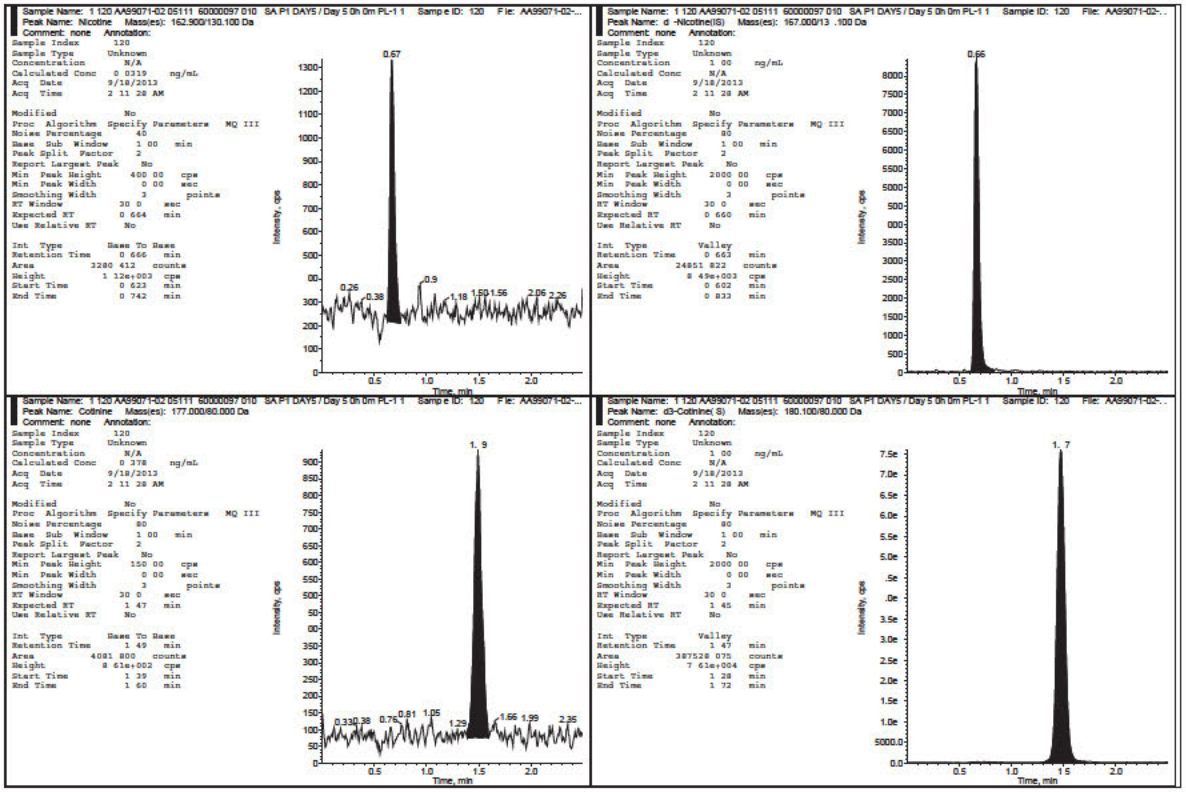

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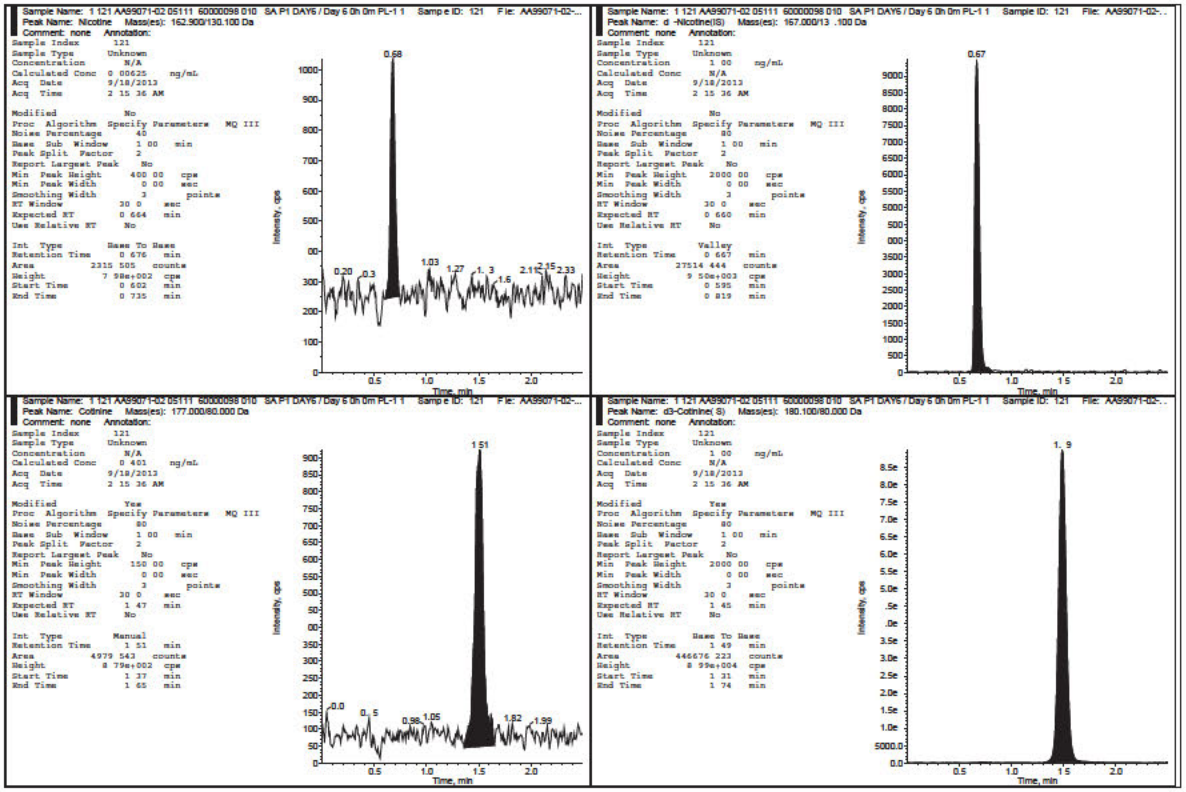

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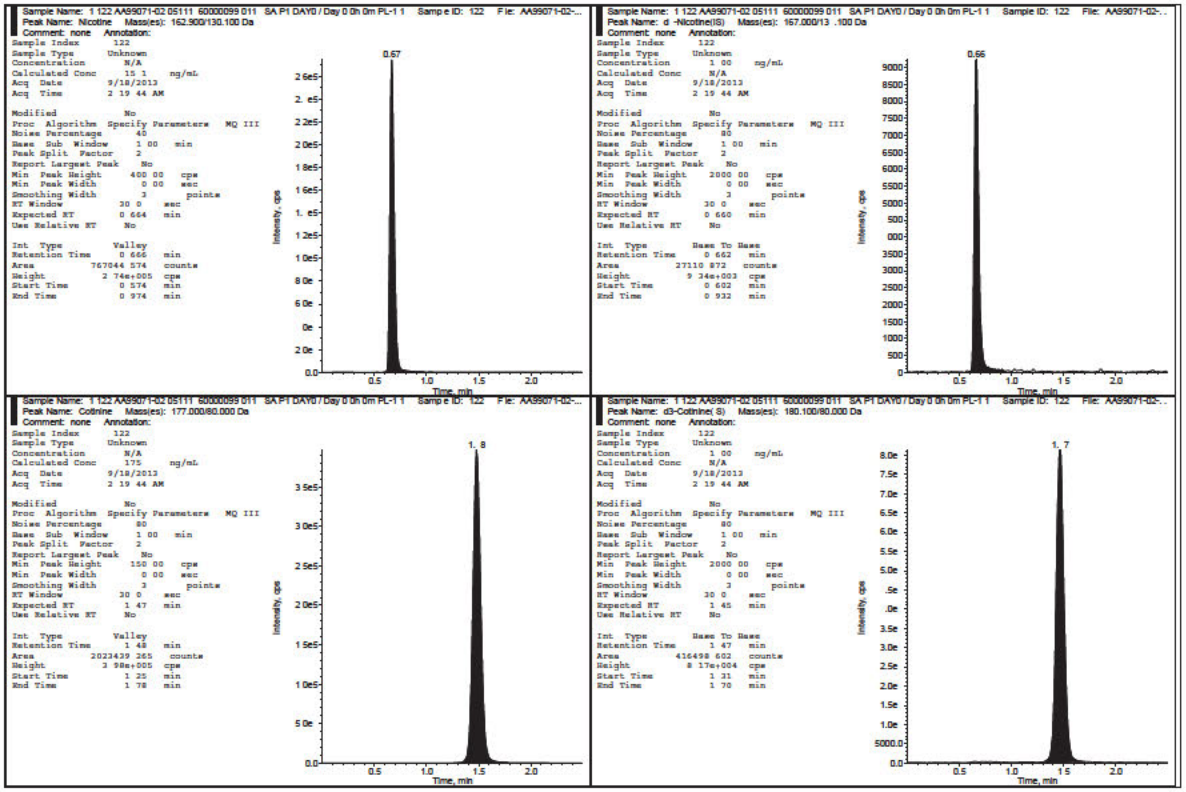

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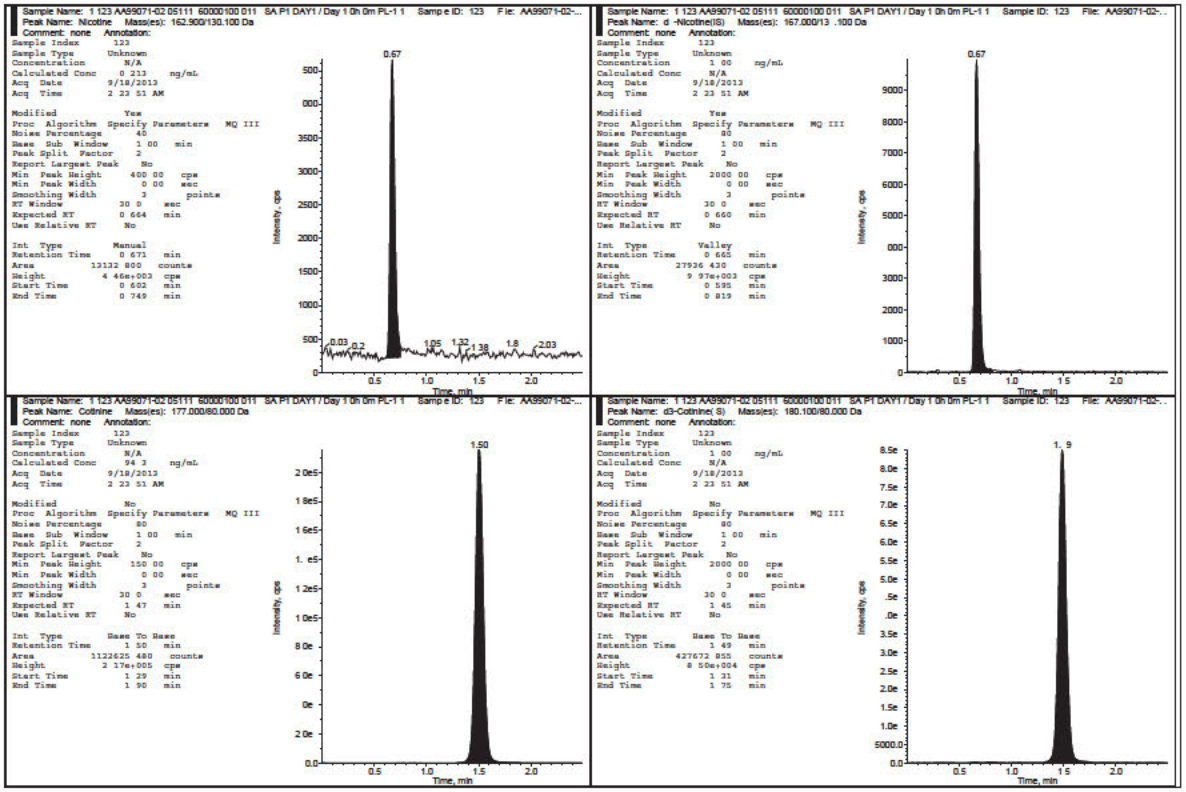

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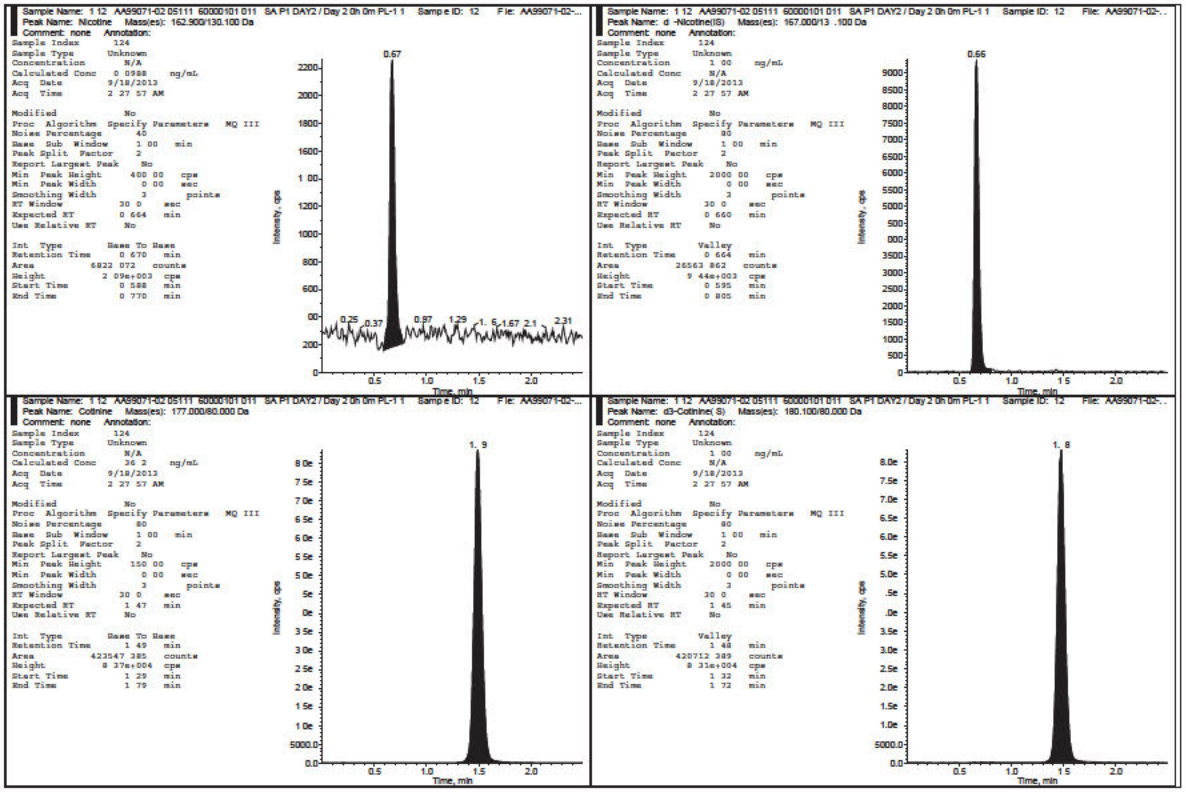

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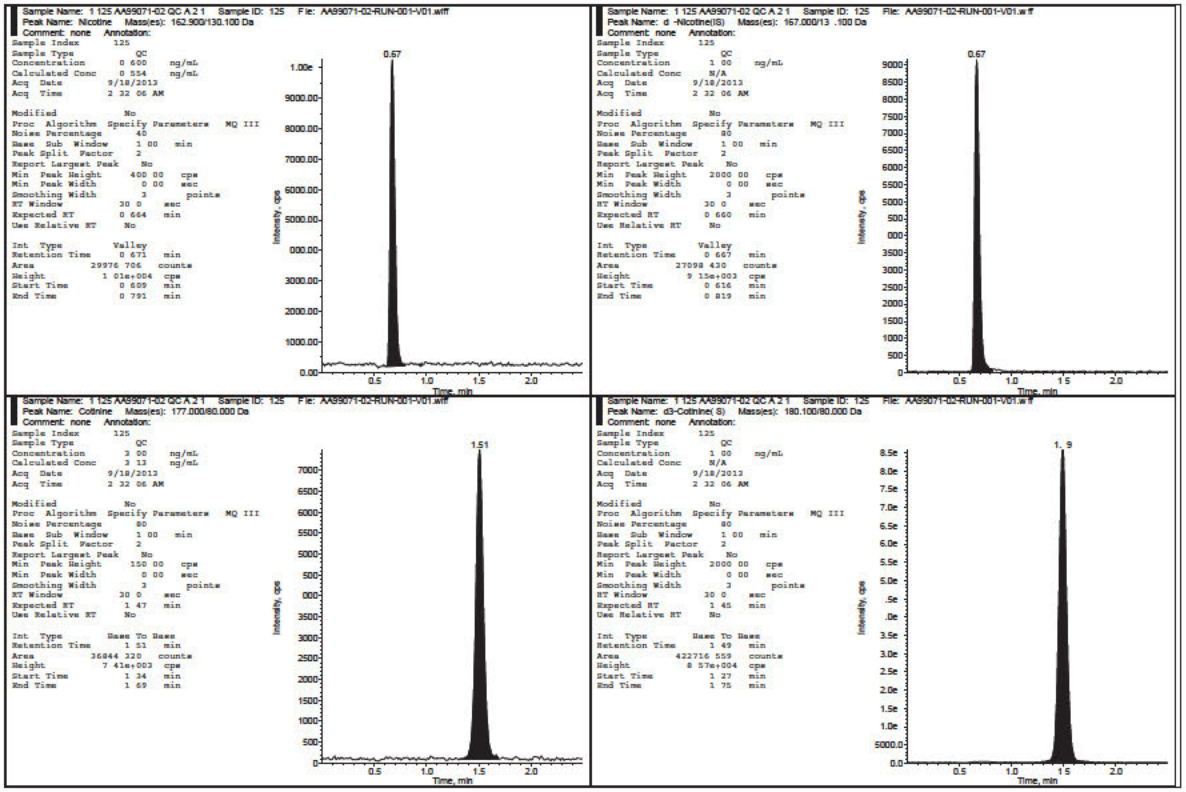

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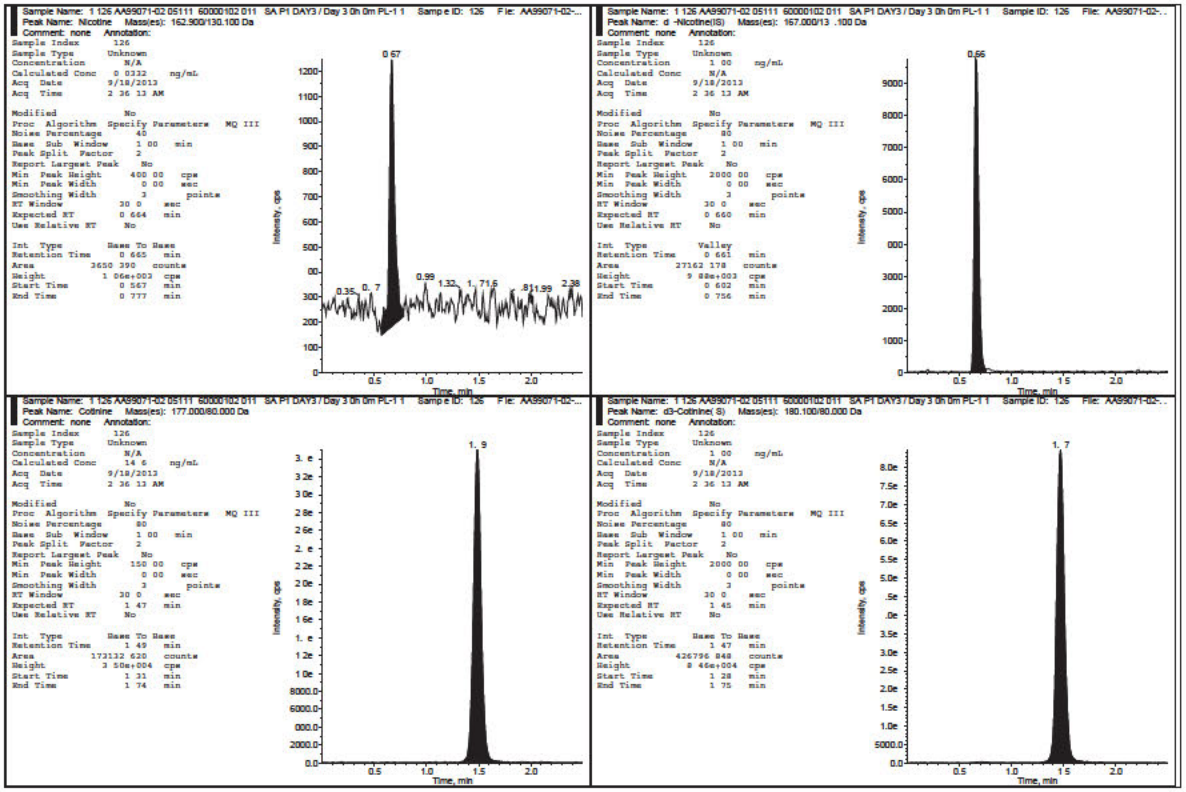

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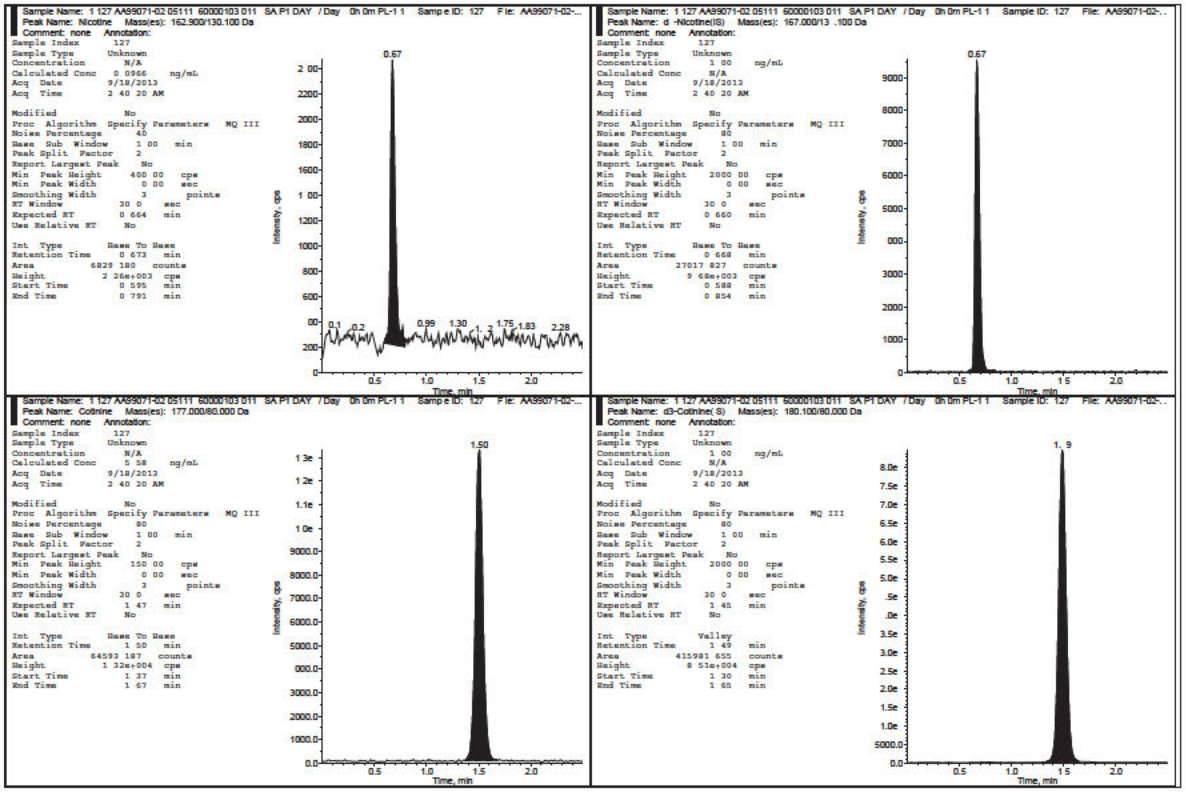

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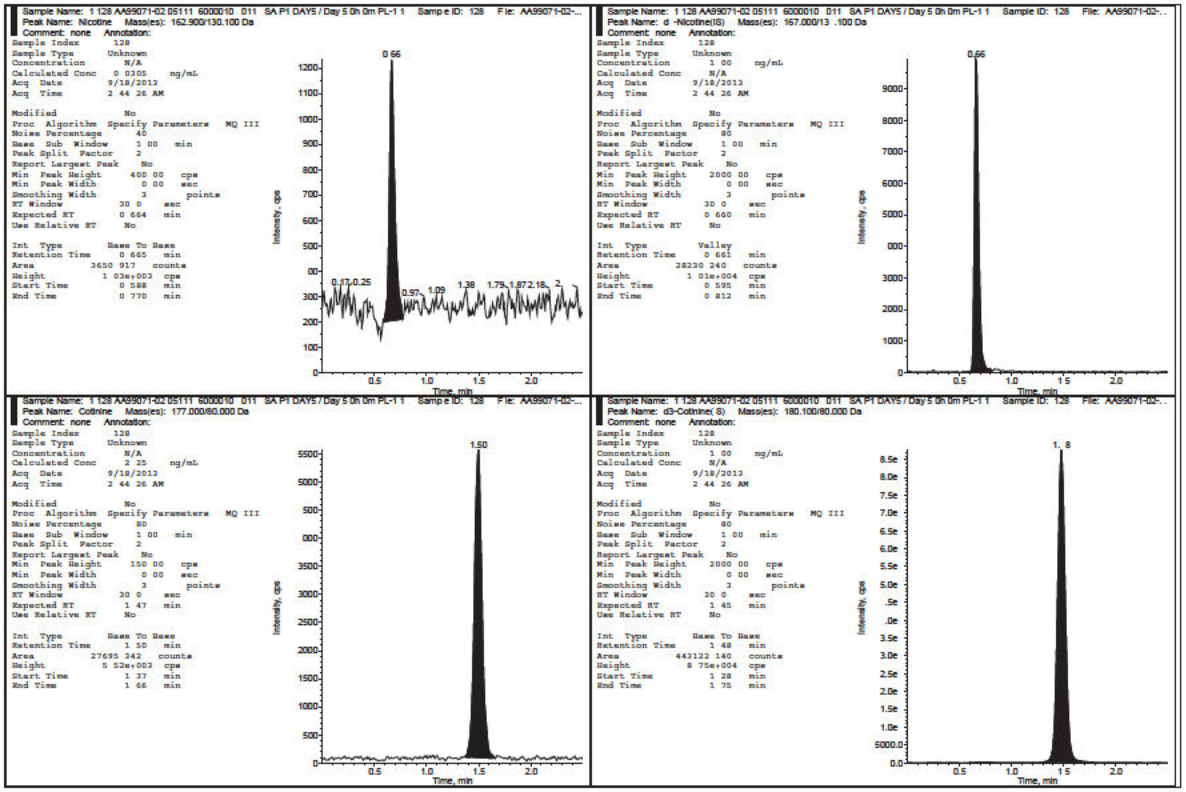

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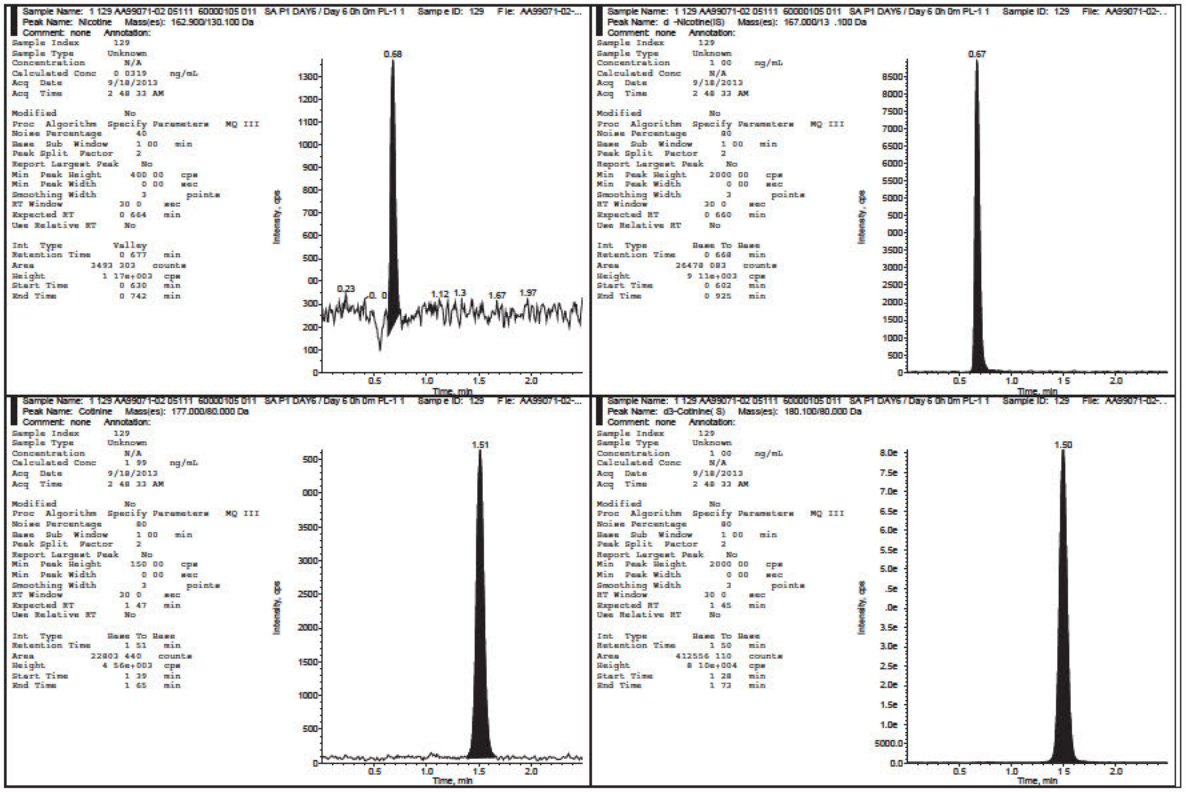

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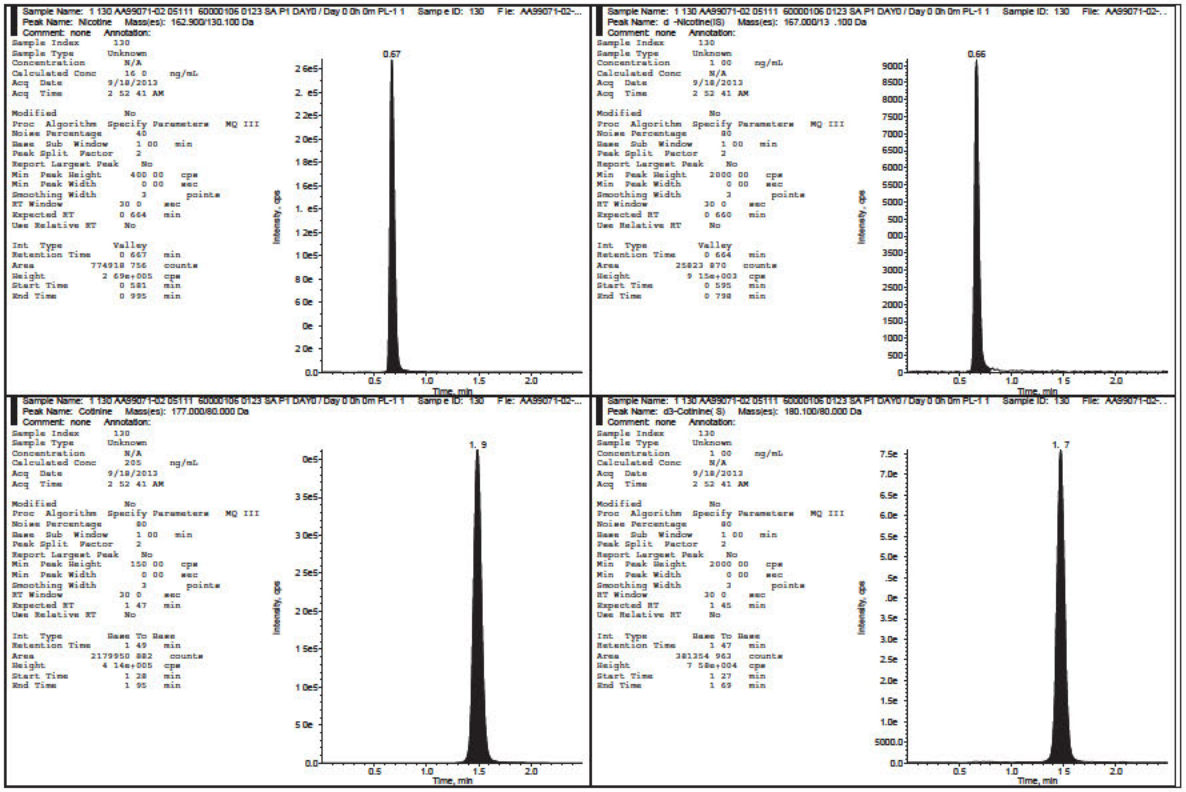

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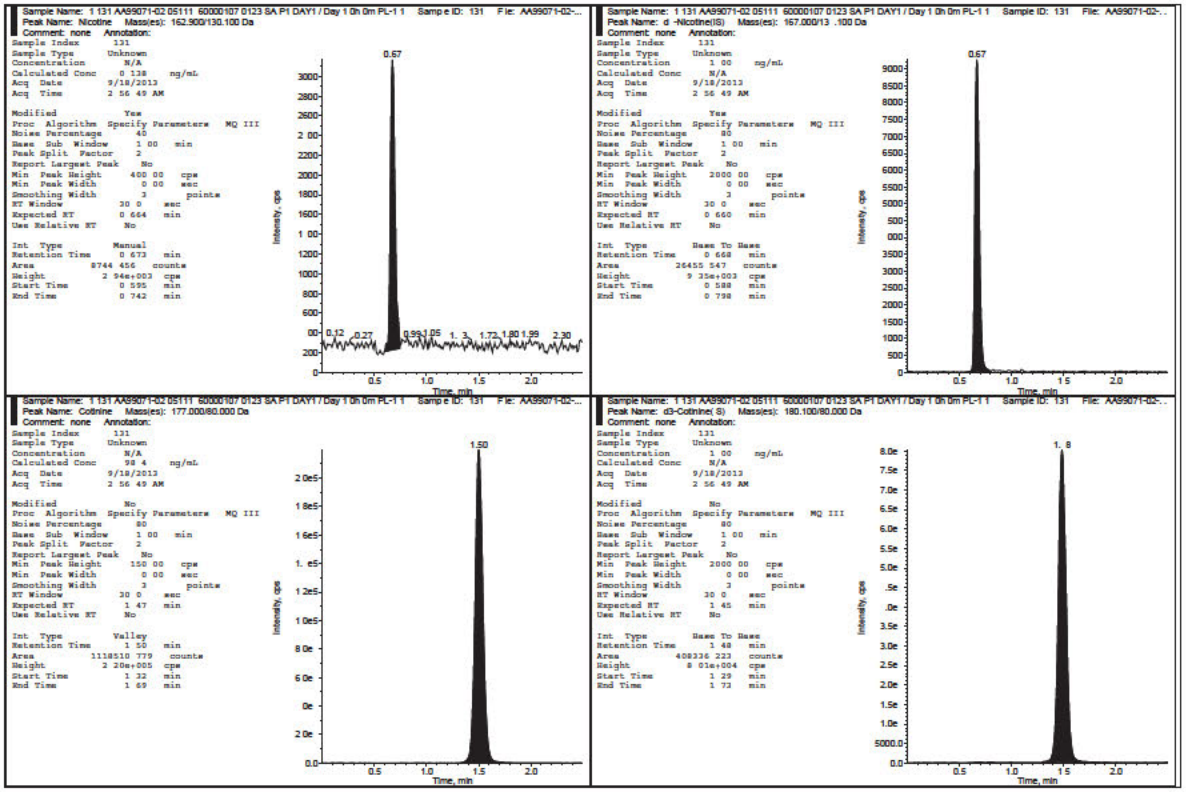

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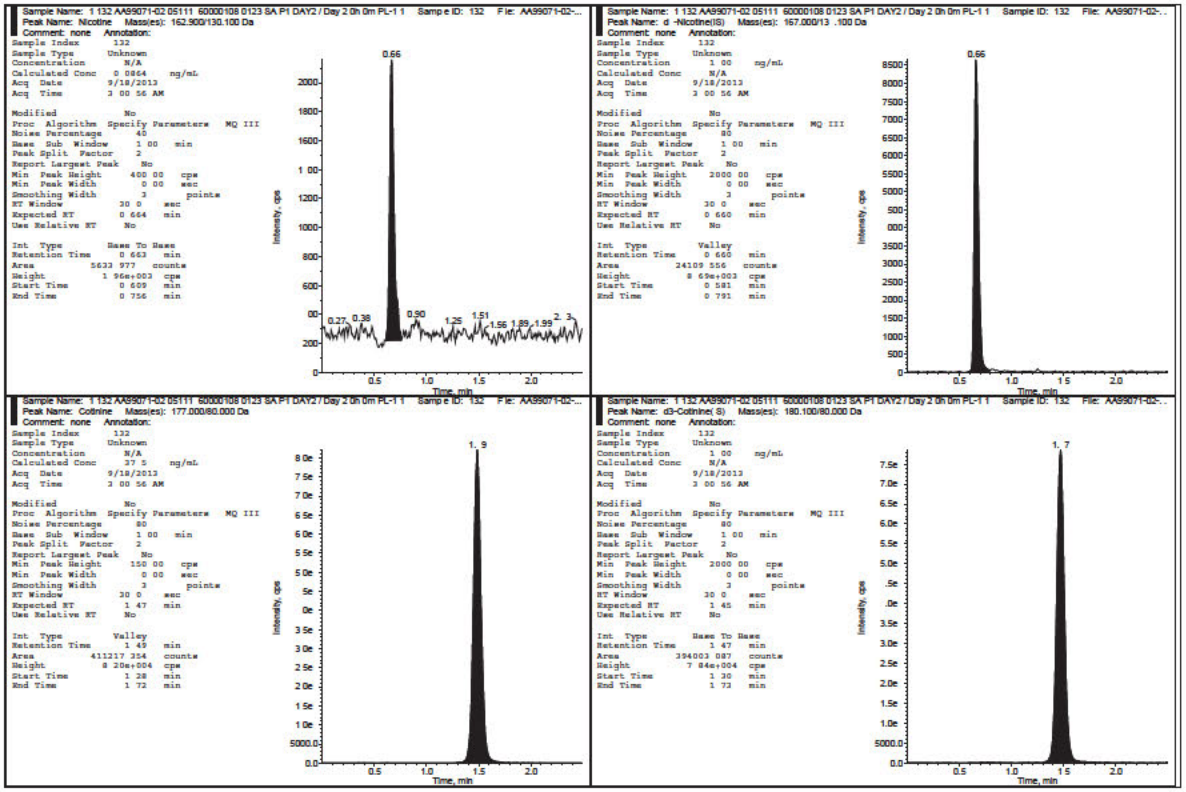

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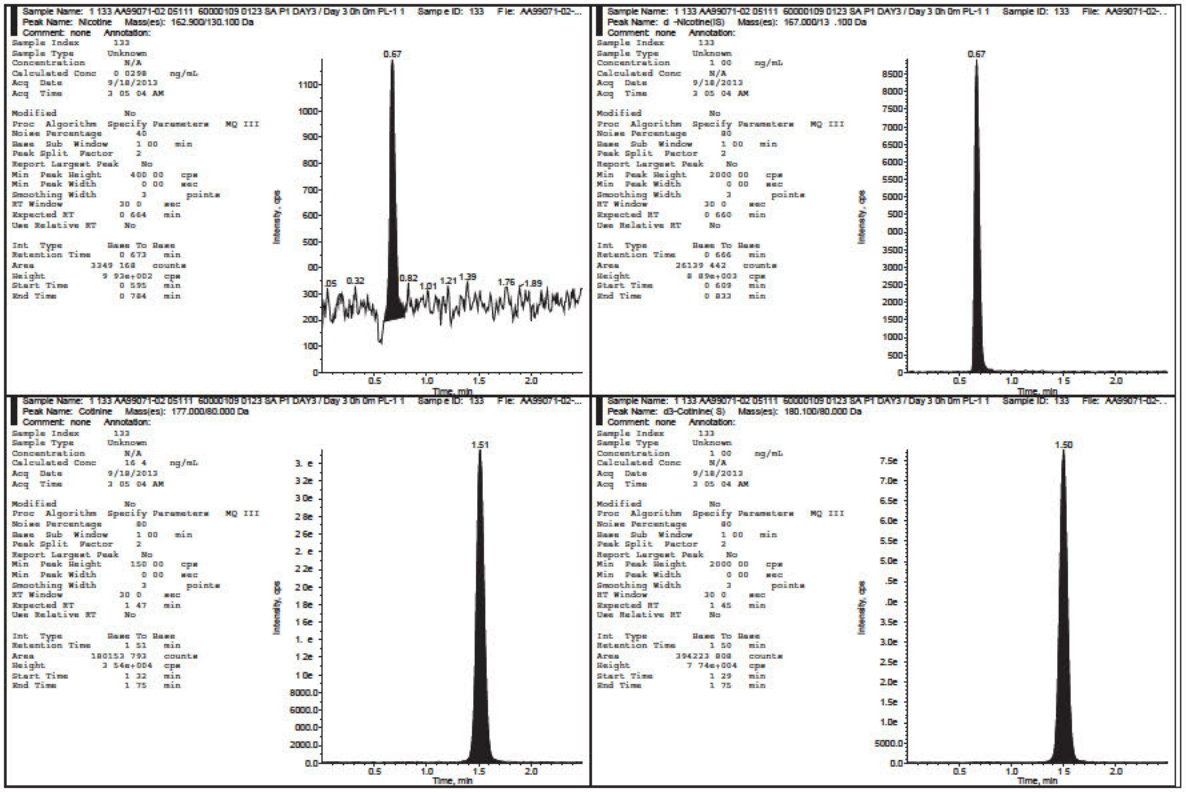

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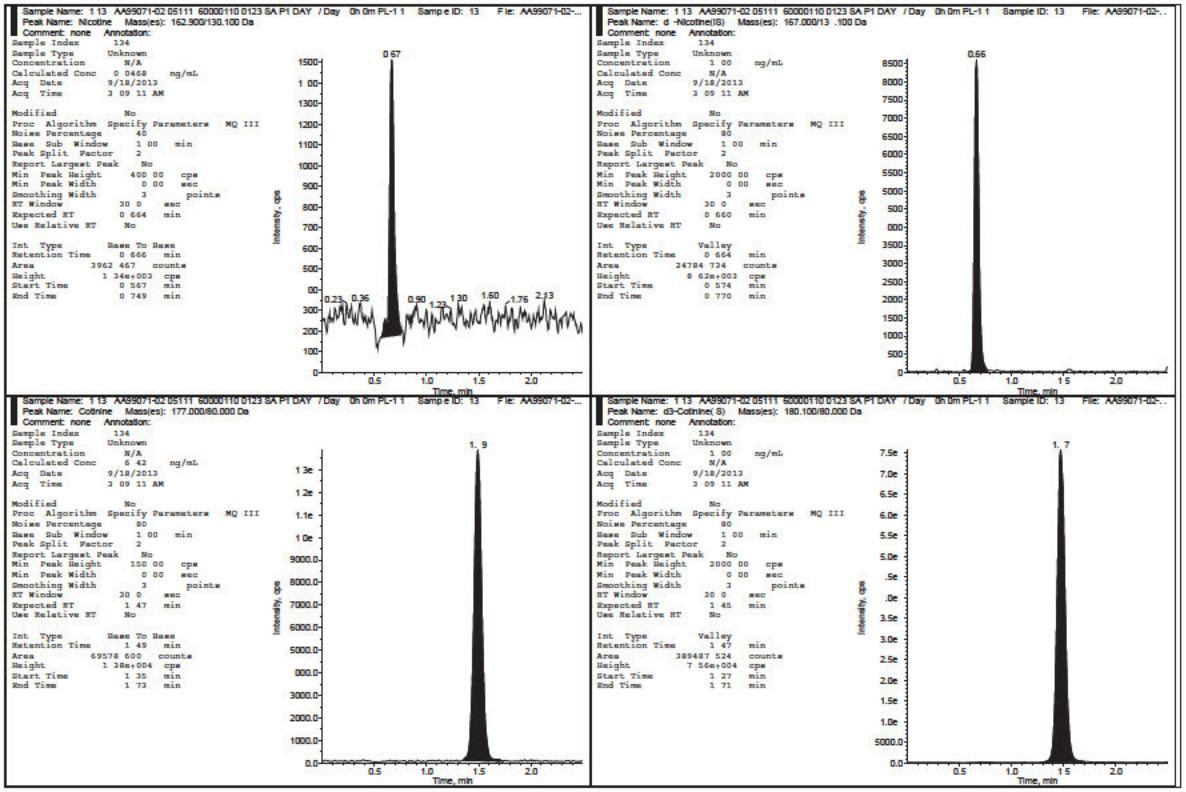

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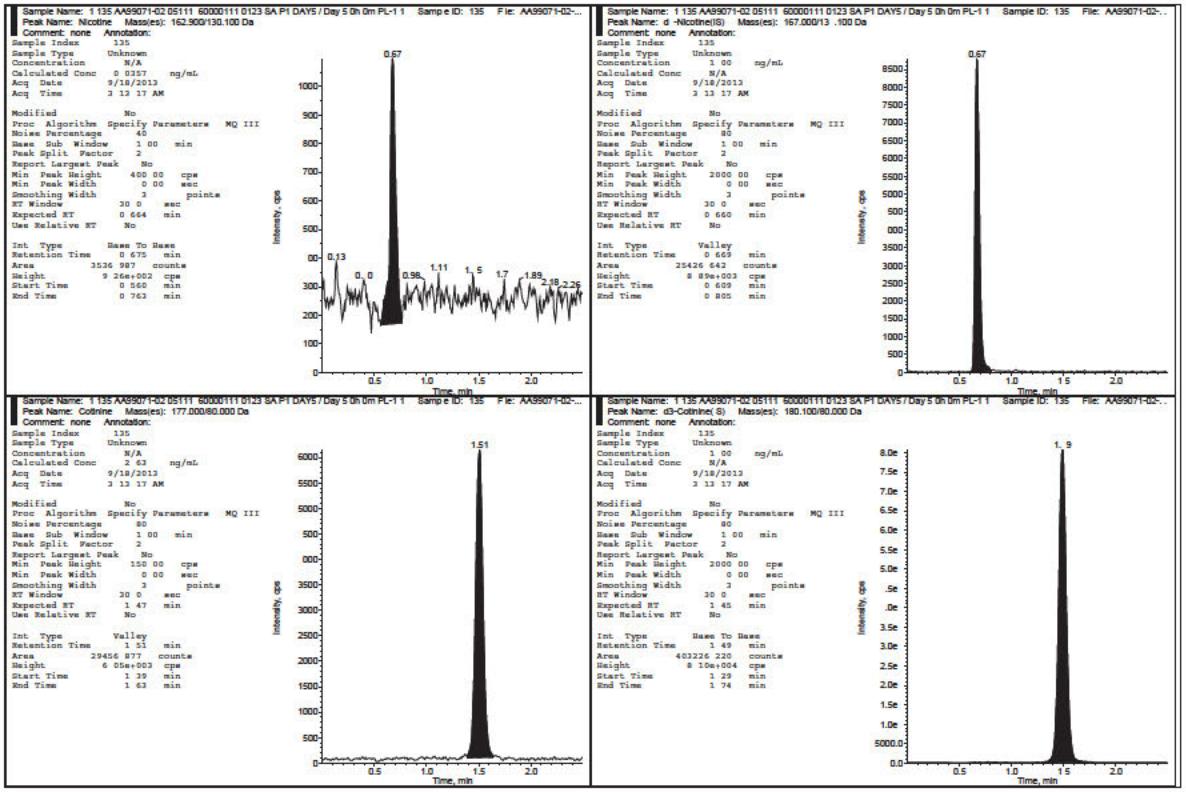

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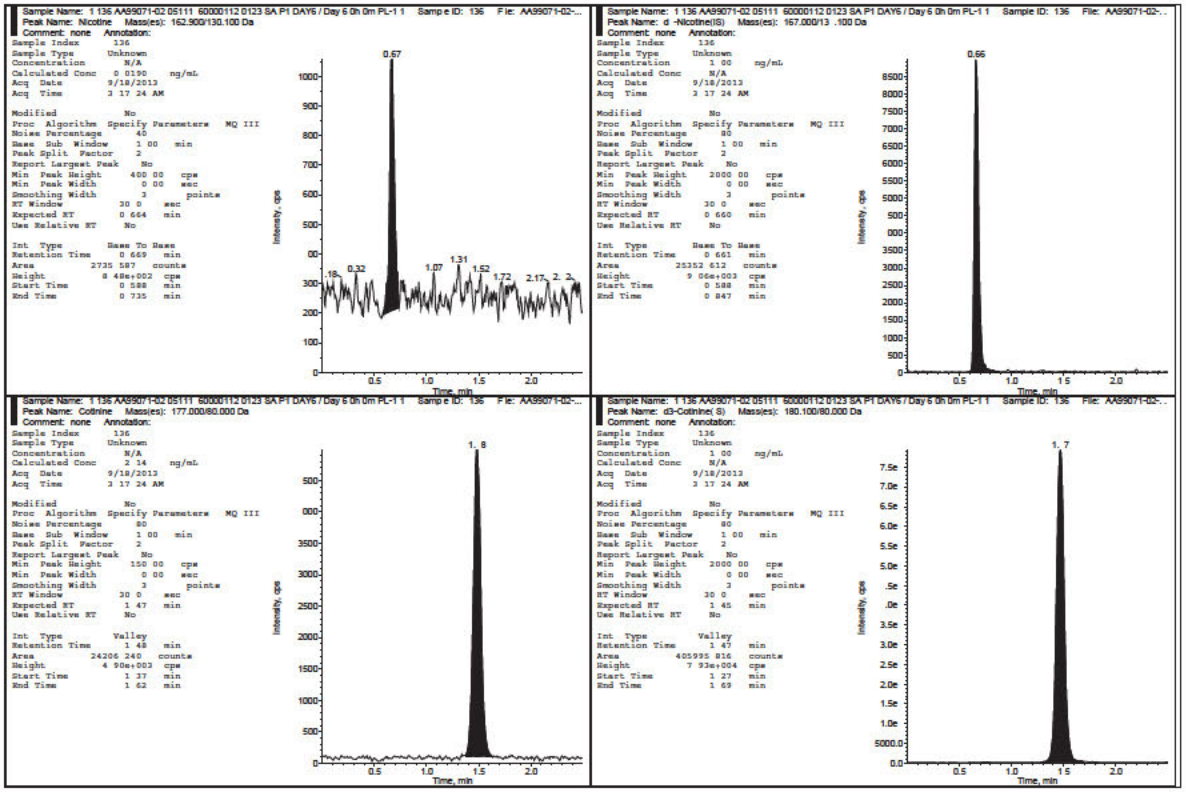

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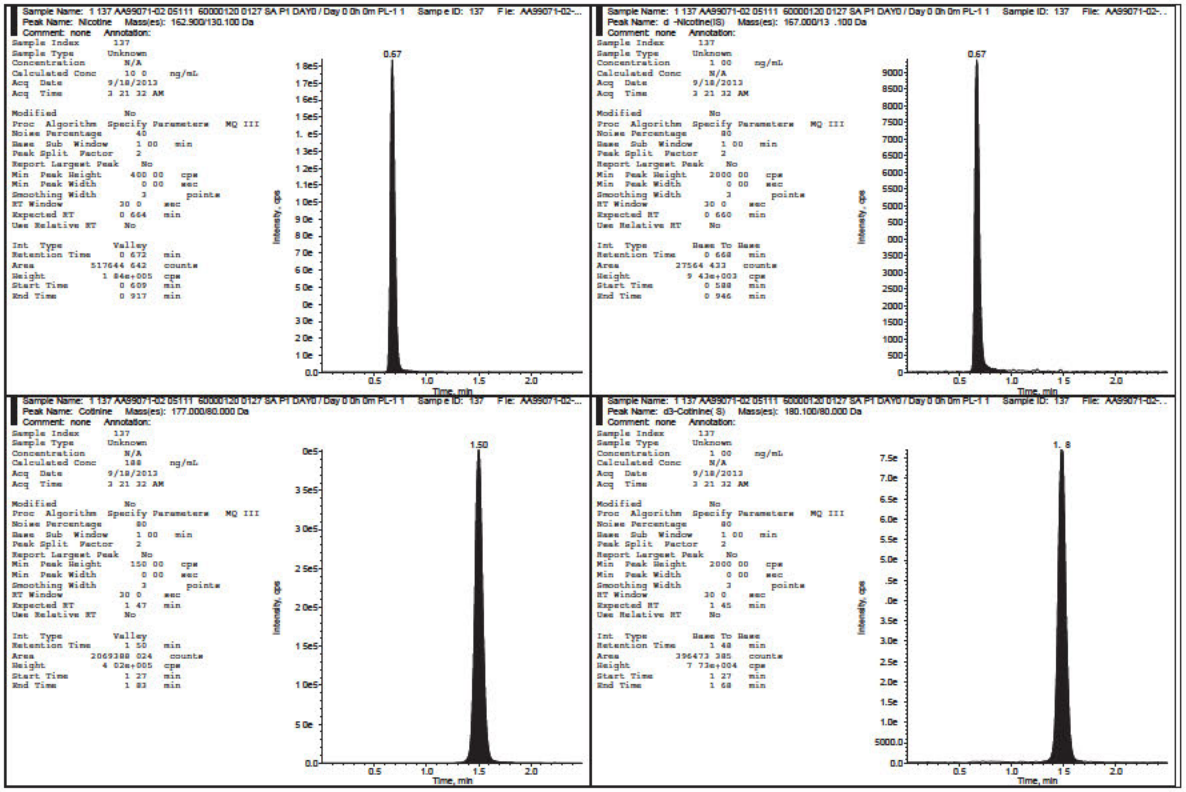

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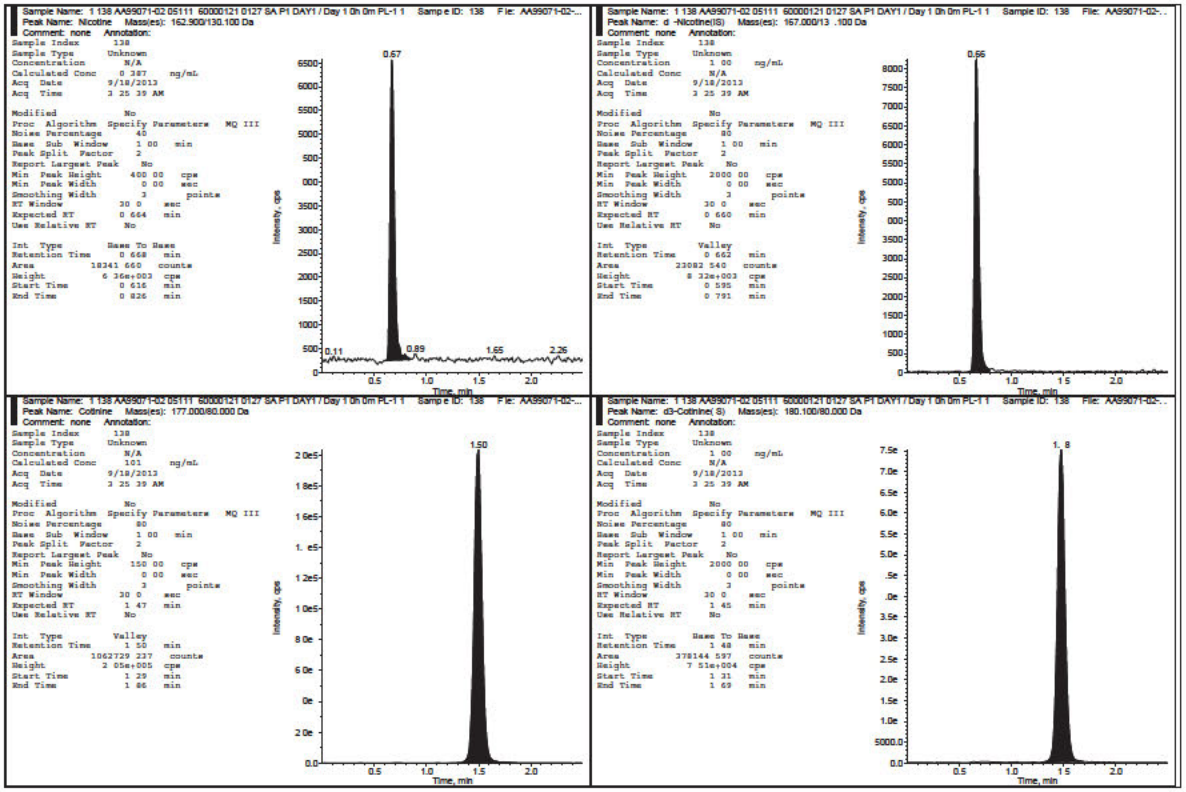

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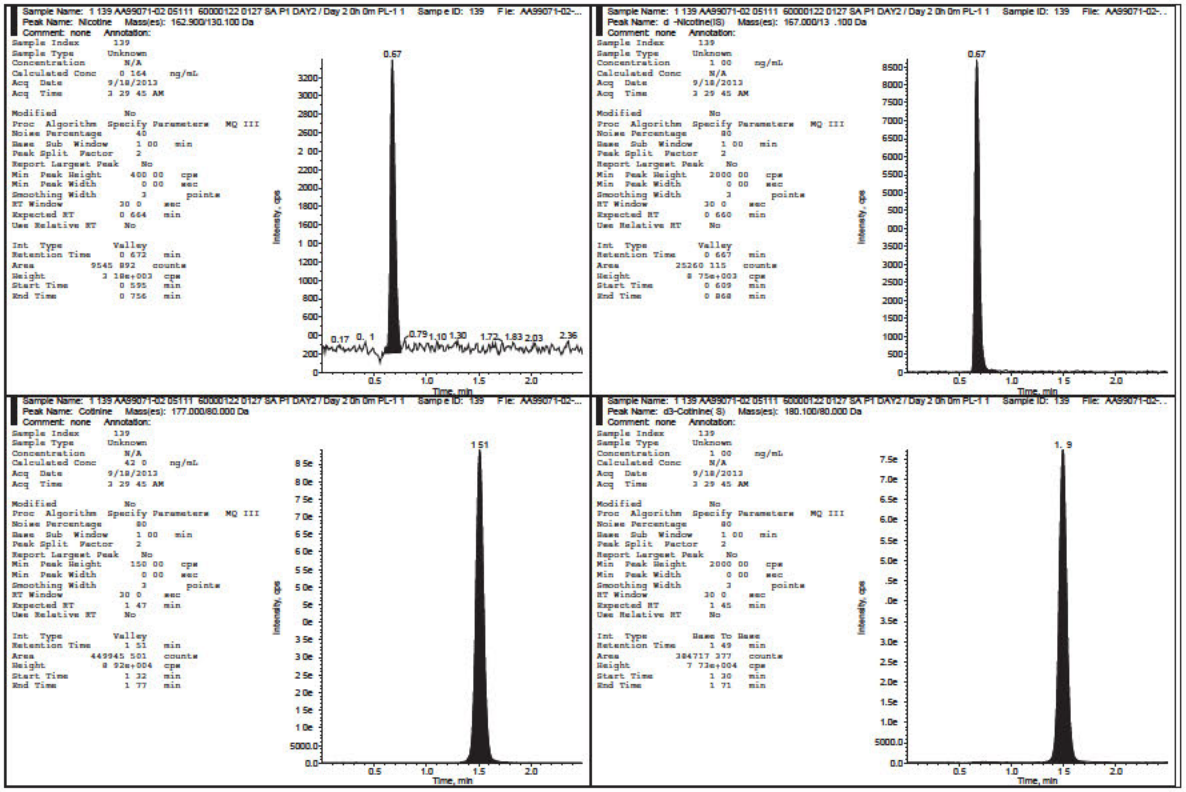

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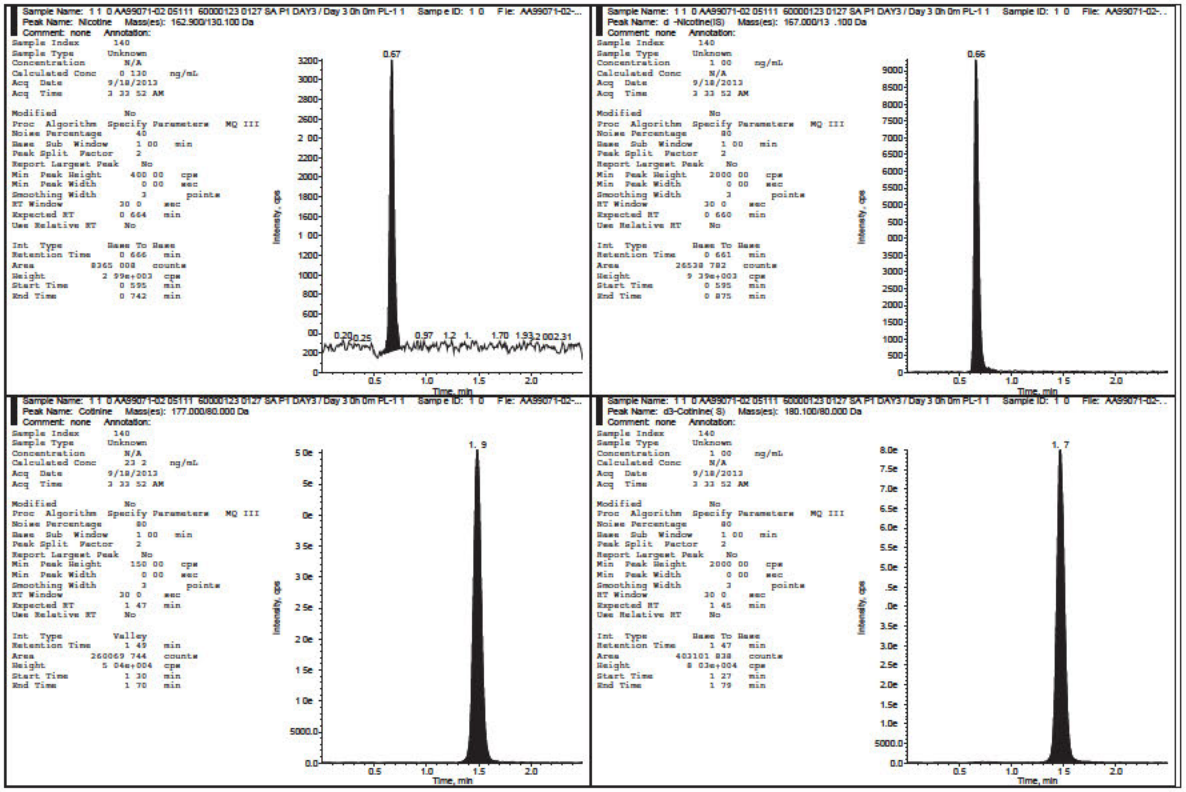

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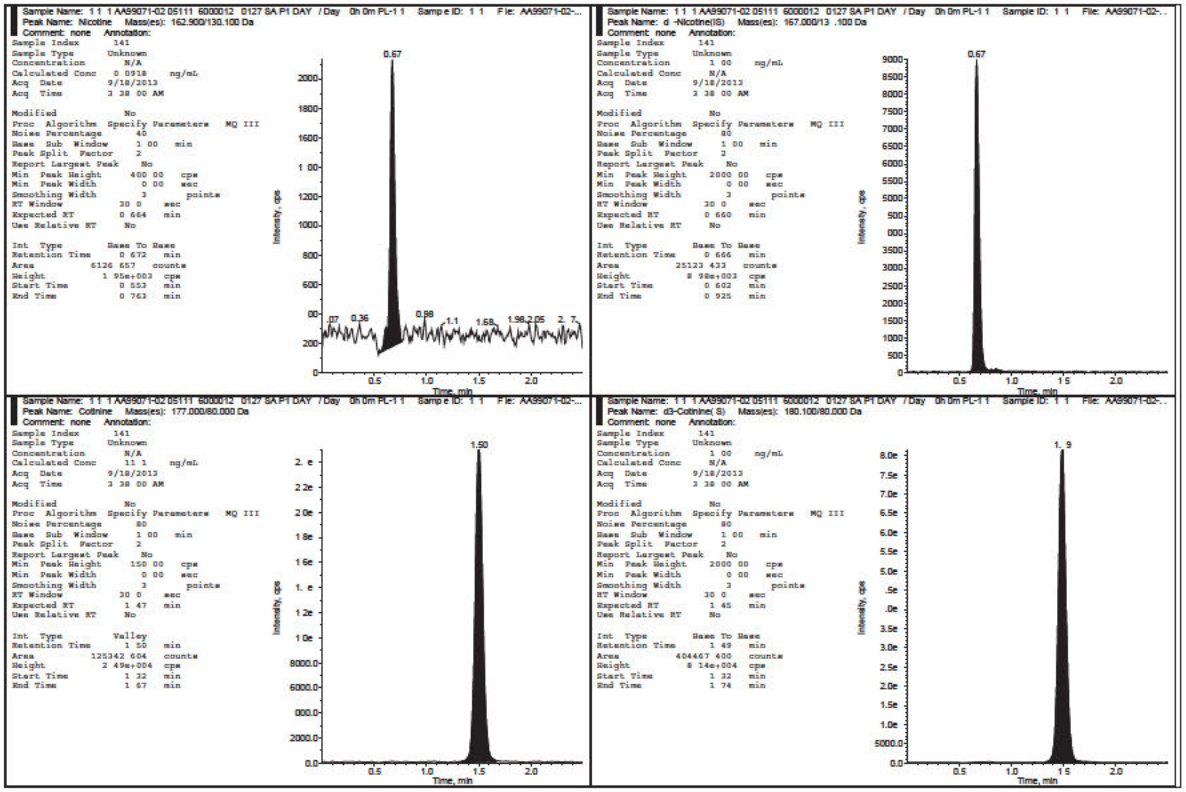

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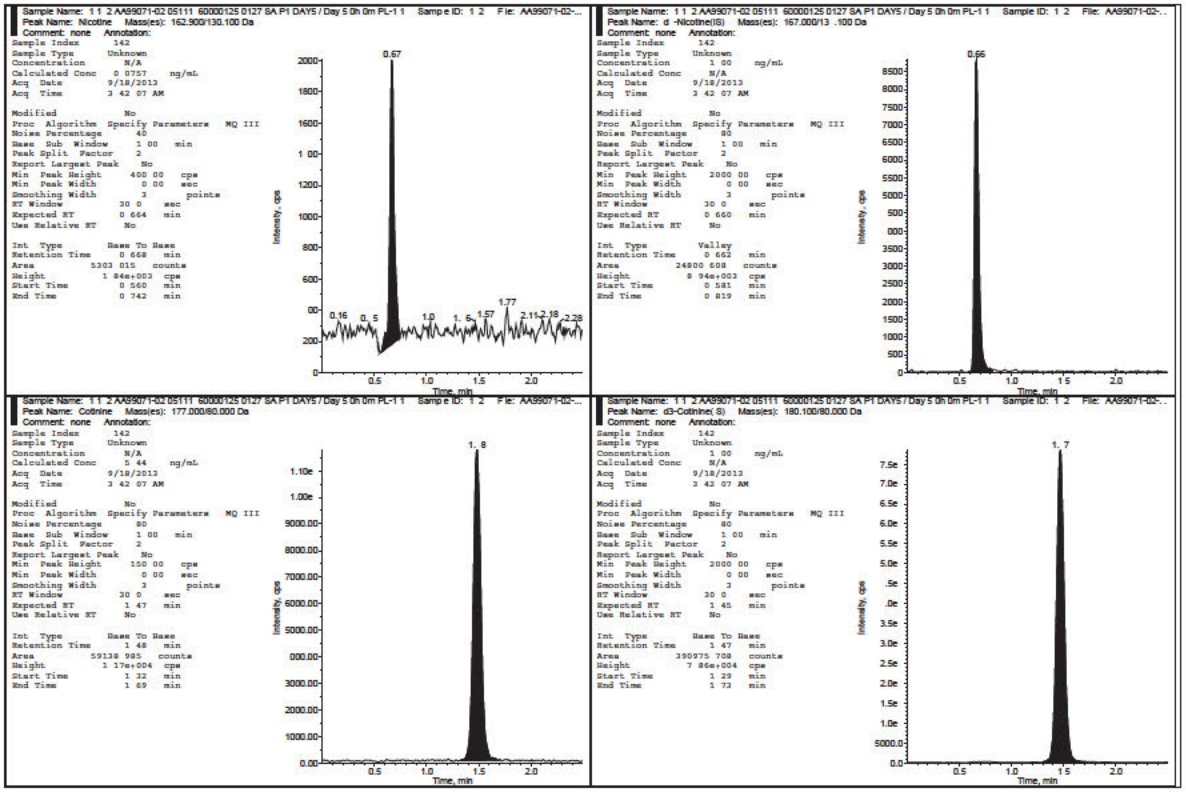

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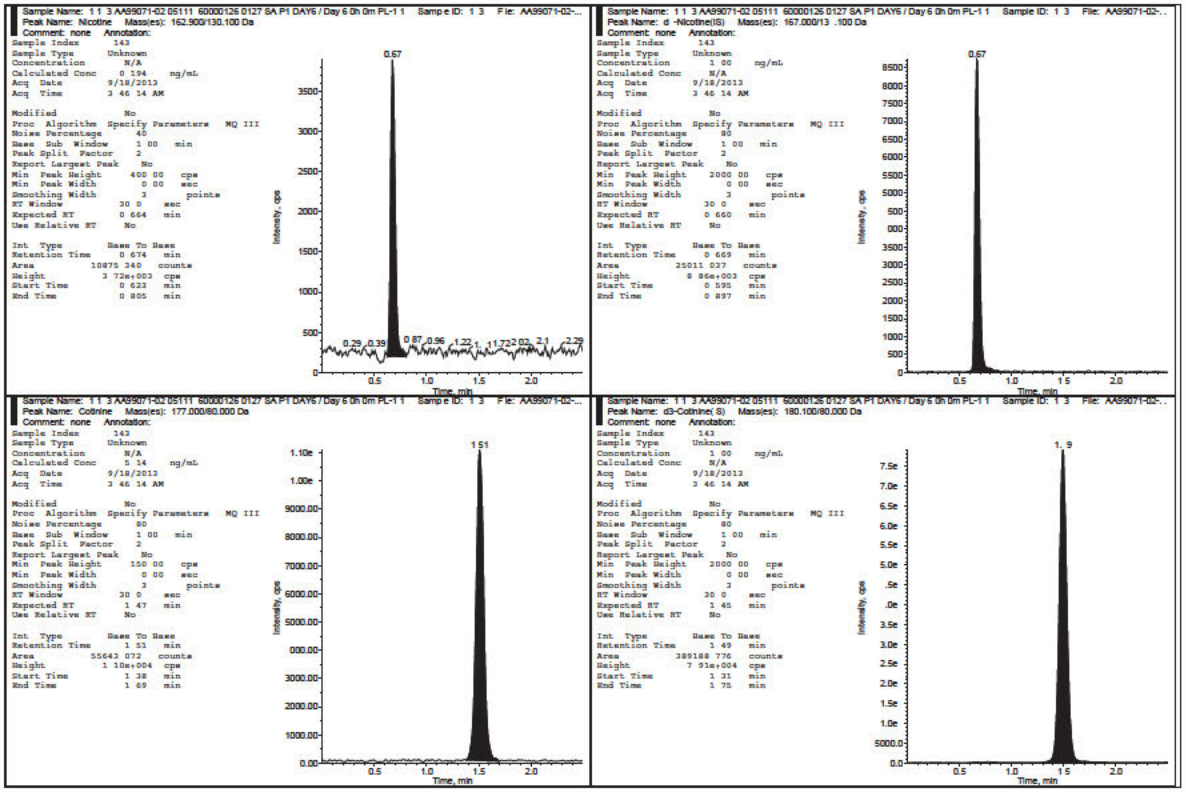

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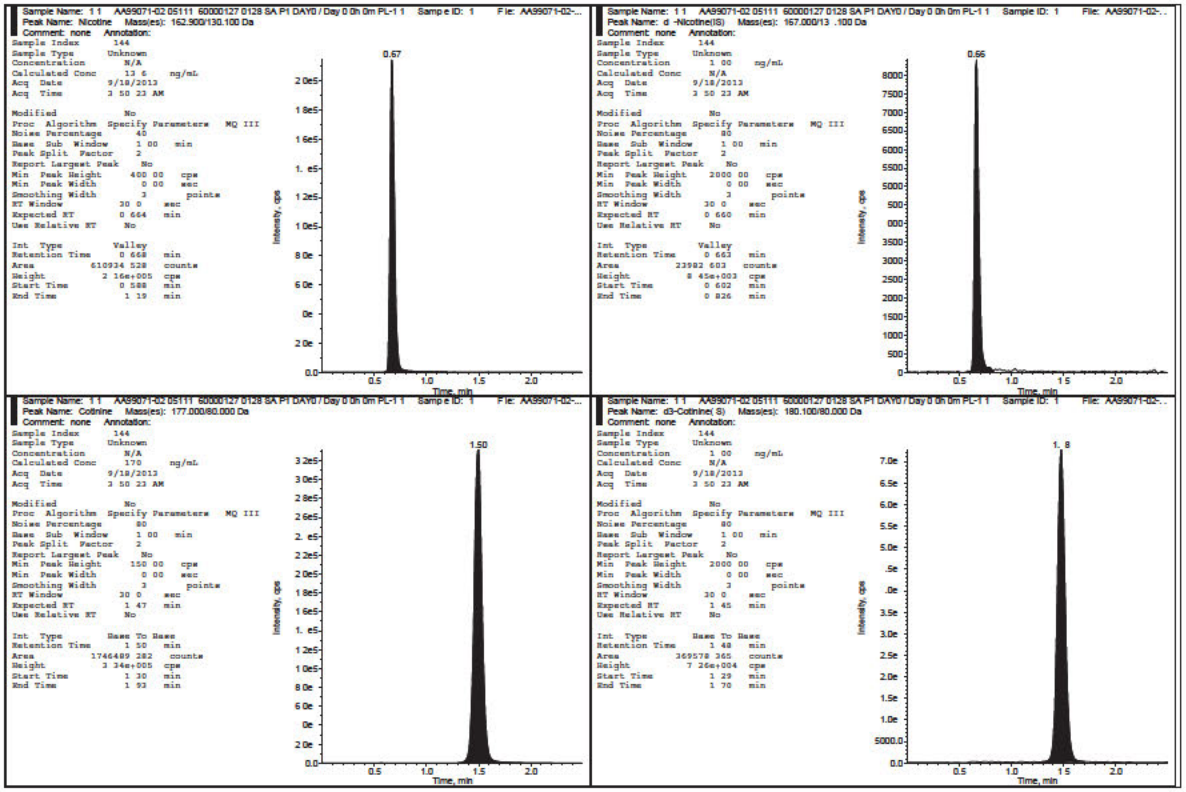

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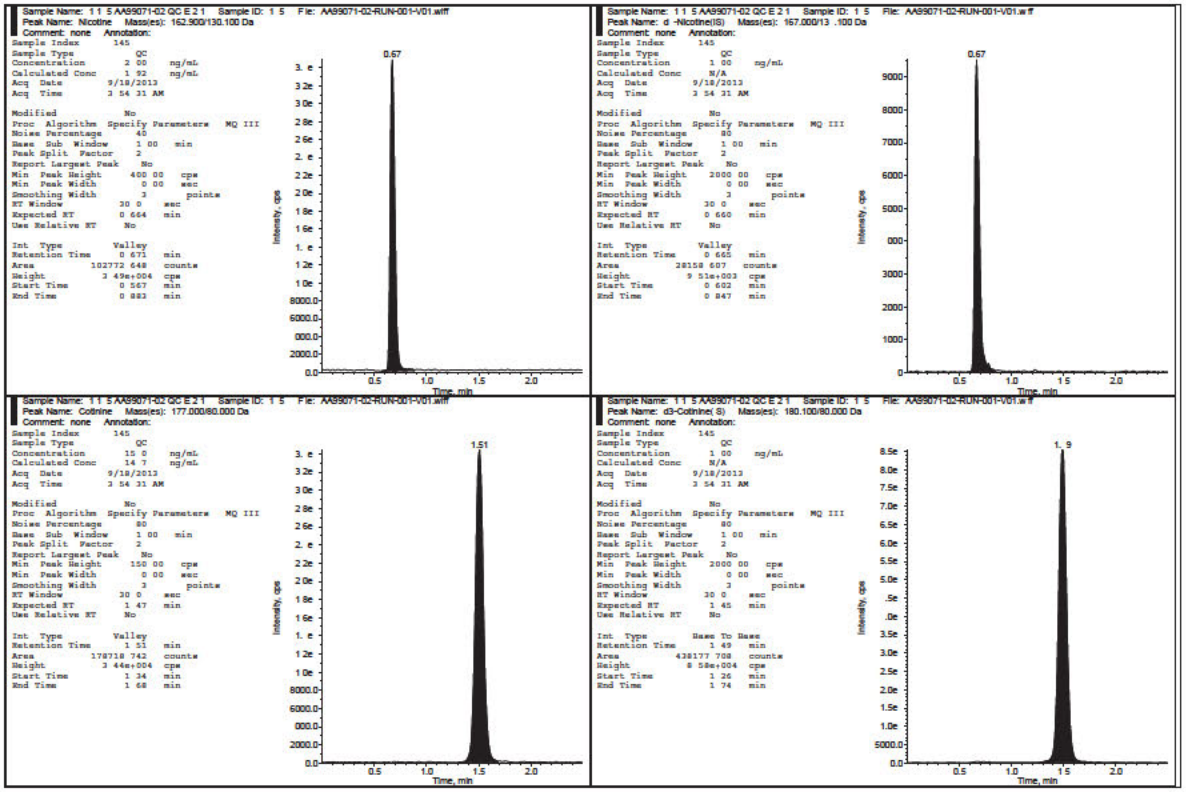

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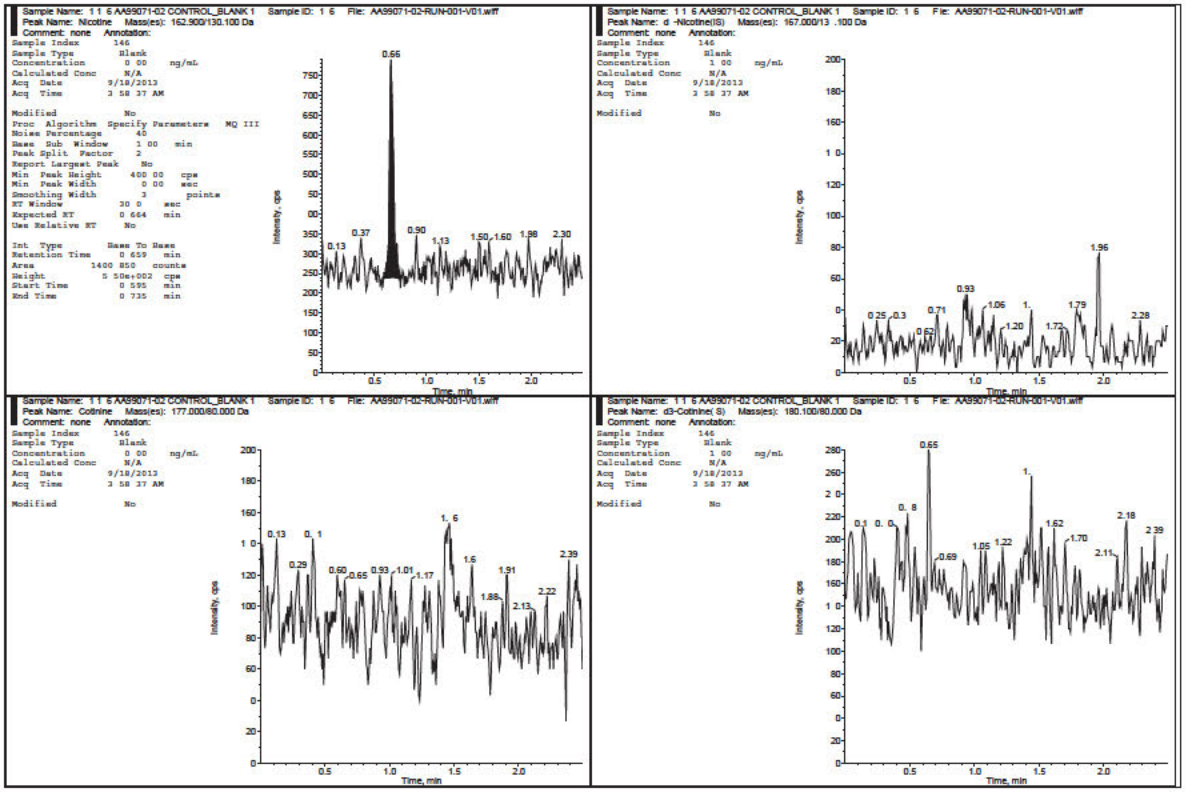

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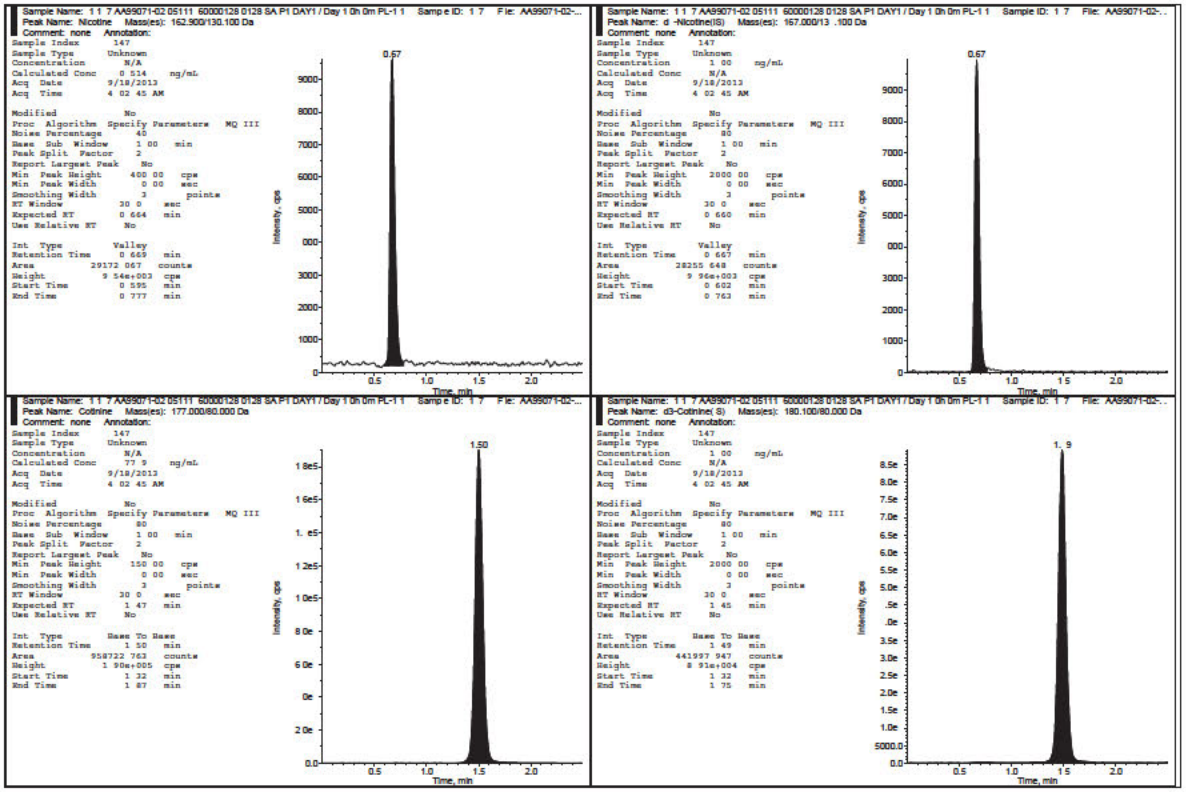

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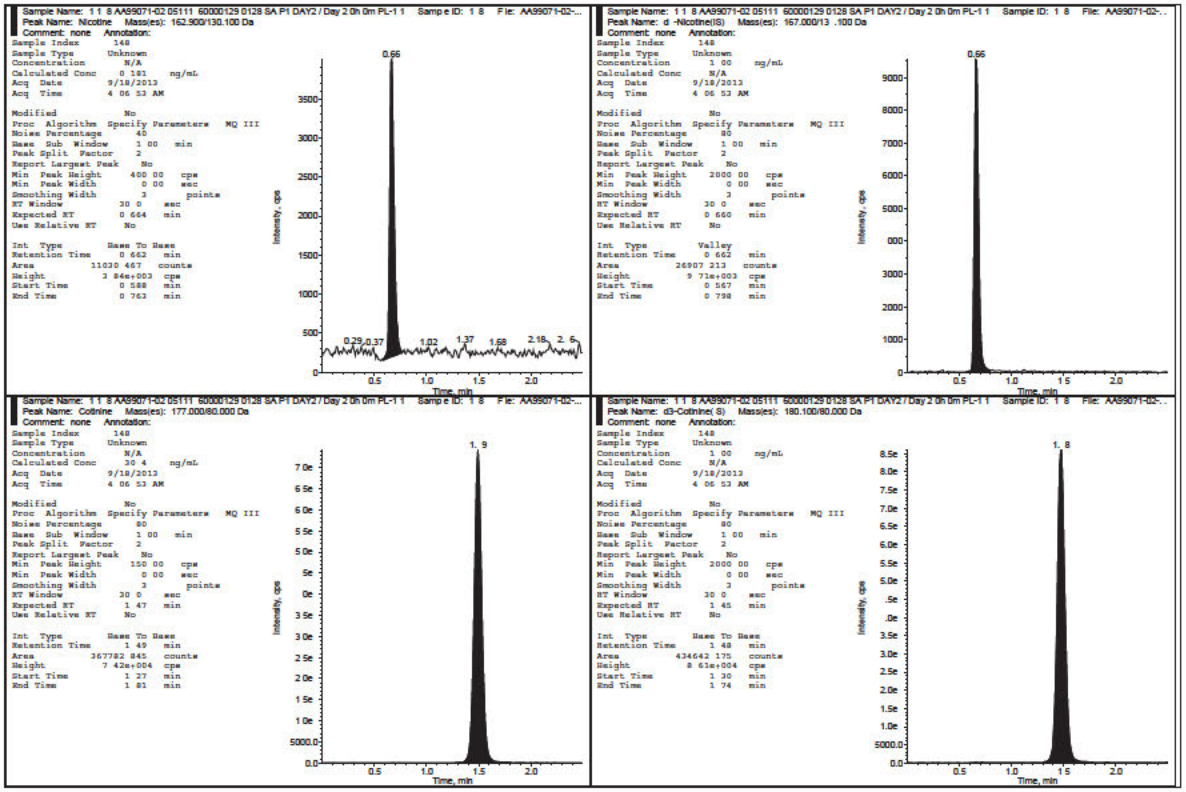

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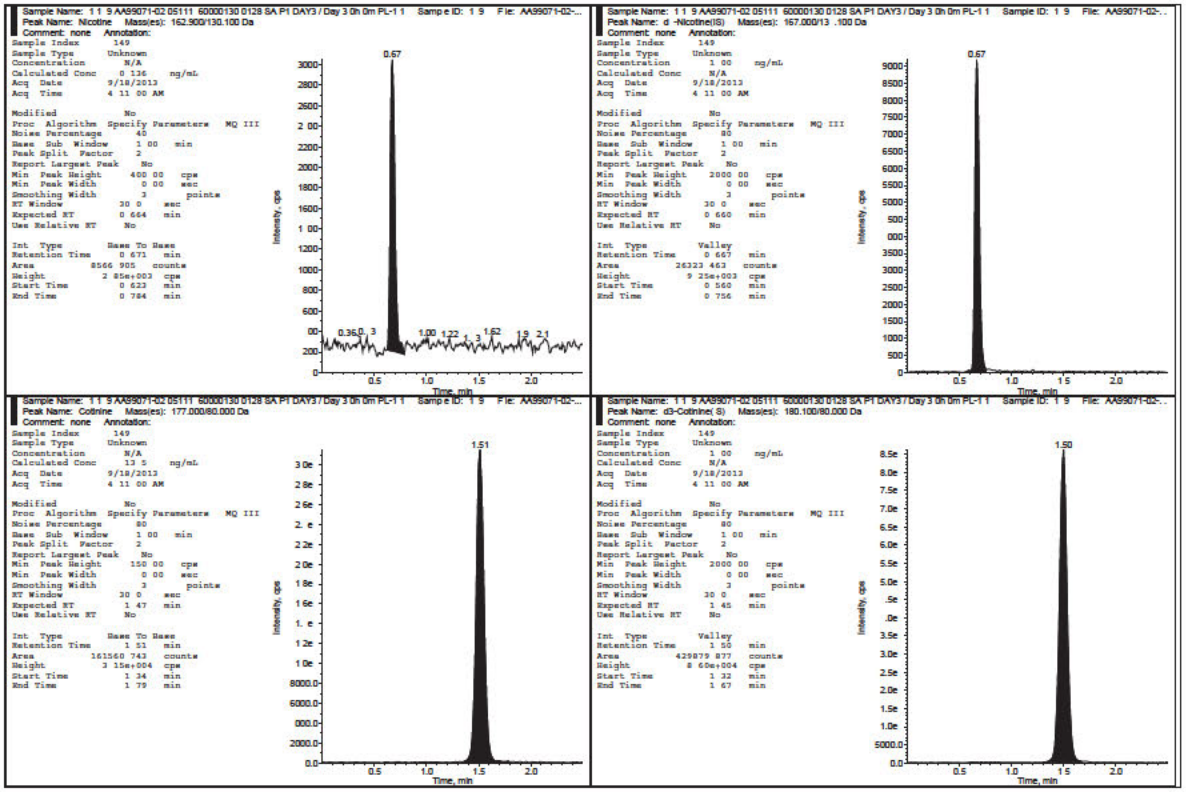

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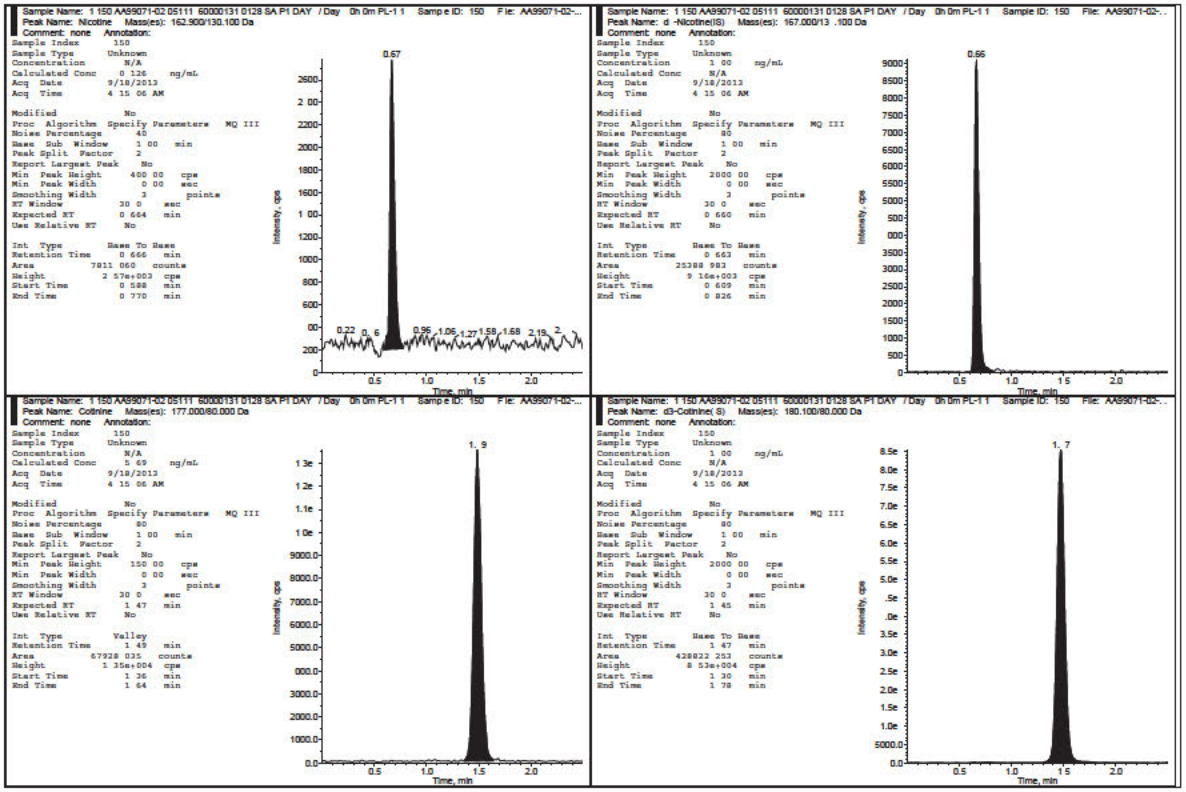

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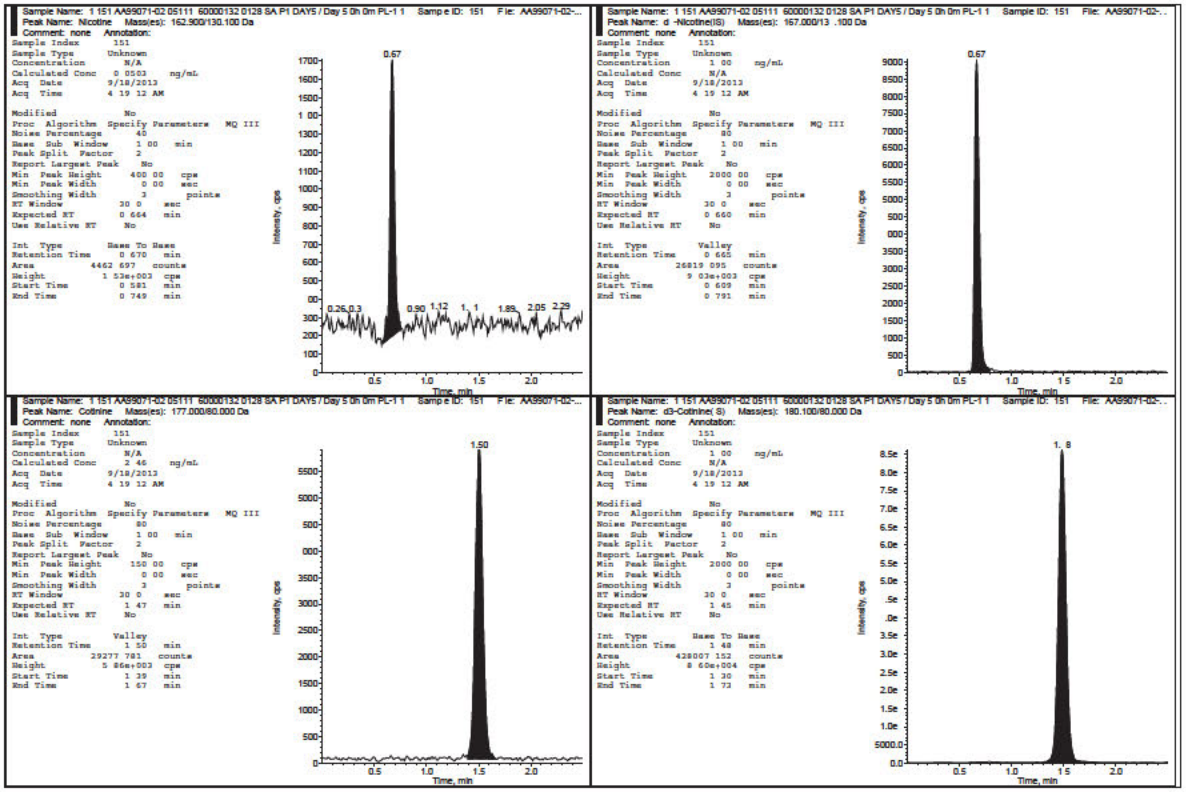

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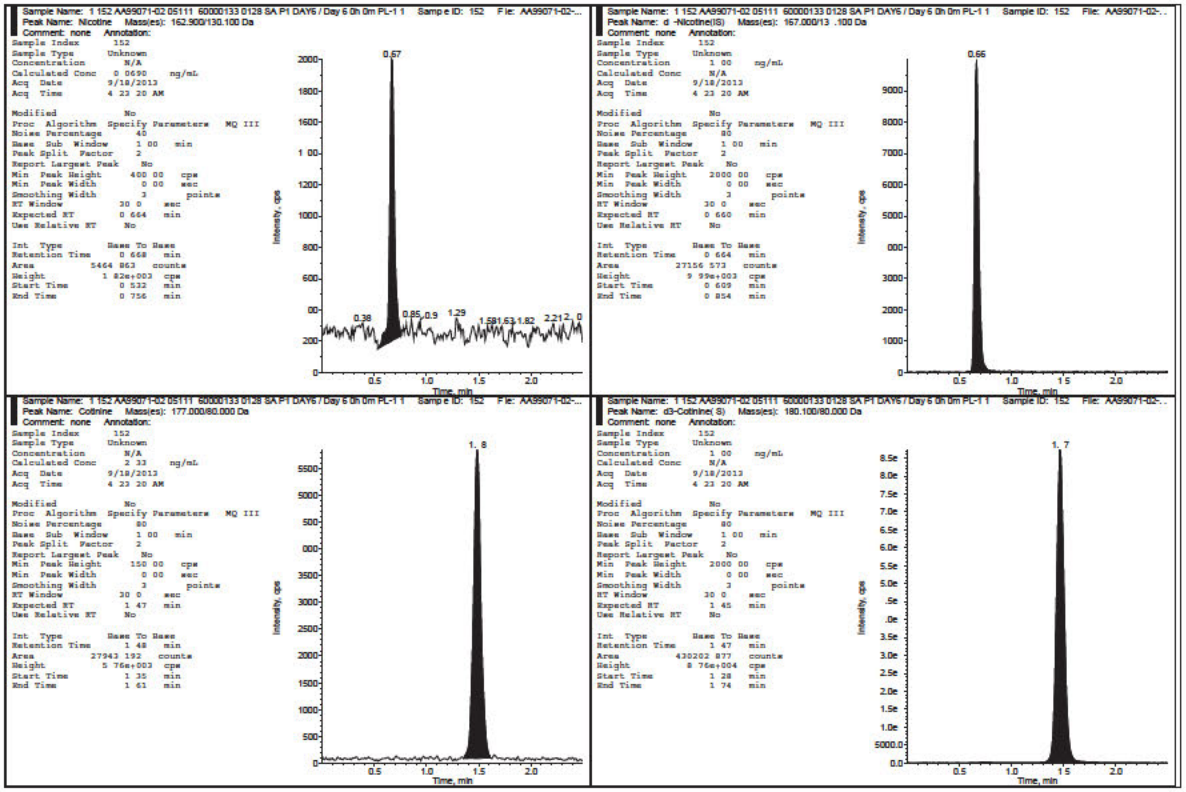

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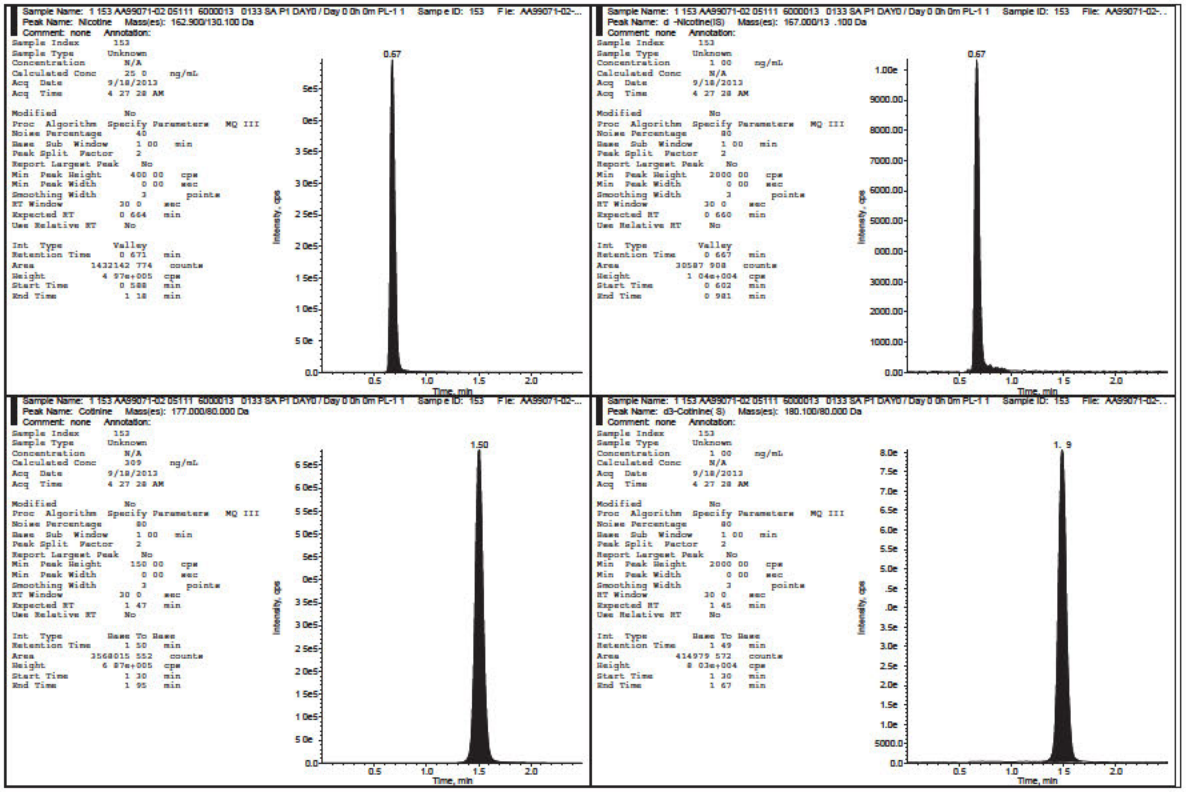

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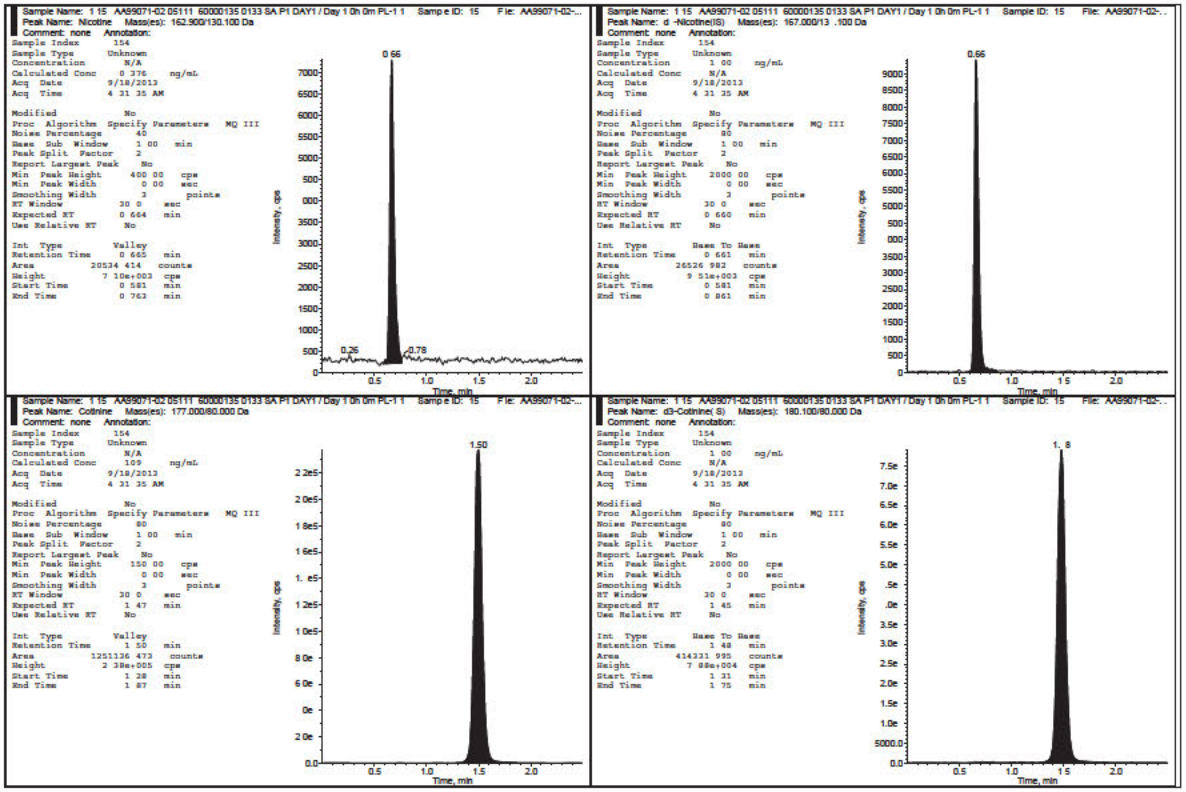

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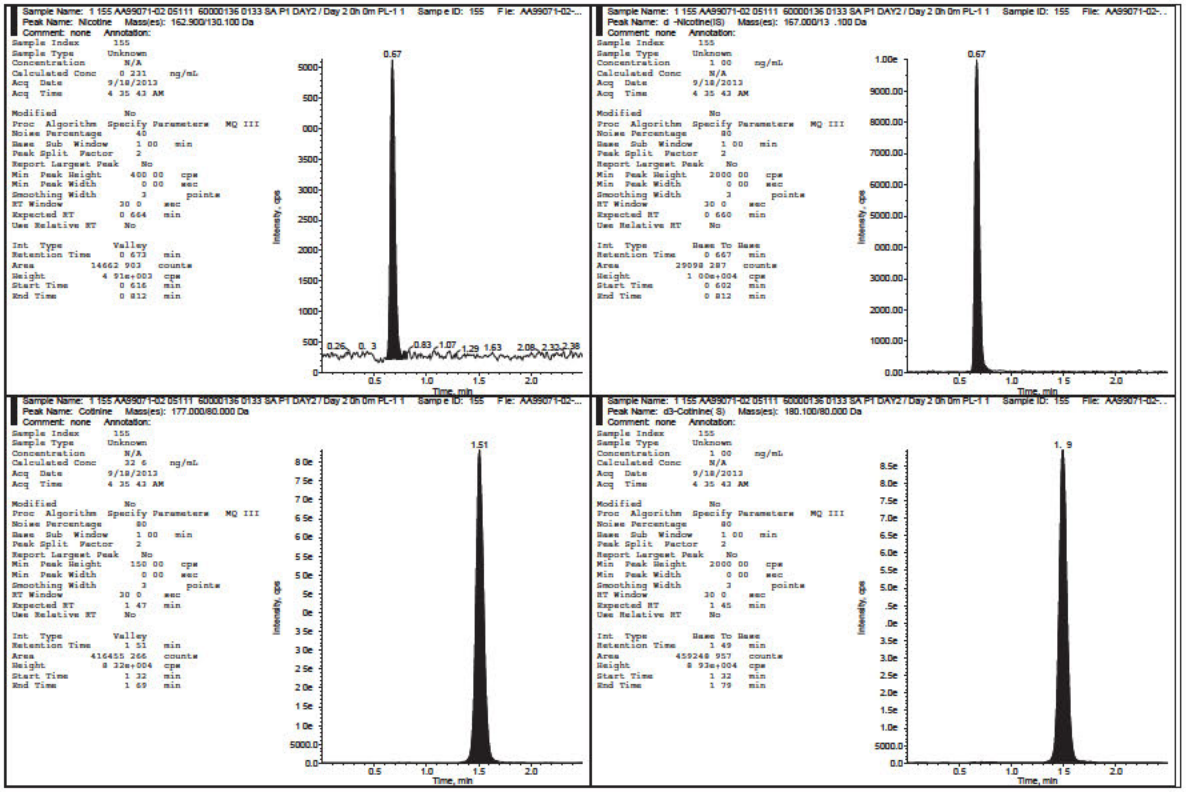

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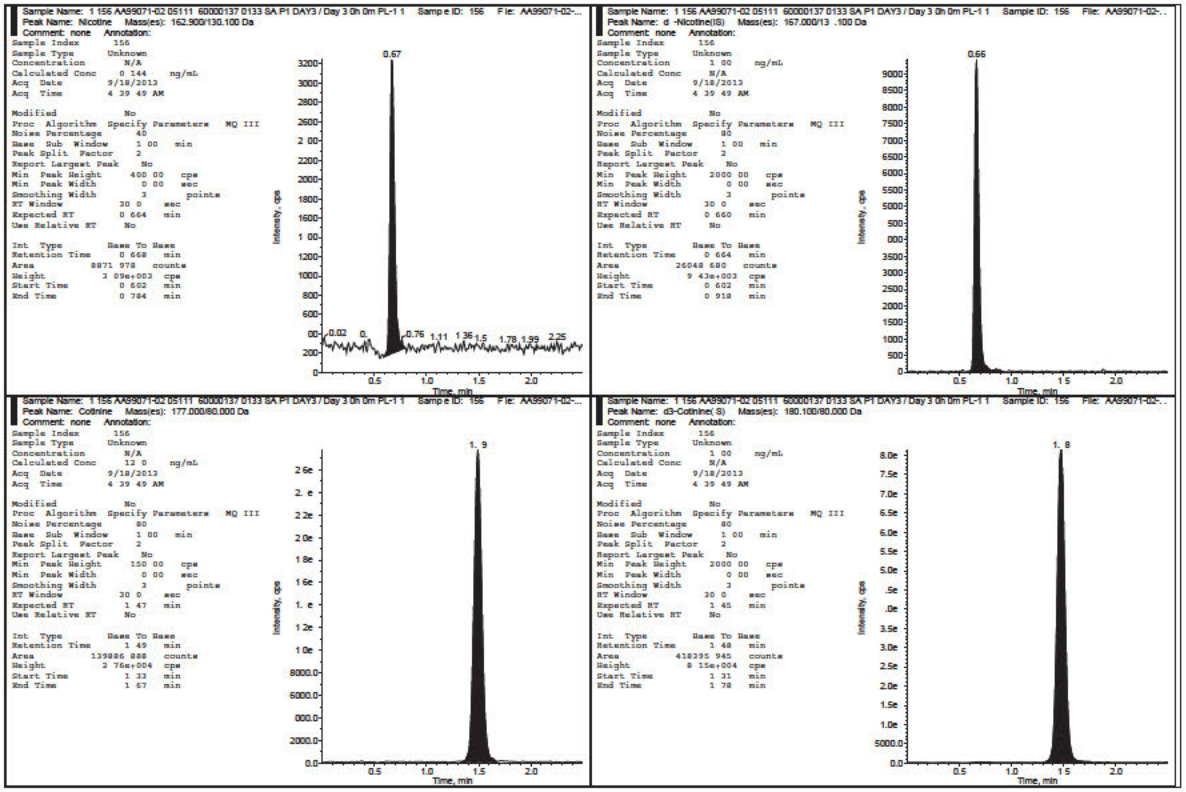

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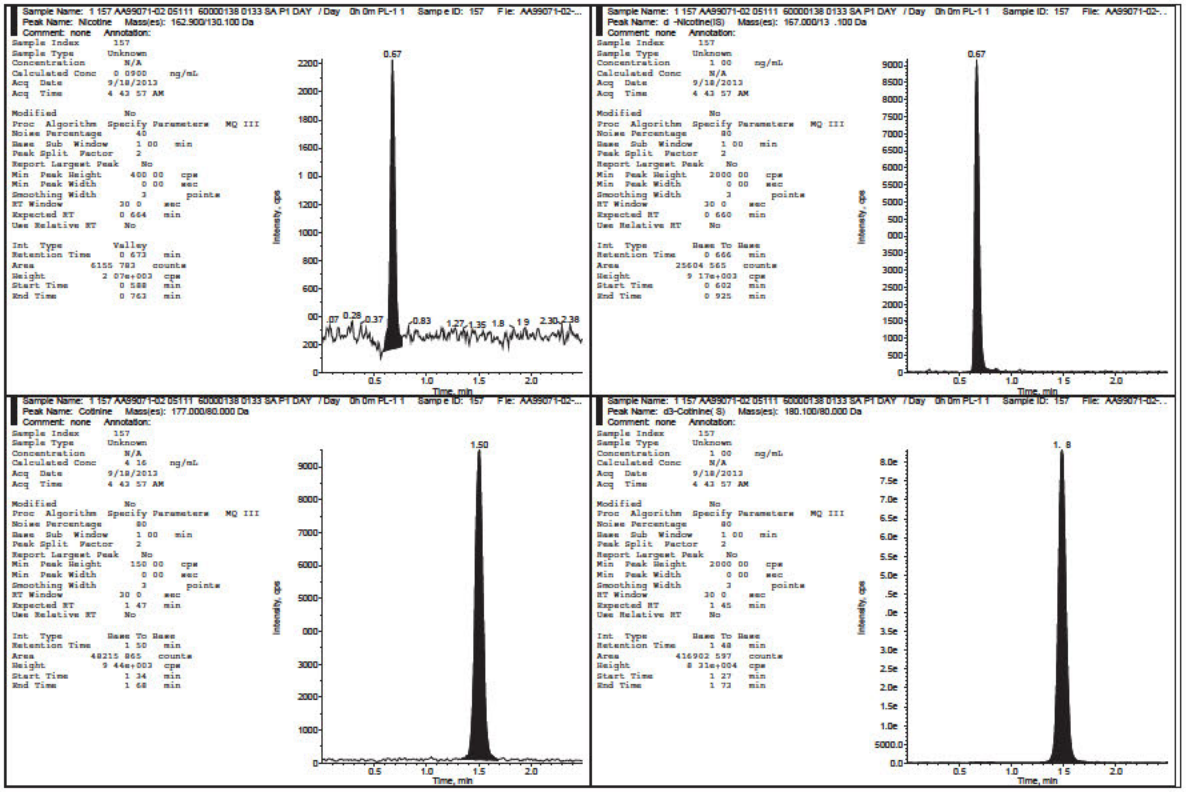

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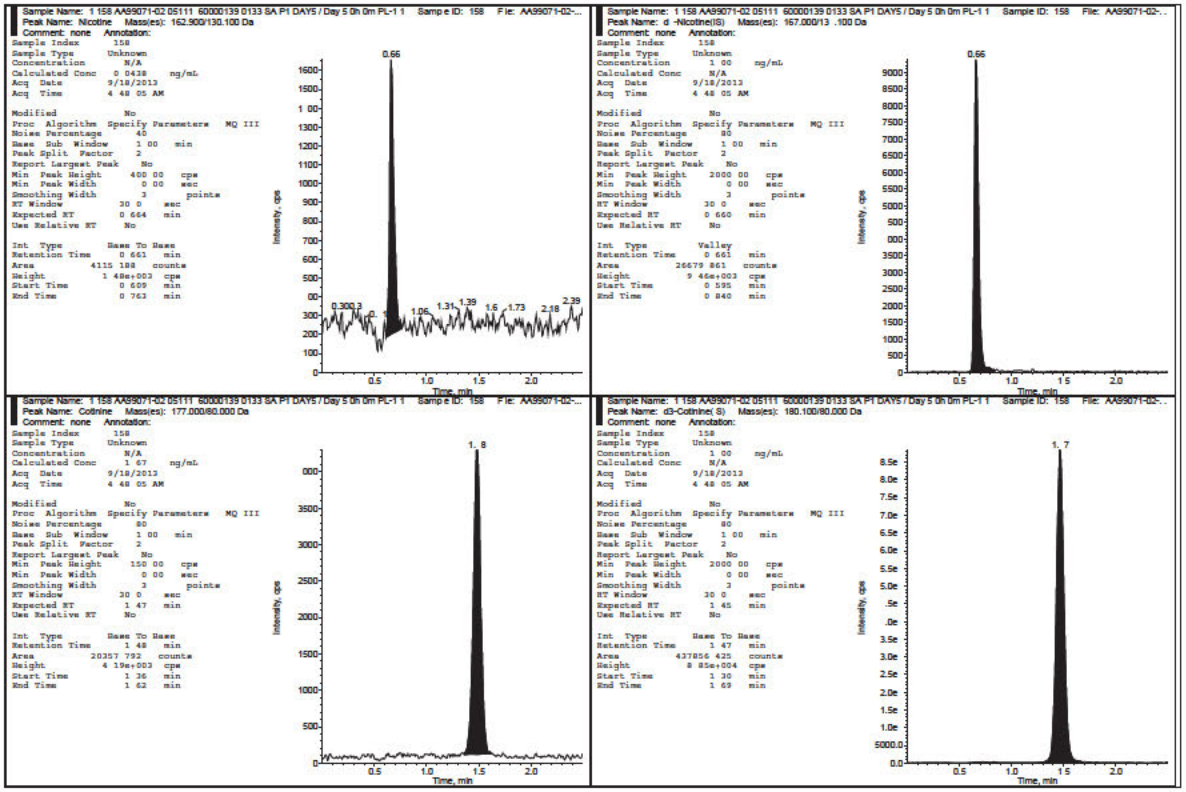

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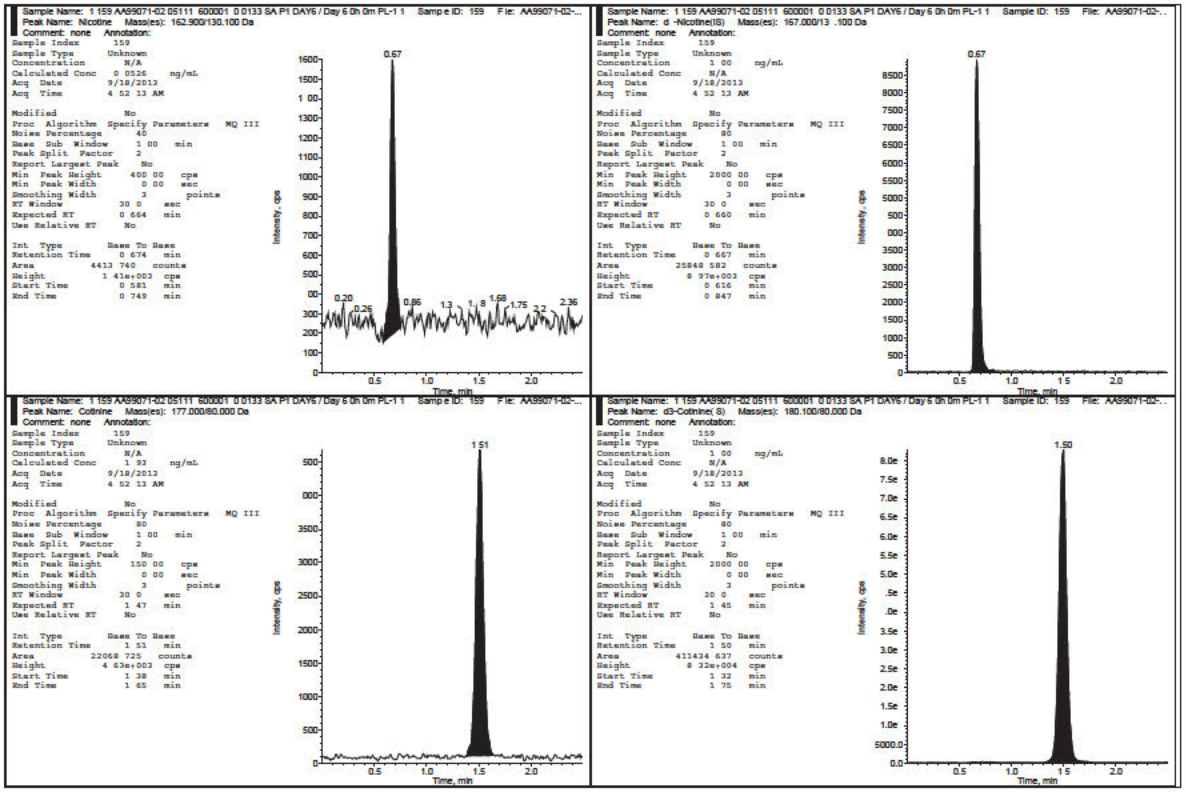

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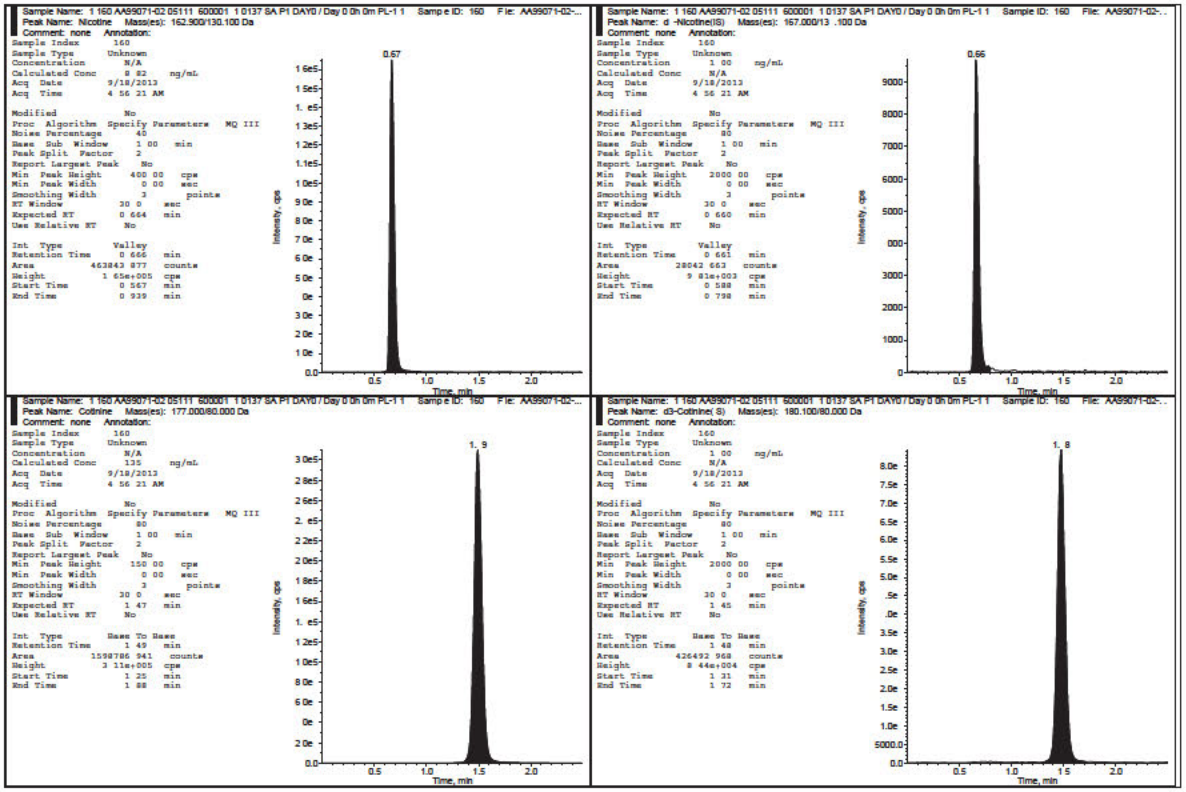

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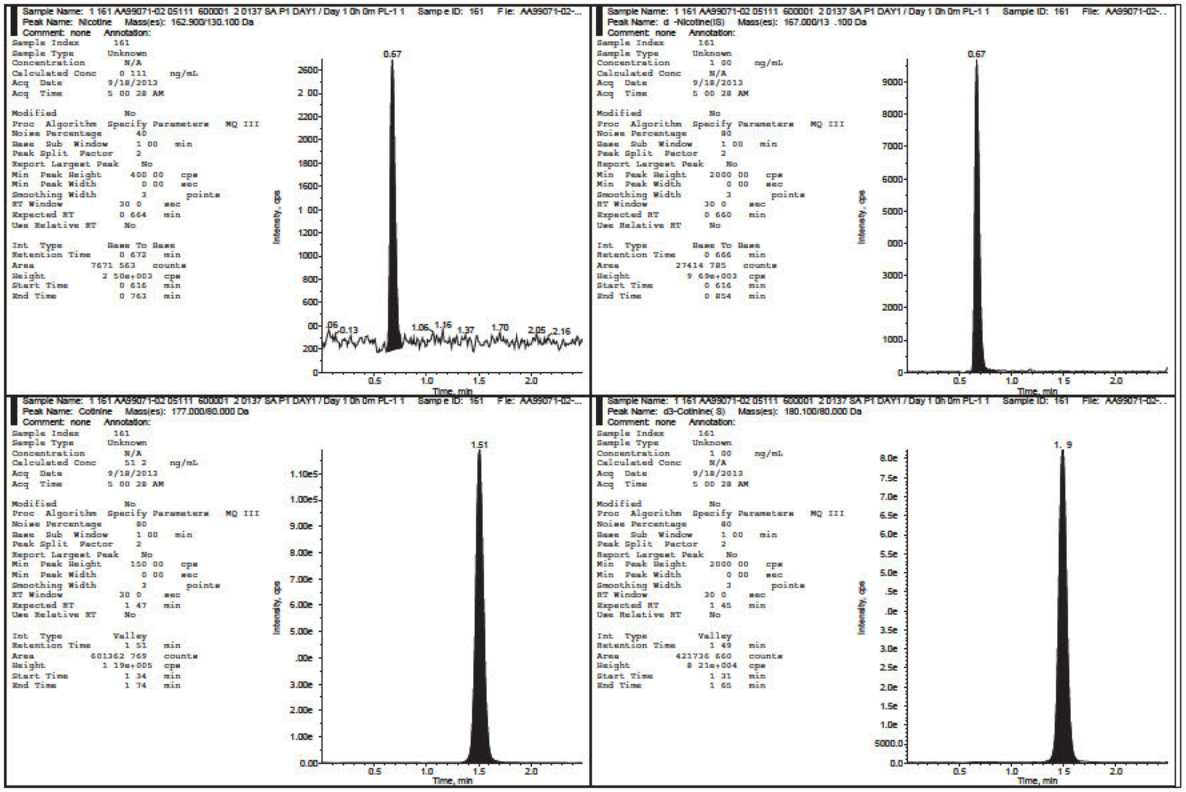

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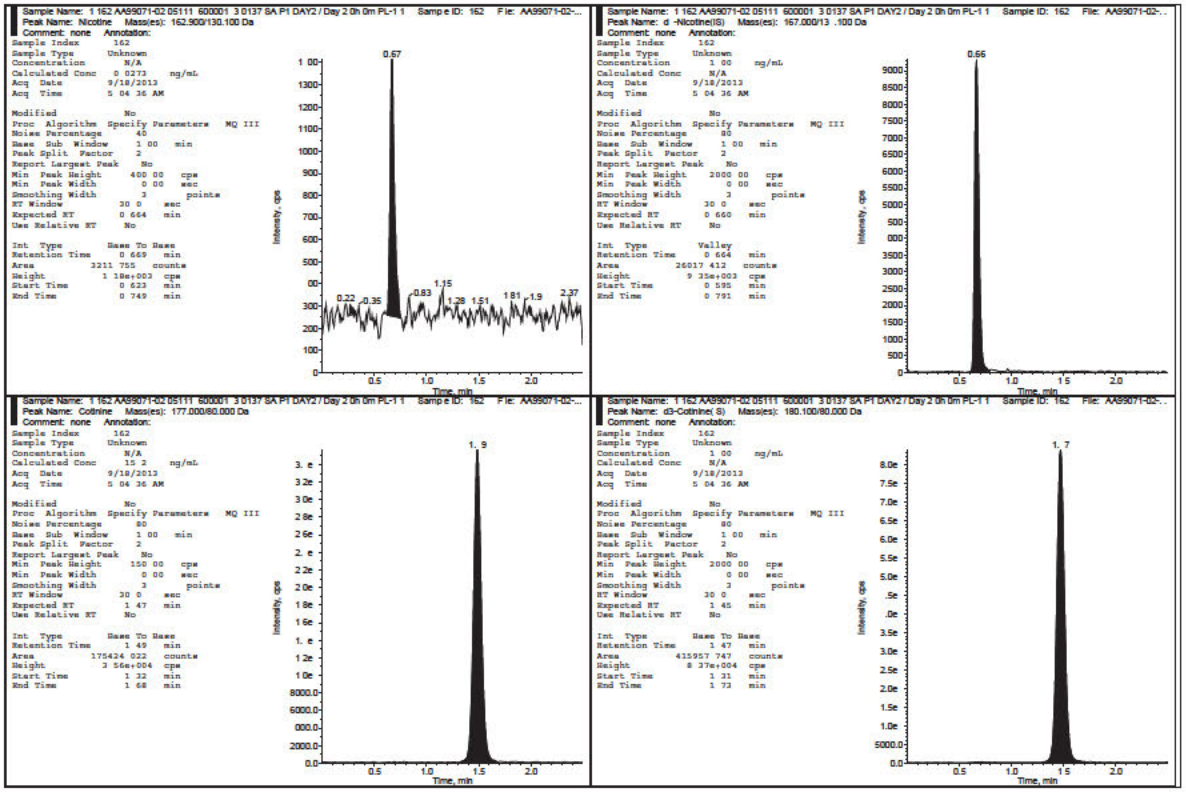

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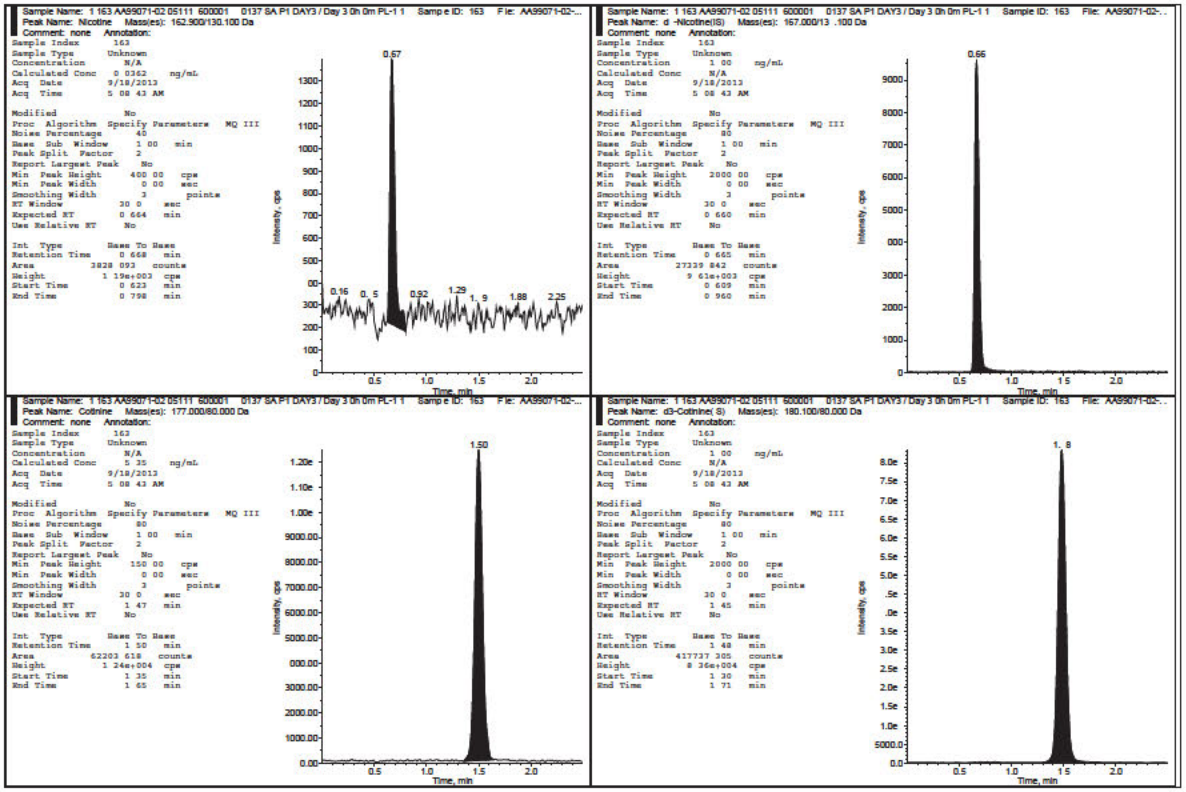

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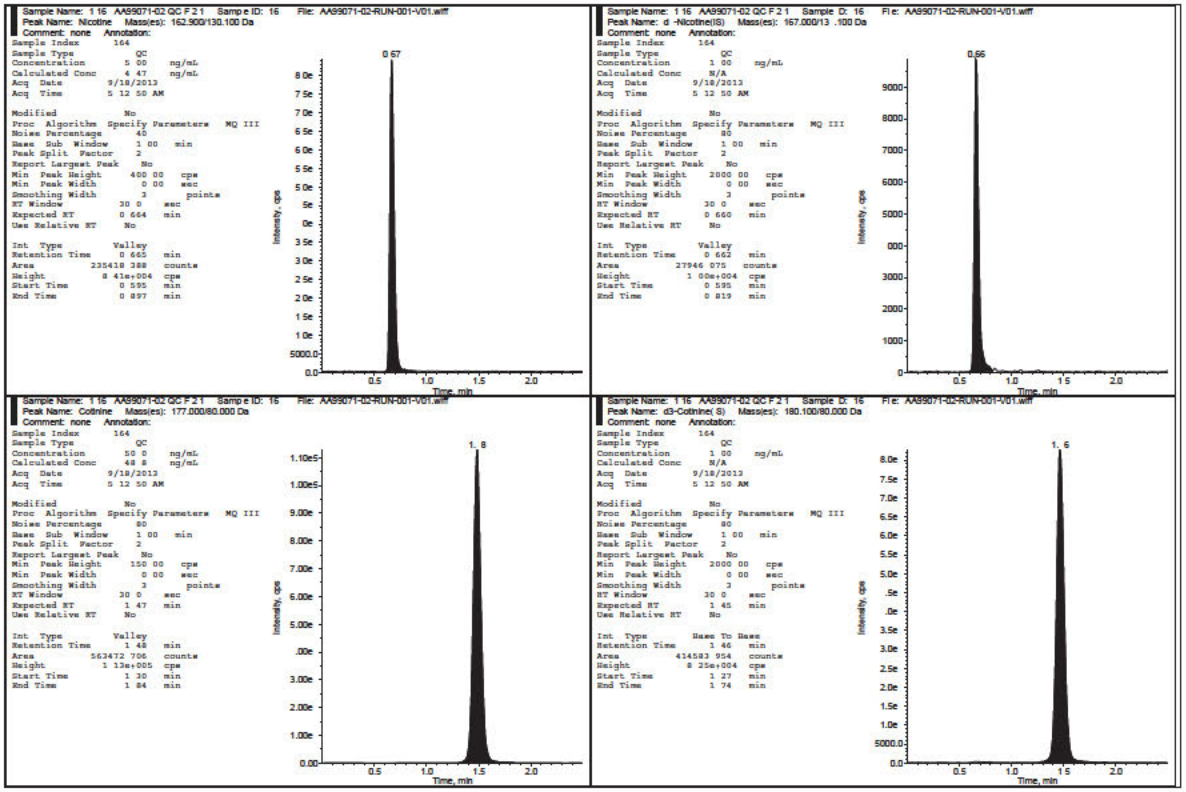

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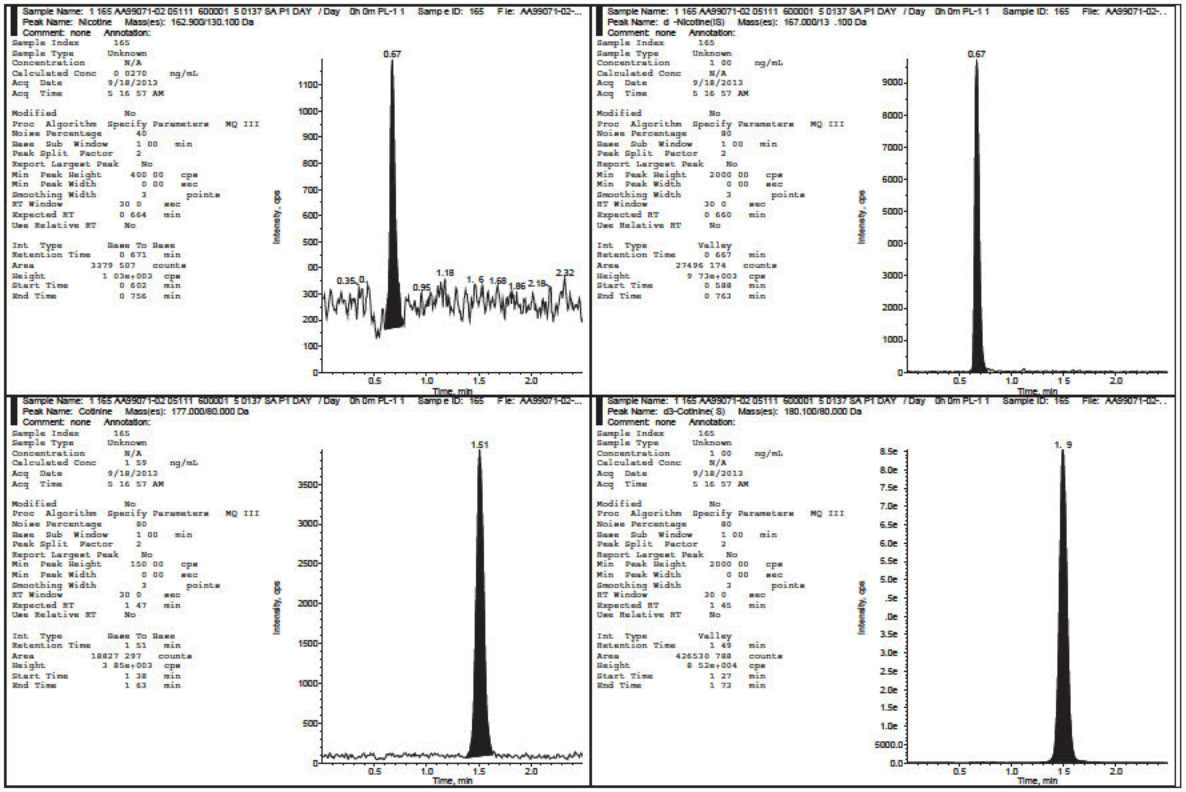

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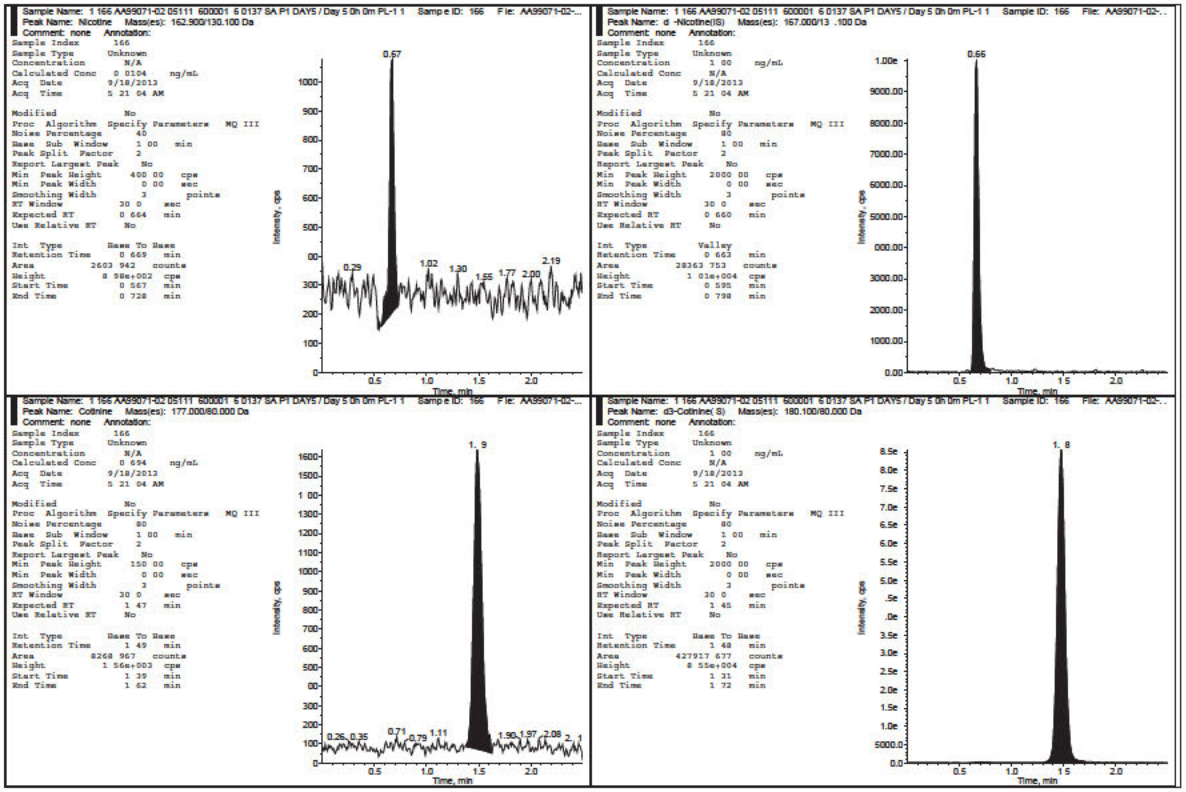

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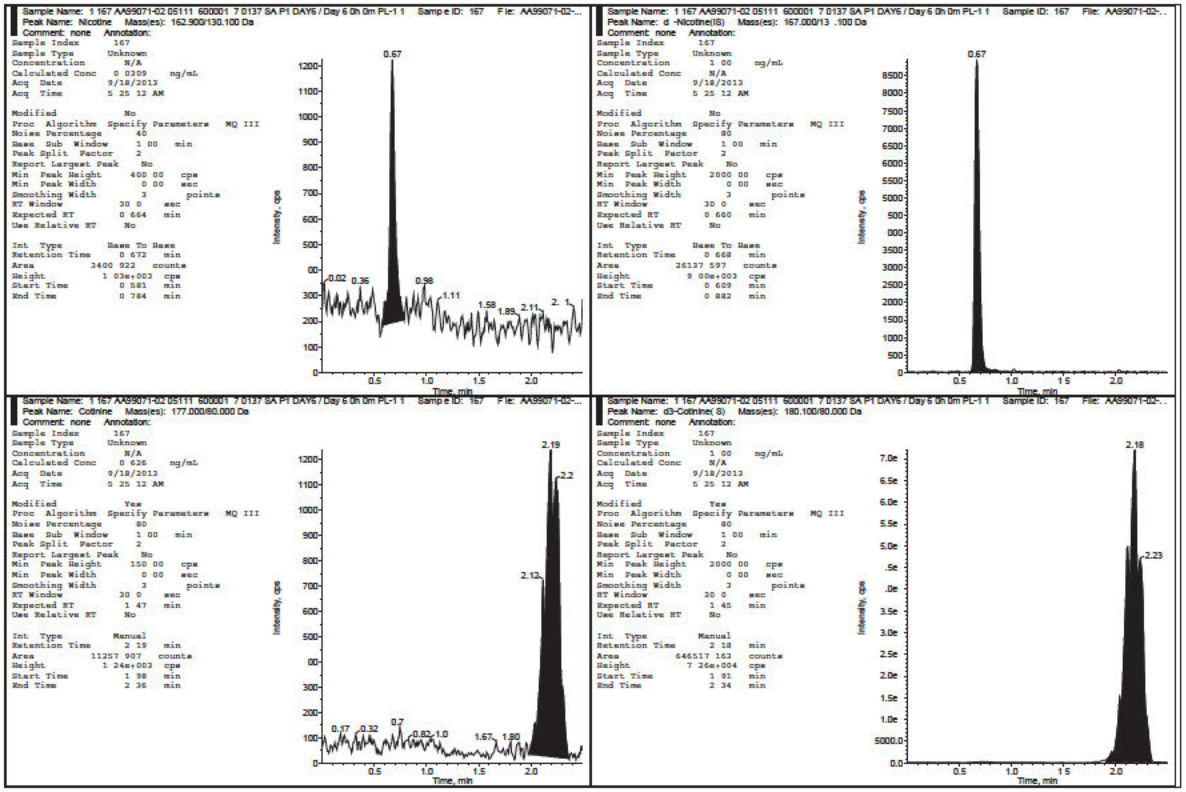

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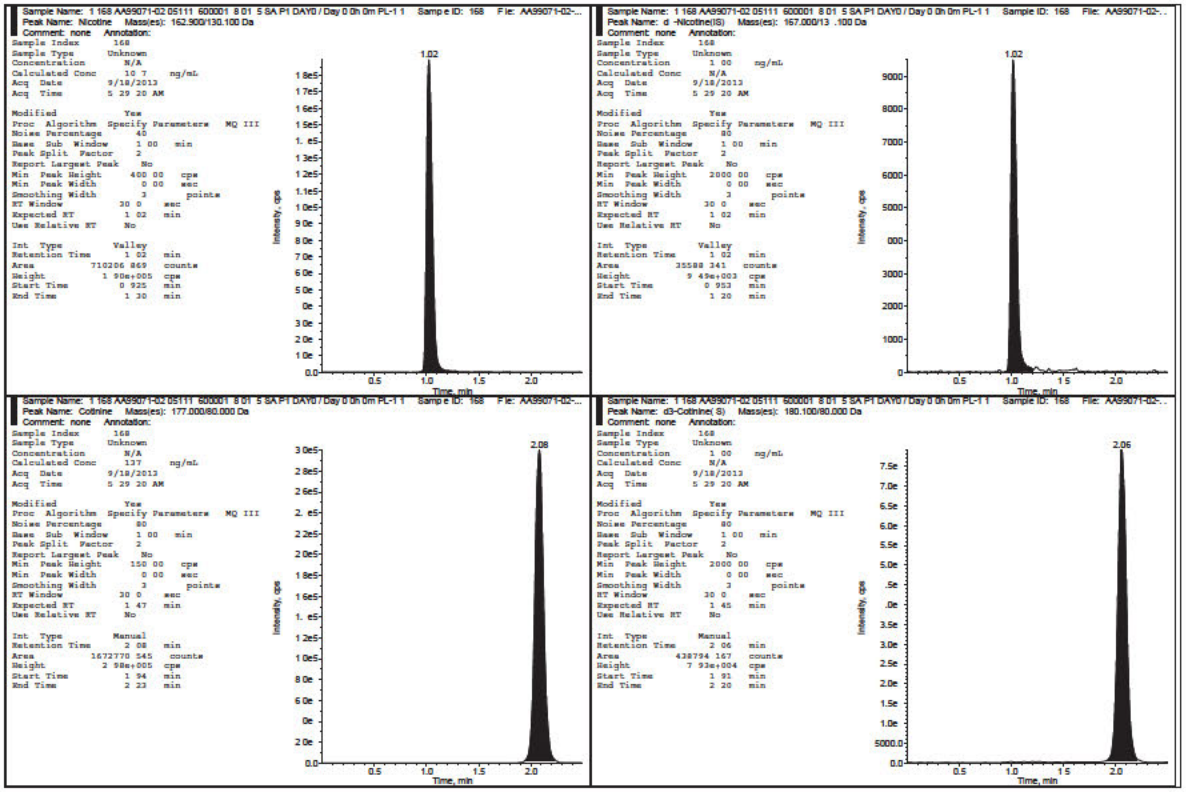

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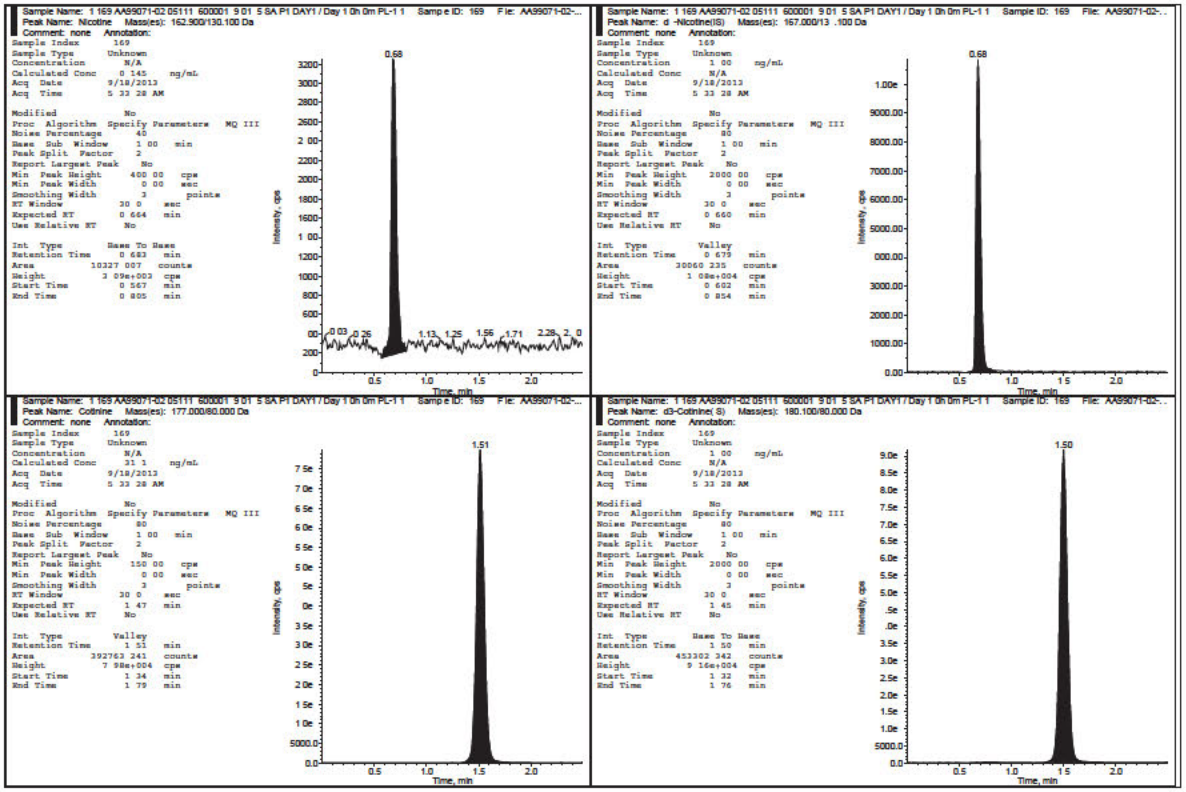

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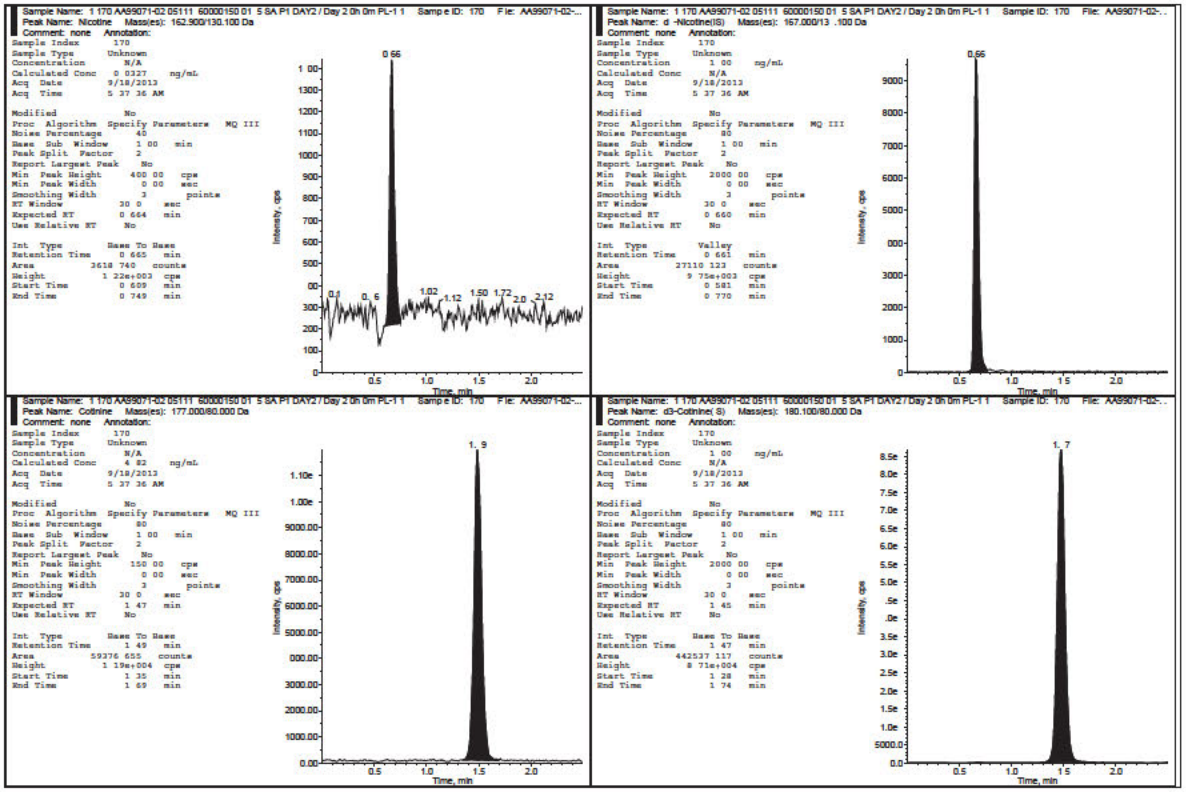

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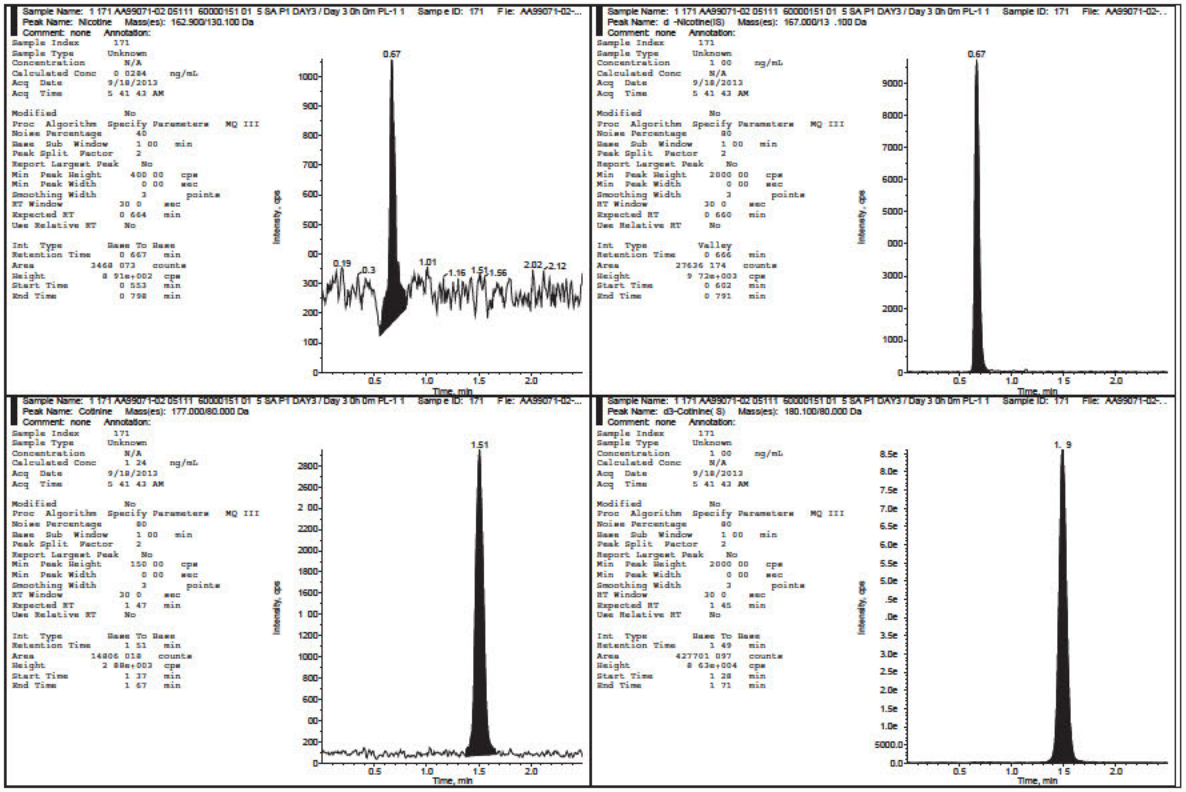

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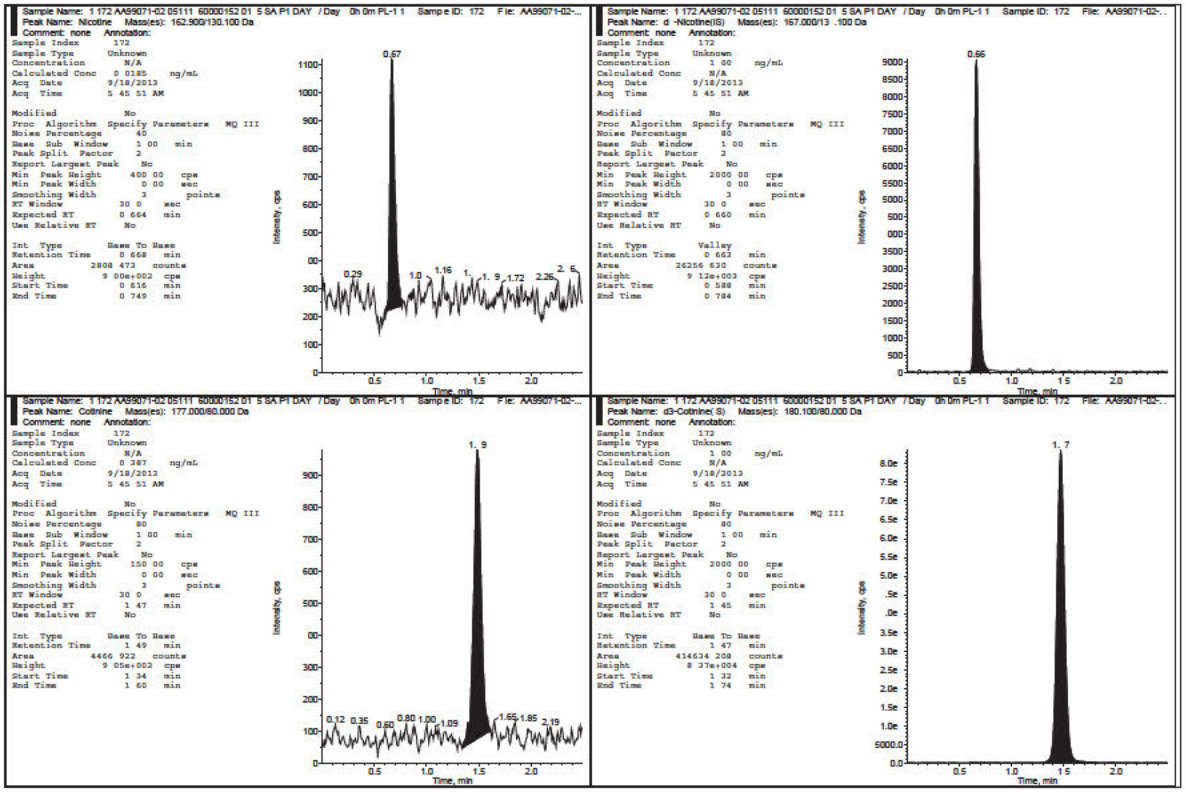

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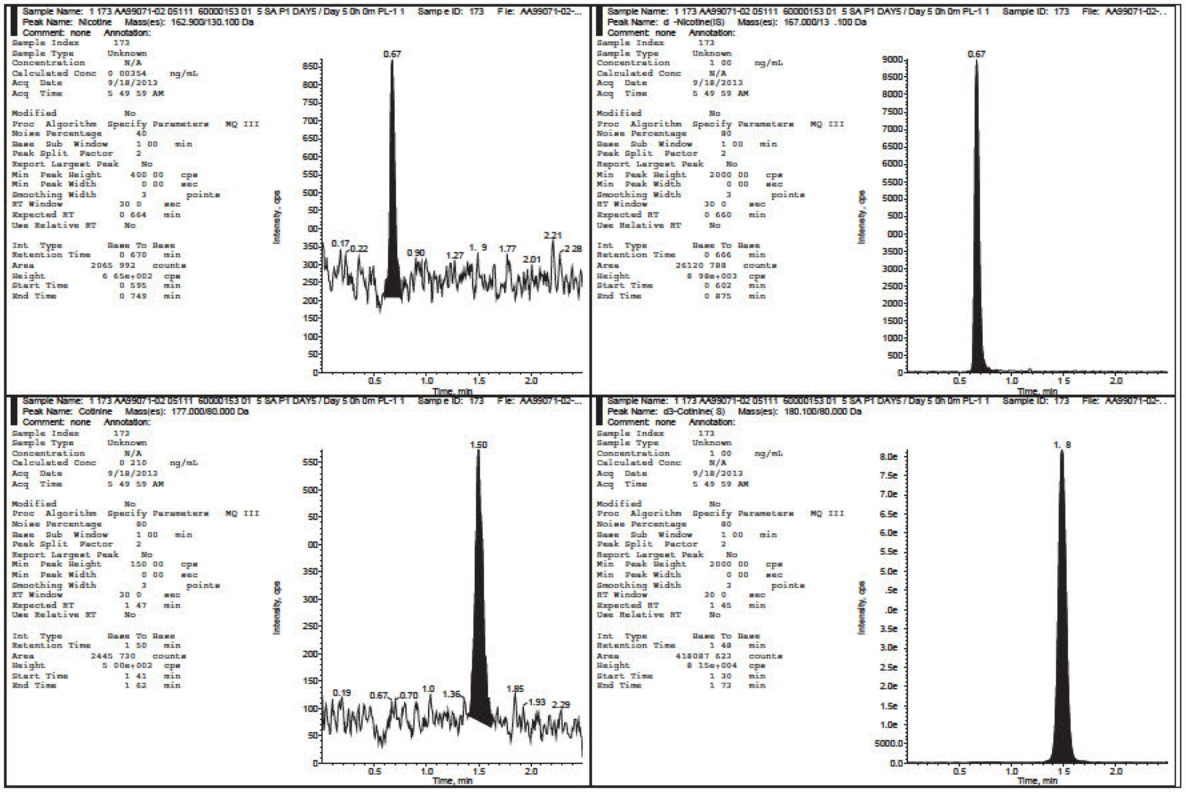

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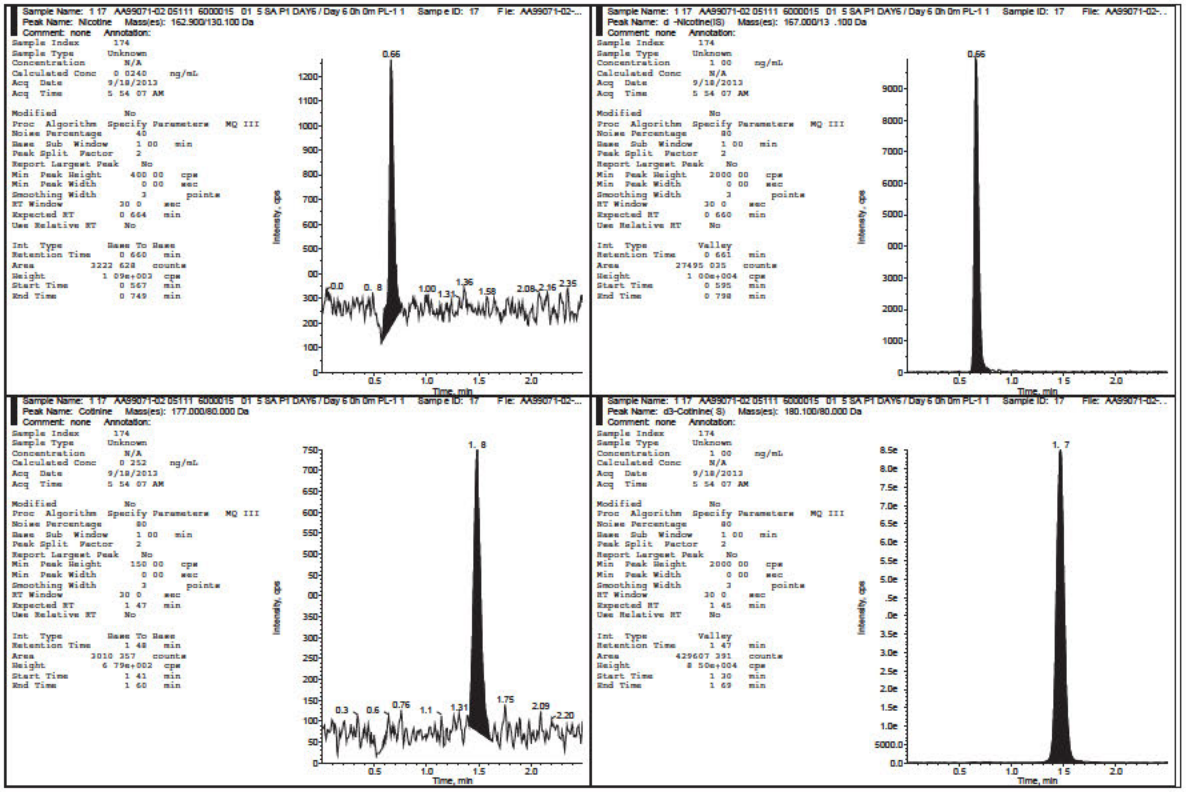

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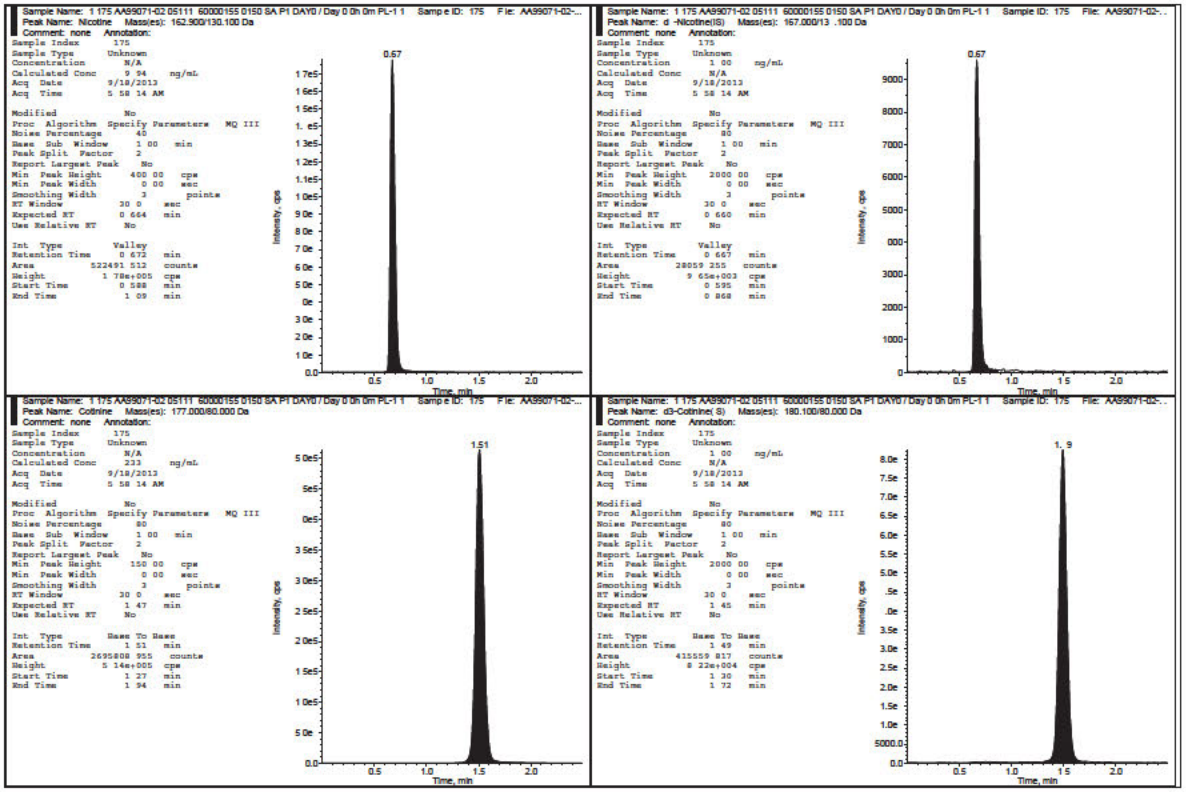

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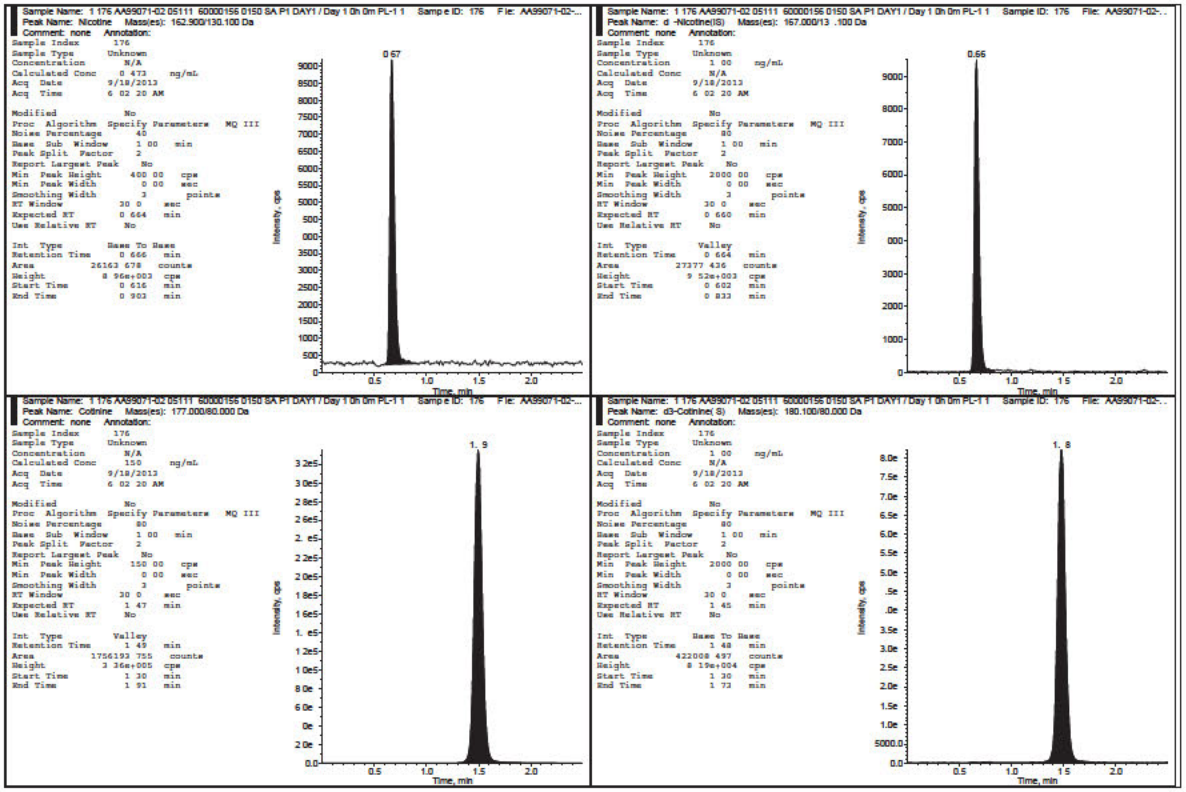

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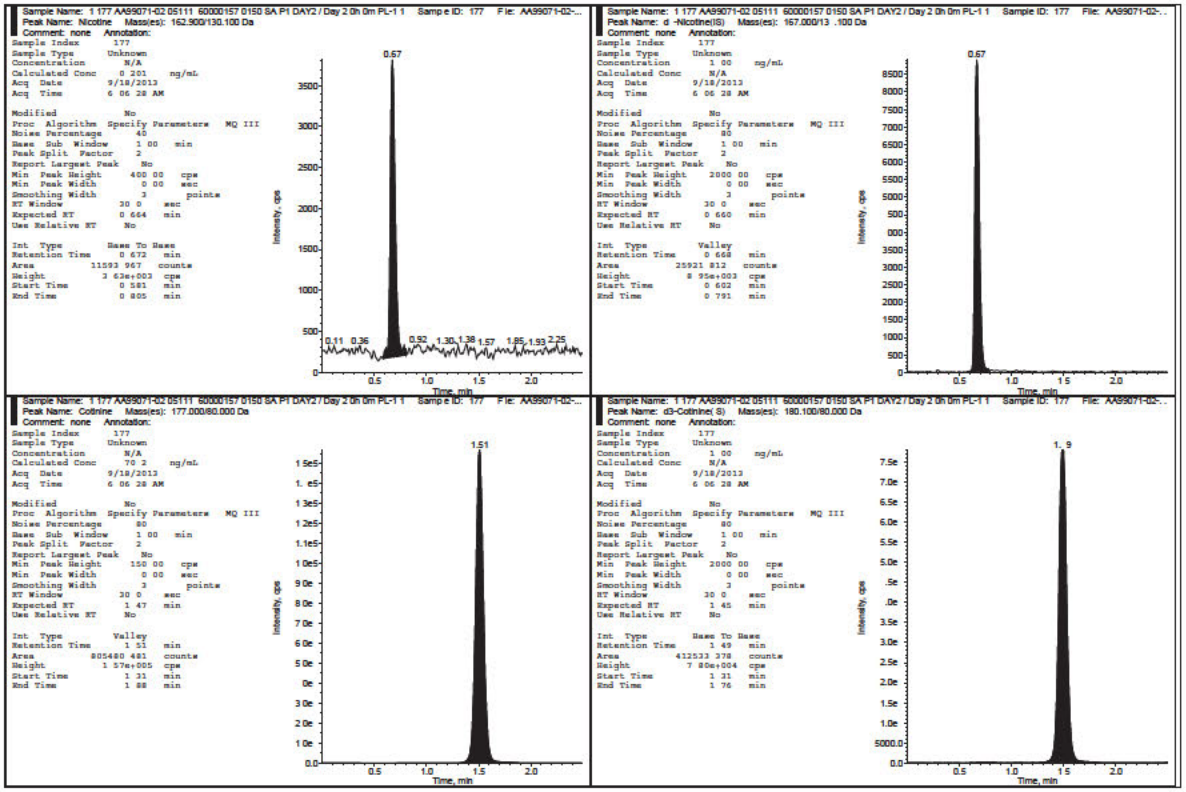

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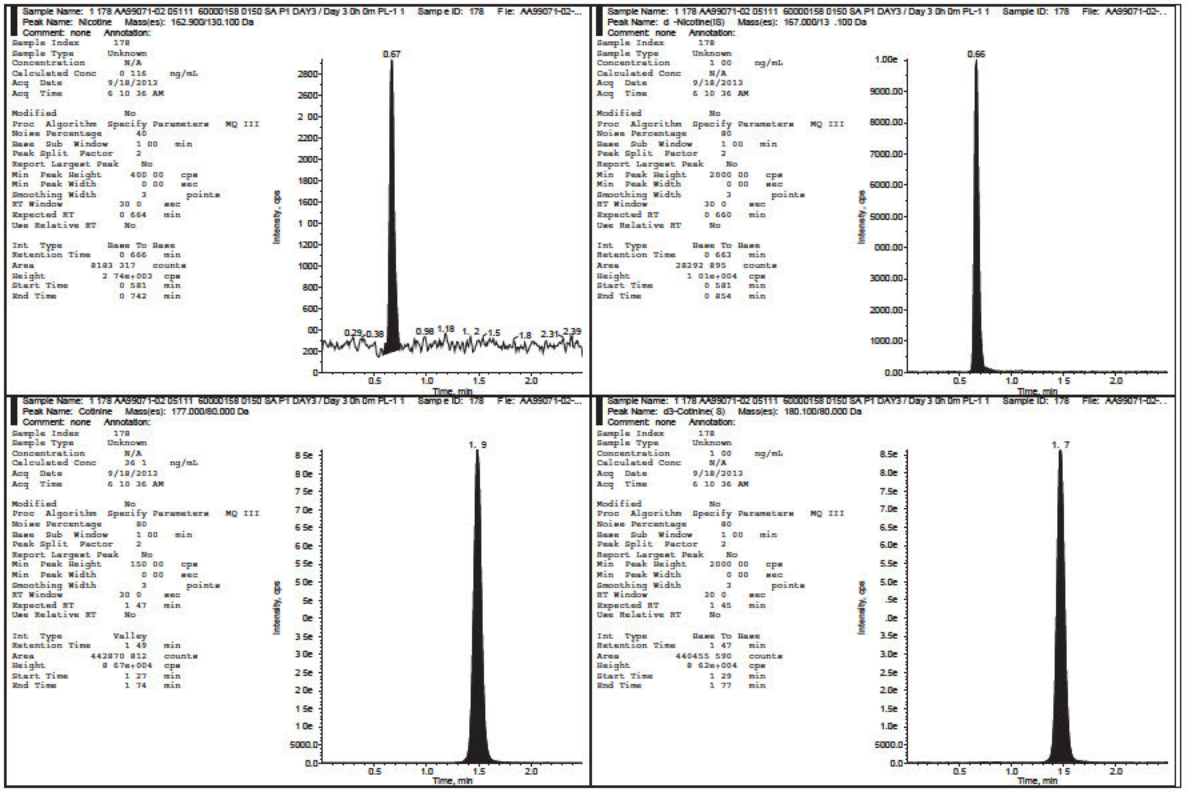

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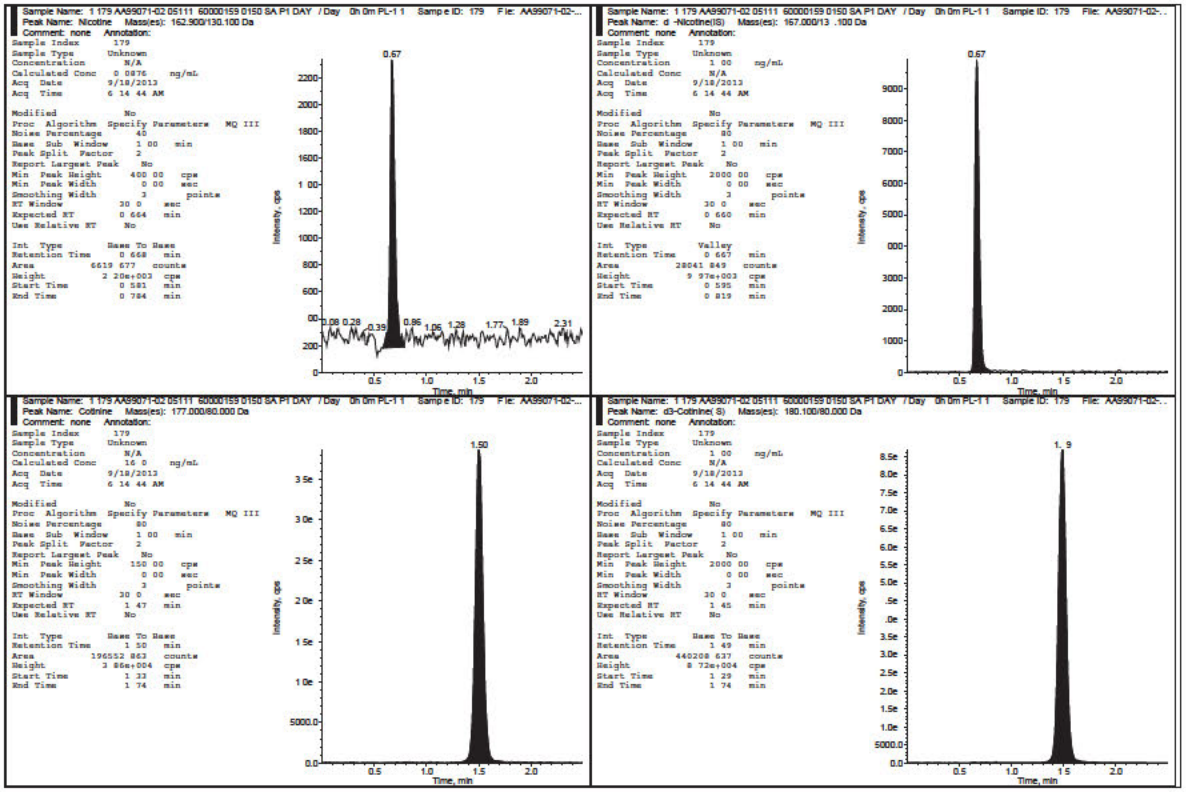

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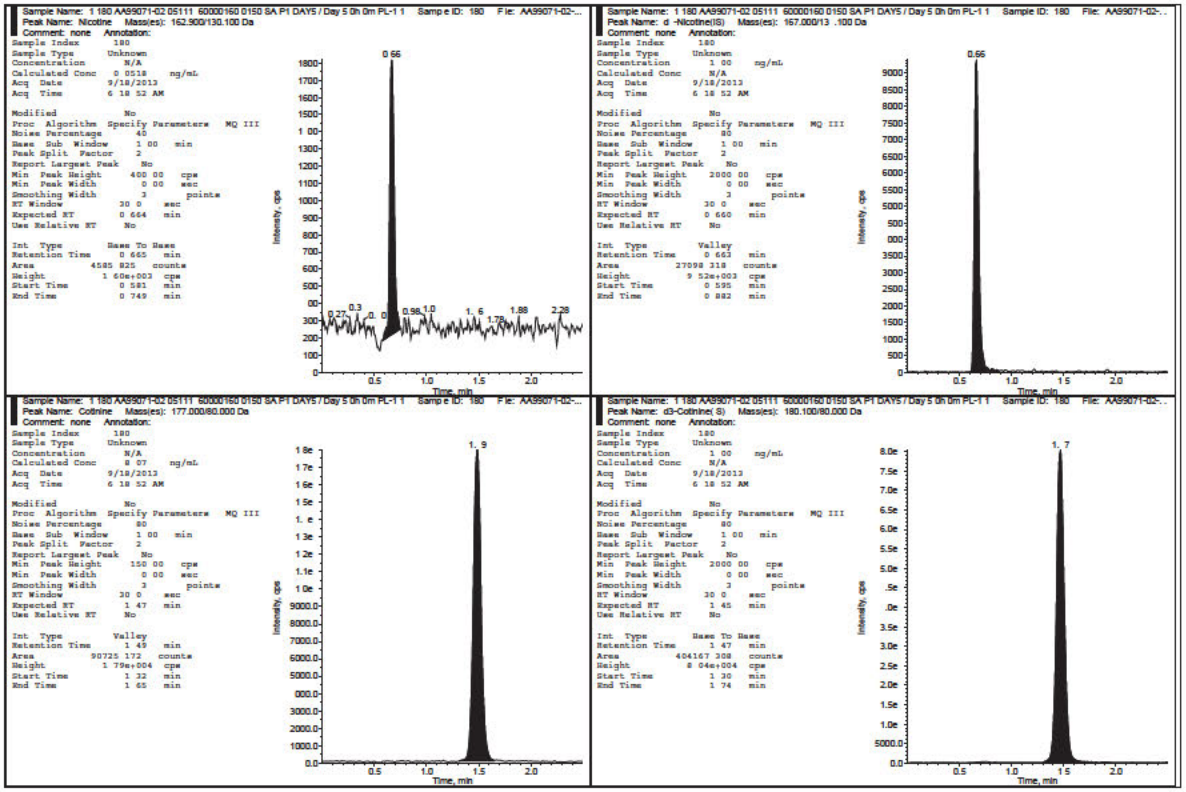

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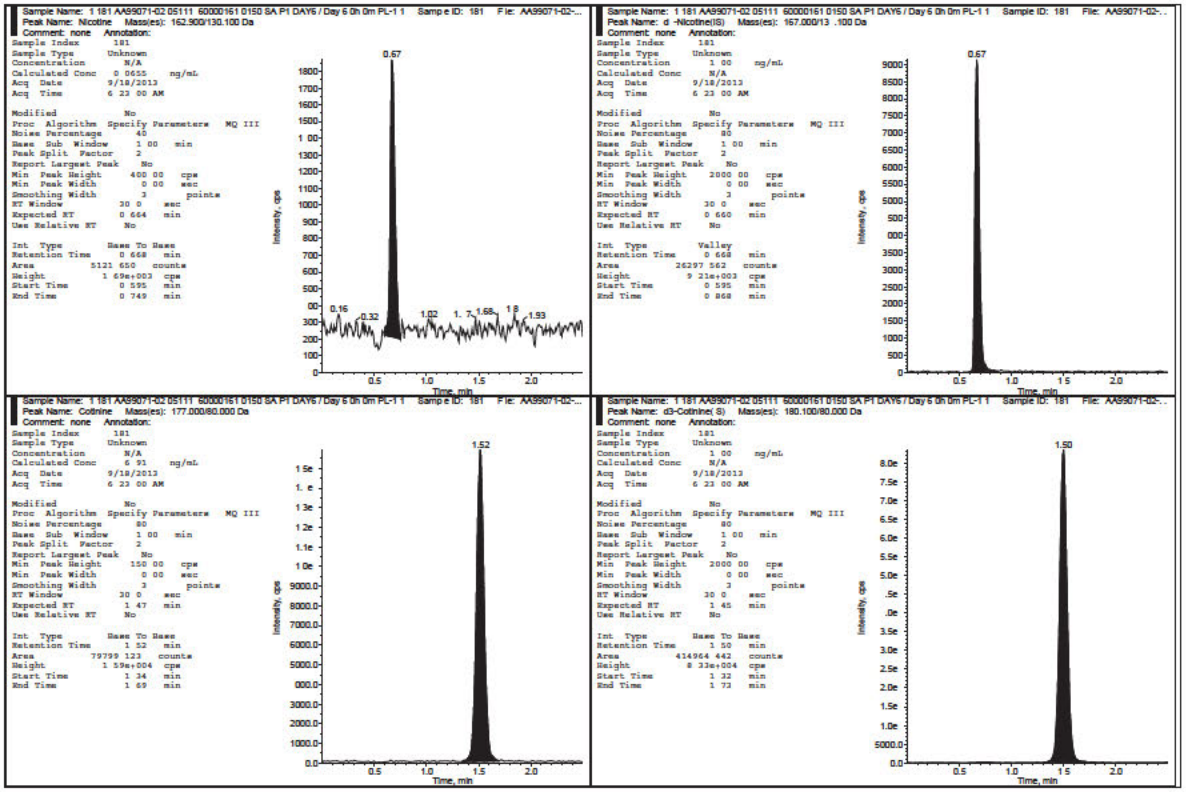

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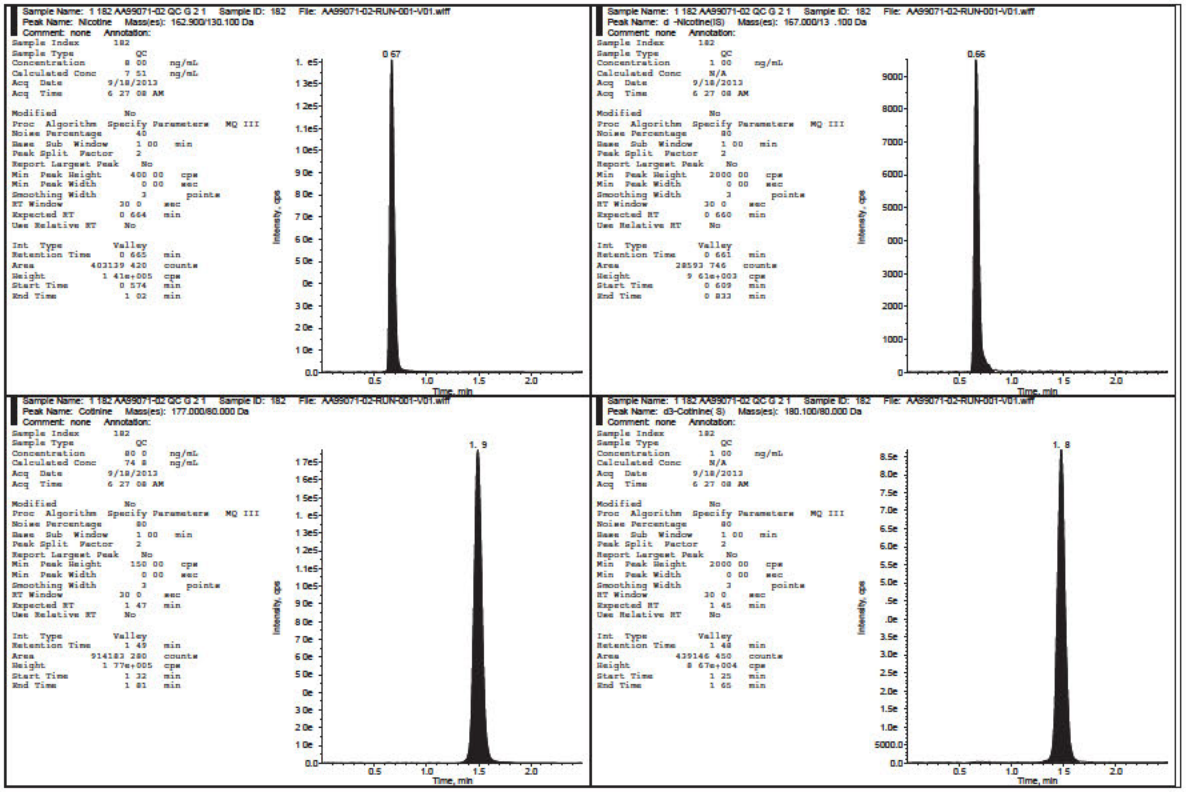

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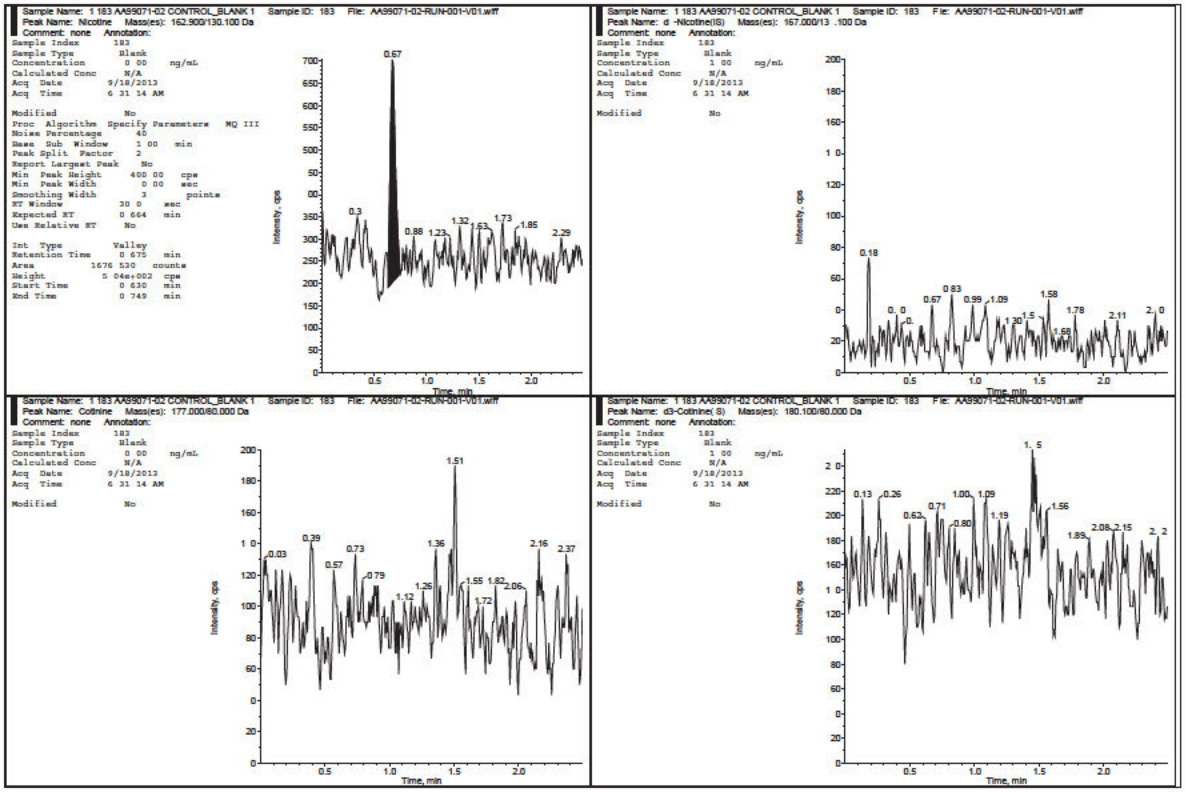

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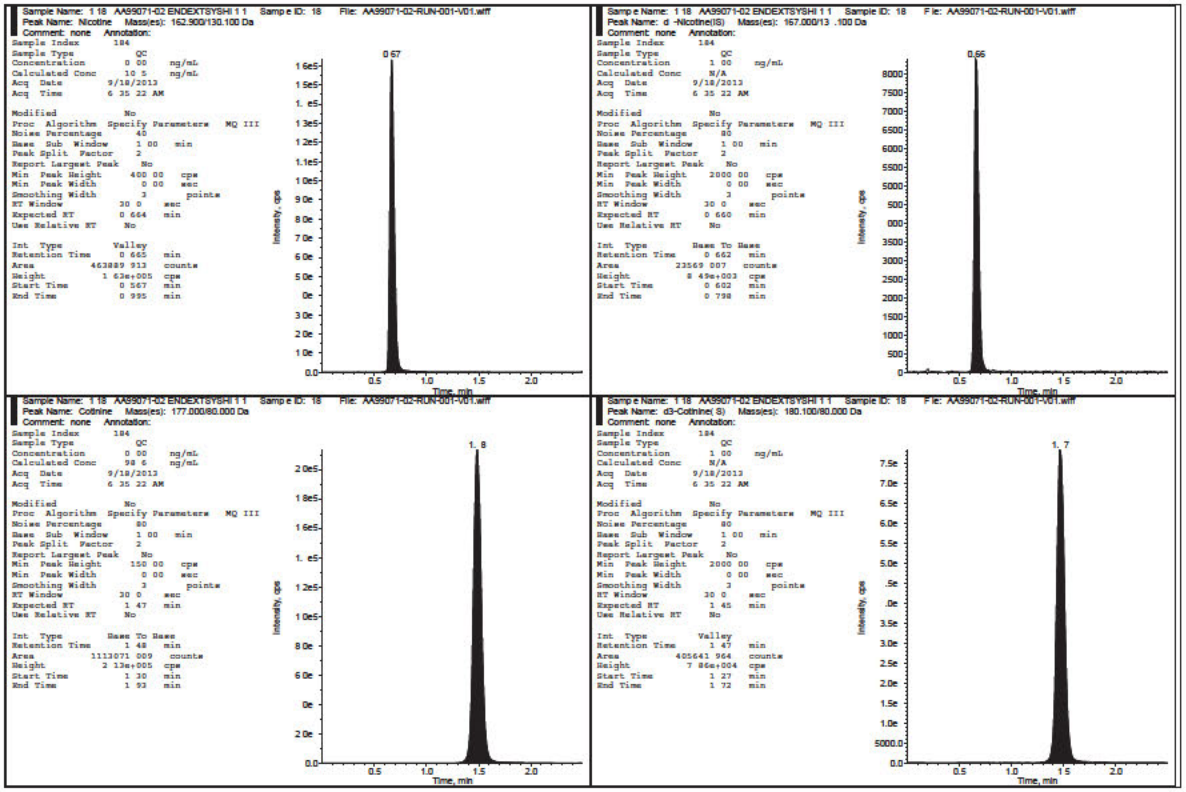

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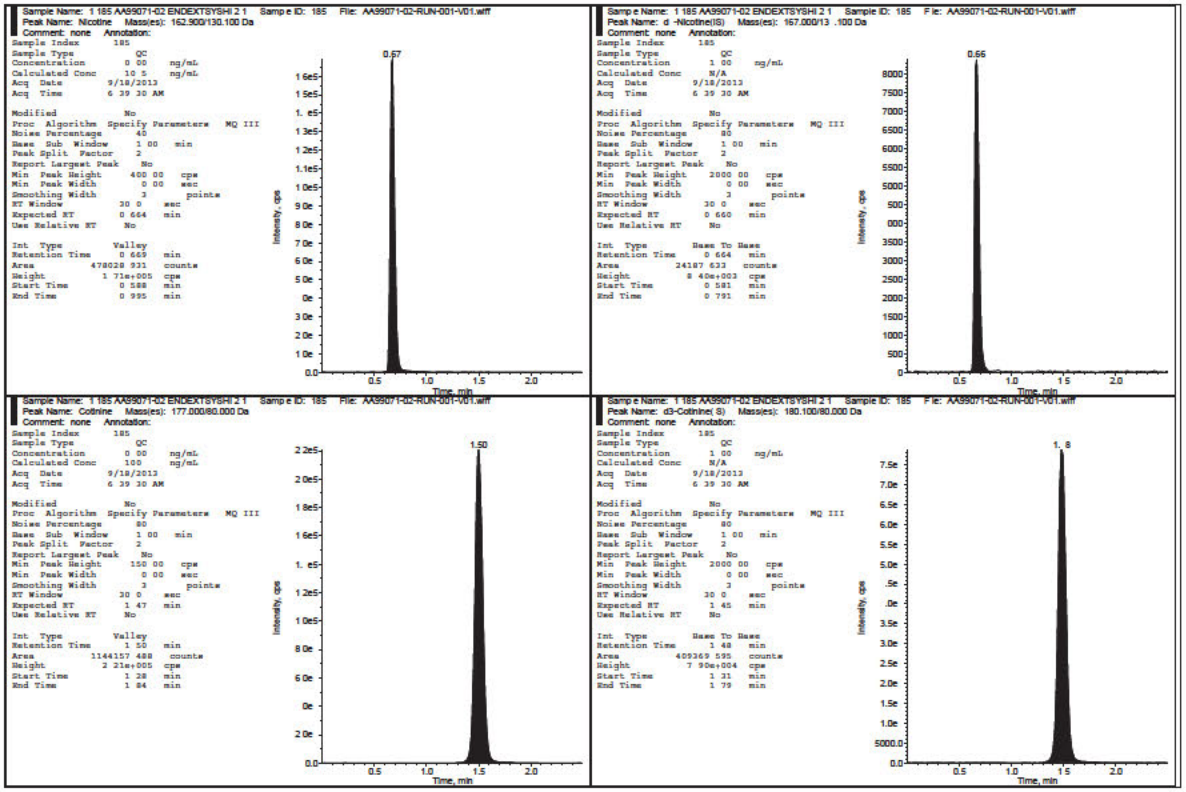

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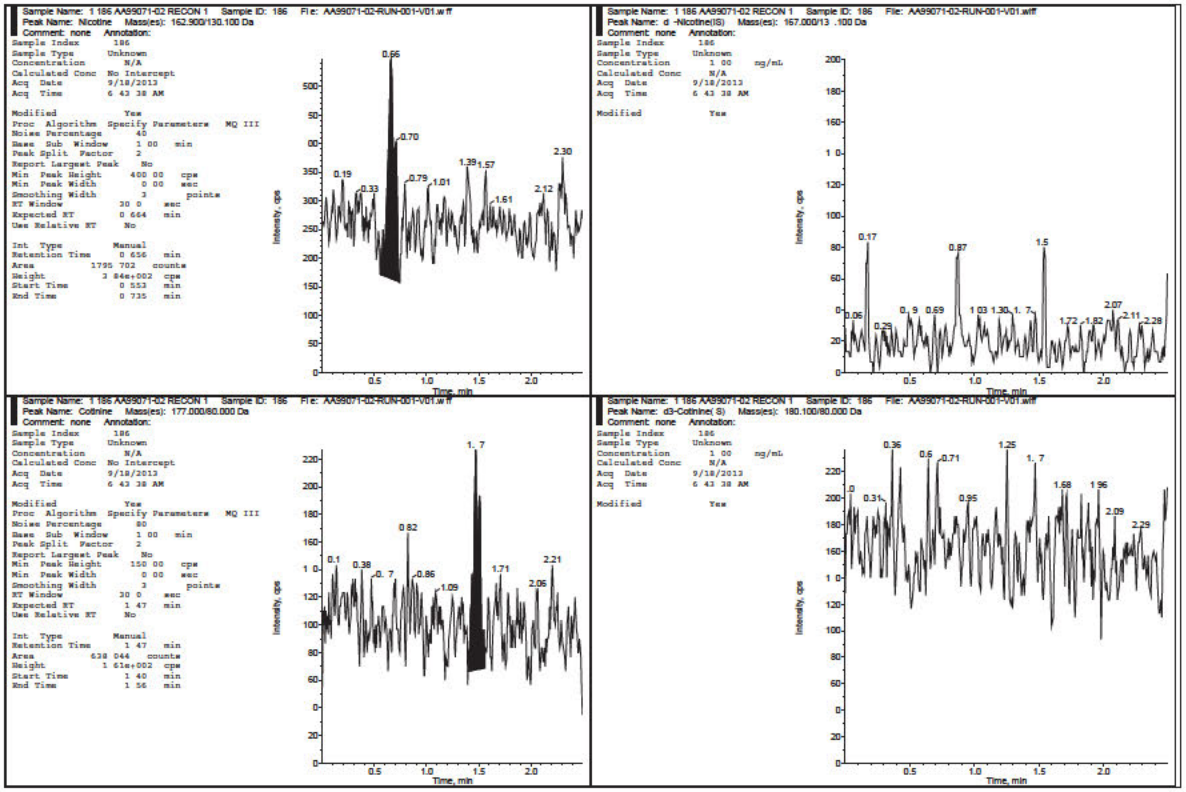
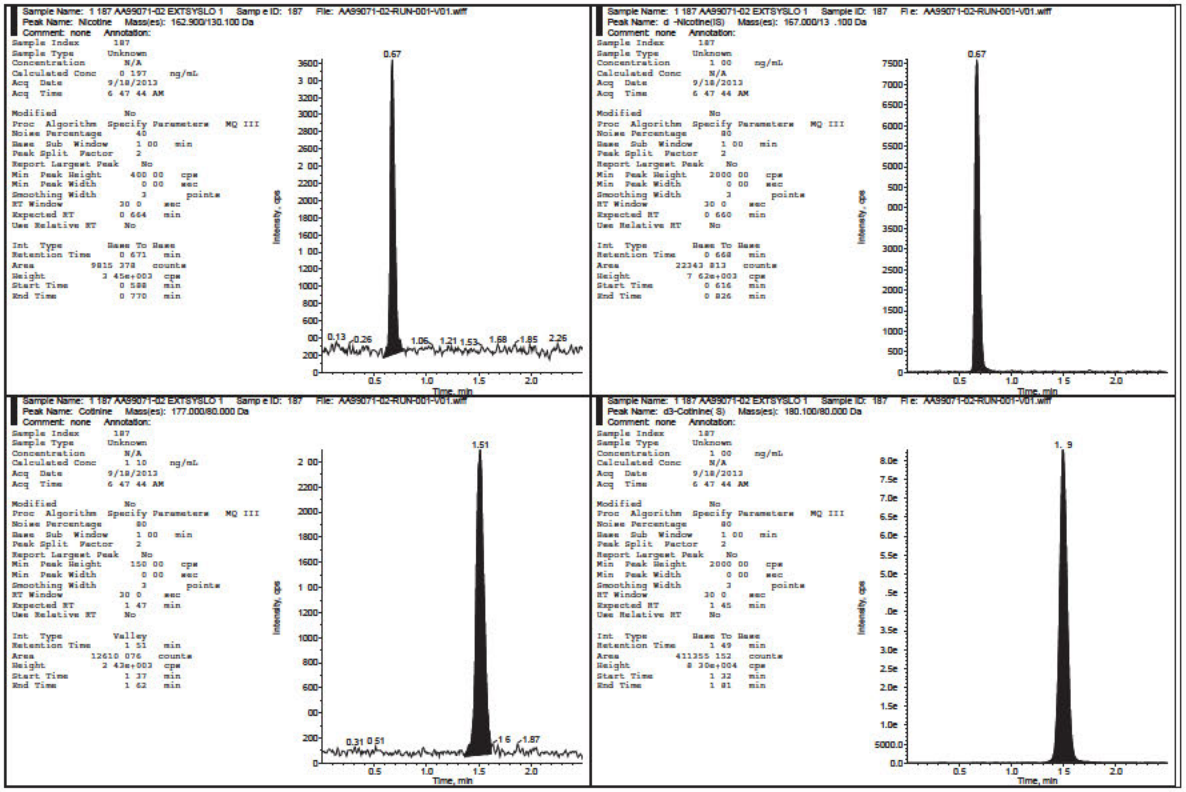
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