Independent Laboratory Validation of Dow AgroSciences LLC Method – Determination of Residues of XDE-208 and its Major Metabolites in Water using Offline Solid-Phase Extraction and Liquid Chromatography with Tandem Mass Spectrometry Detection

ABSTRACT

A study was conducted to provide independent laboratory validation data for the determination of residues of XDE-208 and its major metabolites using Dow AgroSciences residue analytical method (study number 091186) "Determination of Residues of XDE-208 and its Major Metabolites in Water using Offline Solid-Phase Extraction and Liquid Chromatography with Tandem Mass Spectrometry Detection"[7], as well as to support the stated limit of quantitation (LOQ) of the method established at 0.05 µg/L for XDE-208 and its major metabolites in water. For this independent laboratory validation, drinking (tap), surface (pond) and ground (well) water were chosen as the appropriate substrates. Untreated control samples were fortified at 0.05 µg/L, and at 0.5 µg/L with XDE-208 and its metabolites and analyzed by LC-MS/MS.

All individual recovery values for each fortified control sample were within the EPA acceptance range of 70-120 %. Average recoveries at each fortification level were within the EU acceptance range of 70-110 %. The relative standard deviation (RSD) per fortification level for each analyte did not exceed the level of ± 10%, and interferences were negligible (i.e., below the LOD of 0.015 µg/L).

The validation was considered successful as the study results satisfied the requirements of Subdivision N (Environmental Fate), Series 164-1; Publication of Addenda for Data Reporting E, K, and N Requirements for Pesticide Assessment Guidelines and Guideline OPPTS 850.7100 "Public Draft". The study was also conducted to satisfy the requirements of U.S. EPA Guideline OPPTS 860.1340(c)(6) and PR Notice 96-1.

INTRODUCTION

Analytical method, study number 091186, “Determination of Residues of XDE-208 and its Major Metabolites in Water using Offline Solid-Phase Extraction and Liquid Chromatography with Tandem Mass Spectrometry Detection”, was developed and validated at Dow AgroSciences LLC. The method was found to be suitable for the determination of residues of XDE-208 and its major metabolites X11519540, X11579457, and X11719474 in water over the concentration range of 0.05-0.50 µg/L. The validated limit of quantitation of the method was established at a concentration of 0.05 µg/L for each of the water types.

An independent laboratory validation of the method was conducted on drinking (tap), surface (pond), and ground (well) water to satisfy the requirements of the Subdivision N (Environmental Fate), Series 164-1; Publication of Addenda for Data Reporting E, K, and N Requirements for Pesticide Assessment Guidelines; Guideline OPPTS 850.7100 "Public Draft"; PR Notices 96-1 and 86-5.

The Study Director and analysts participating in the ILV were unfamiliar with the method, both in its development and subsequent use in analyzing samples. The independent laboratory used all of its own equipment and supplies; so that there was no common link between Dow AgroSciences and the ILV analysts. Throughout the conduct of the study, any communications between Dow AgroSciences and the Study Director and/or the participating analysts at JRFA were documented for inclusion in the report. No employees from Dow AgroSciences visited JRF America during the ILV trial. For this reason, the responsible laboratory fully maintained the integrity of the ILV study.

ANALYTICAL

Preparation and Storage of Samples

Drinking (Tap) Water

Water was collected on 13-May-2010 from the laboratory tap of JRF America located in King of Prussia, Pennsylvania. The appearance of the water was clear and without any detectable odor. The water was characterized by Agvise for physical and chemical properties as follows: pH 8.1, turbidity: 0.33 NTU, hardness: 224 mg equivalent $CaCO_3$/L, total suspended solids: 12 ppm, alkalinity: 161 mg $CaCO_3$/L, total organic carbon: 1.9 ppm, dissolved organic carbon: 1.6 ppm.

Surface (Pond) Water

Water was collected on 13-May-2010 from a pond located within Upper Merion Township; King of Prussia, Pennsylvania. The appearance of the water was light yellowish and without any detectable odor. The water was characterized by Agvise for physical and chemical properties as follows: pH 7.7, turbidity: 1.84 NTU, hardness: 118 mg equivalent $CaCO_3$/L, total suspended solids: 6 ppm, alkalinity: 73 mg $CaCO_3$/L, total organic carbon: 7.4 ppm, dissolved organic carbon: 7.1 ppm.

Ground (Well) Water

Water was collected on 13-May-2010 from a private well located in West Chester, Pennsylvania. The appearance of the water was clear. The water was characterized by Agvise for physical and chemical properties as follow: pH 6.7, turbidity: 0.37 NTU, hardness: 143 mg equivalent $CaCO_3$/L, total suspended solids: 8 ppm, alkalinity: 40 mg $CaCO_3$/L, total organic carbon: 1.4 ppm, dissolved organic carbon: 1.4 ppm.

Upon receipt at the laboratory, all control water matrices were stored refrigerated at all times, except when removed from the refrigerator for analysis.

Preparation of Solutions and Standards

The reagents (obtained from VWR Scientific) used within the study were of comparable grade to those described in the method (Page 11). Solutions were prepared as described in page 13 of the method.

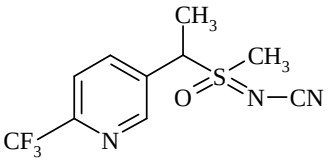
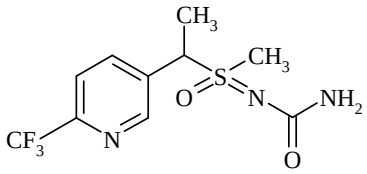
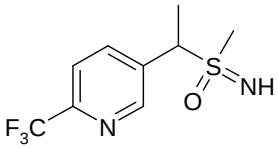
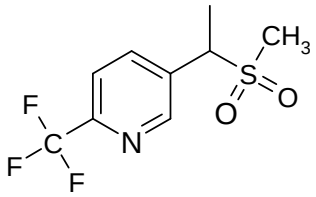
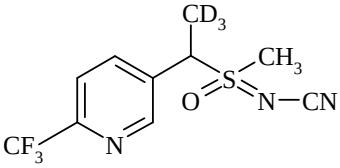
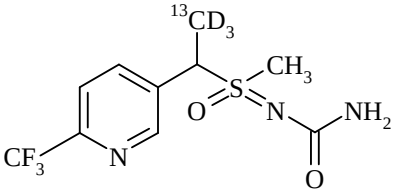
1. Acetonitrile containing 0.01% formic acid (mobile phase B)
   One hundred µL of formic acid was pipetted into a 1000-mL graduated cylinder containing approximately 900 mL of acetonitrile and mixed. The solution was diluted to volume with acetonitrile and mixed thoroughly.
2. Acetonitrile/water (80:20) (v/v) containing 0.1% formic acid
   Eighty mL of acetonitrile was added to a 100-mL graduated cylinder. One hundred µL of formic acid and approximately 15 mL of MilliQ water were added into the cylinder and mixed. The solution was allowed to equilibrate to room temperature and diluted to volume with water.
3. Water containing 0.01% formic acid (mobile phase A)
   One hundred µL of formic acid was pipetted into a 1000-mL graduated cylinder containing approximately 900 mL of MilliQ water. The solution was diluted to volume with MilliQ water and mixed.
4. Water/ acetonitrile (95/5) (v/v) containing 0.01% formic acid
   Fifty mL of acetonitrile was measured and poured into a 1000-mL graduated cylinder. One hundred µL of formic acid was added to the graduated cylinder. The solution was diluted to volume with MilliQ water and mixed.

The following analytical standards were received from the sponsor and utilized during the independent laboratory method validation:

Test Substance/ Analytical Standard	AGR/TSN Number	Percent Purity	Certification Date	Reference	Re-Certification Date
XDE-208	TSN105878	99.7	10-Feb-2009	DECO ML-AL MD-2008-003623REV	19-Jun-2010
X11519540[a]	TSN106498	98	05-Oct-2009	FAPC 09-228627	23-Oct-2011
X11579457[a]	TSN030941-0002	99	14-Jan-2010	FAPC 10-241389	07-Jan-2012
X11719474[a]	TSN030626-0003	99.5	20-Apr-2010	FAPC 10-254183	14-Aug-2012
X11843864[b]	TSN030721-0002	99.8	24-Feb-2010	FAPC 09-236732	17-Feb-2012
X11944782[c]	TSN031118-0001	97	16-Dec-2009	FAPC 09-203293	03-Feb-2011

[a] Test substance/analytical standard
[b] Internal standard of XDE-208
[c] Internal standard of X11719474

XDE-208 and Its Metabolites and Related Compounds

Common Name of Compound	Structural Formula and Chemical Name
XDE-208 (sulfoxaflor) Molecular Formula: $C_{10}H_{10}F_3N_3OS$ Formula Weight: 277.27 Nominal Mass: 277 CAS Number 946578-00-3	 [1-(6-trifluoromethylpyridin-3-yl)ethyl](methyl)-oxido-λ^4-sulfanylidenecyanamide
X11719474 Molecular Formula: $C_{10}H_{12}F_3N_3O_2S$ Formula Weight: 295.29 Nominal Mass: 295 CAS Number not available	 N-(methyl)oxido){1-[6-(trifluoromethyl)pyridine-3-yl]ethyl}-λ^4-sulfanylidene) urea
X11579457 Molecular Formula: $C_9H_{11}F_3N_2OS$ Formula Weight: 252.26 Nominal Mass: 252 CAS Number not available	 [5-[1-(S-methylsulfonimidoyl)ethyl]-2-(trifluoromethyl)pyridine
X11519540 Molecular Formula: $C_9H_{10}F_3NO_2S$ Formula Weight: 253.24 Nominal Mass: 253 CAS Number not available	 5-(1-methylsulfonyl)ethyl)-2-(trifluoromethyl)pyridine
X11843864 (XDE-208 M+3) stable-isotope Molecular Formula: $C_{10}D_3H_7F_3N_3OS$ Formula Weight: 280.29 Nominal Mass: 280 CAS Number not available	 [1-(6-trifluoromethylpyridin-3-yl)-2,2,2-^{2}H3-ethyl](methyl)-oxido-λ^4-sulfanylidenecyanamide
X11944782 (X11719474 M+4) stable-isotope Molecular Formula: $^{13}CC_9D_3H_9F_3N_3O_2S$ Formula Weight: 299.30 Nominal Mass: 299 CAS Number not available	 N-(methyl)oxido){2-^{13}C-2,2,2-^{2}H3-1-[6-(trifluoromethyl)pyridine-3-yl]ethyl}-λ^4-sulfanylidene) urea

Preparation of XDE-208 (Sulfoxaflor) and Metabolite Stock Solutions

The stock standard solutions were prepared from the solid reference material obtained from the Sonsor. All sock standard solutions were prepared in 100% acetonitrile and stored in a refrigerator when not in use. The stable isotope standard X11843864 was received as a 100-µg/ml solution, which was used as the stock standard solution.

Analyte	Adjusted Weight (g)	Dilution volume (mL)	Concentration (µg/mL)	Date
X11422208 (XDE-208)	0.0100	10.0	1000	10-May-2010
X11519540	0.0100	10.0	1000	10-May-2010
X11579457	0.0100	10.0	1000	10-May-2010
X11719474	0.0100	10.0	1000	10-May-2010
X11843864	-	-	100	10-May-2010
X11944782	0.0060	6.0	1000	10-May-2010

Fortification standard solutions were prepared by diluting the above stock solutions with acetonitrile as follows:

Concentration of Stock Soln.	Aliquot of Stock Soln.	Final Soln. Volume	Final Soln. Conc	Preparation Date
(µg/mL)	(mL)	(mL)	(µg/mL)	
1000	0.5 x 4	20.0	25	10-May-2010
25	2.0	20.0	2.5	10-May-2010
2.5	10	20.0	1.25	10-May-2010
2.5	4.0	20.0	0.5	10-May-2010
2.5	2.0	20.0	0.25	10-May-2010
0.25	10	20.0	0.125	10-May-2010
0.25	4.0	20.0	0.05	10-May-2010
0.25	2.0	20.0	0.025	10-May-2010
0.025	10	20.0	0.0125	10-May-2010
0.025	4.0	20.0	0.005	10-May-2010
0.025	2.0	20.0	0.0025	10-May-2010
0.0025	12	20.0	0.0015	10-May-2010

Preparation of the Mixed Staple-Isotope Internal Standard Solution

Mixed internal standard solution was prepared by pipetting 0.5 mL of the 100-µg/mL X11843864 and 0.05 mL of 1000-µg/mL X11944782 solutions into a single 50-mL volumetric flask. The solution was diluted to volume with acetonitrile to obtain a mixed solution containing 1.00 µg/mL of each compound.

Preparation of Calibration Standards for Samples

The calibration standards were prepared by dispensing 250 µL of the 1.00-µg/mL mixed stable isotope internal standard solution and 1000 µL of the 0.0015-1.25-µg/mL fortification standards into a series of 20-mL volumetric flask and diluting to volume with a solution of water/acetonitrile solution (95:5) containing 0.01% formic acid. Each calibration standard solution contained equal concentrations for XDE-208 and X11519540, X11579457, X11719474, and 12.5 ng/mL of each internal standard X11843864 and X11944782.
The concentrations of the calibration standards are as follows:

Concentration of Spiking Soln.	Aliquot of Spkg. Soln.	Final Soln. Volume	Calib Soln. Final Conc.	Preparation Date
µg/mL	mL	mL	ng/mL	
1.25	1.00	20.0	62.5	11-May-2010
0.5	1.00	20.0	25	11-May-2010
0.25	1.00	20.0	12.5	11-May-2010
0.125	1.00	20.0	6.25	11-May-2010
0.05	1.00	20.0	2.5	11-May-2010
0.025	1.00	20.0	1.25	11-May-2010
0.0125	1.00	20.0	0.625	11-May-2010
0.005	1.00	20.0	0.25	11-May-2010
0.0025	1.00	20.0	0.125	11-May-2010
0.0015	1.00	20.0	0.075	11-May-2010

Preparation of XDE-208 (X11422208) Standards to Determine Isotopic Crossover

One thousand µL of the 0.250-µg/mL X11422208 mixed fortification solution were diluted to 20-mL with a solution of water/acetonitrile solution (95:5) containing 0.01% formic acid. The resulting solution contained 12.5 ng/mL of a mixed X11422208 solution.

Preparation of XDE-208 Mixed Internal Standards to Determine Isotopic Crossover

Two hundred fifty µL of the 1.00 µg/mL XDE-208 mixed internal standard solution were diluted to 20-mL with a solution of water/acetonitrile solution (95:5) containing 0.01% formic acid. The resulting solution contained 12.5 ng/mL of a mixed XDE-208 internal standard solution.

Fortification of Recovery Samples

The samples in the analytical sets for each water type consisted of the following:

1 reagent blank (containing no matrix or analyte)
2 unfortified control samples for each water type
5 control samples fortified at 0.050 µg/L with XDE-208, X11519540, X11579457, and X11719474 (the LOQ of the method)
5 control samples fortified at 0.50 µg/L with XDE-208, X11519540, X11579457, and X11719474 (10 x LOQ).

Sample Extraction, Purification and Analysis

The reagent blank, one of the control samples receiving no fortification and 5 controls fortified at 0.05 µg/L were analyzed using SPE purification procedure for each water type. Another unfortified control and 5 controls fortified at 0.5 ug/L were analyzed without SPE purification for each water type.

Analysis Procedure Without SPE Purification

1. 4.0 mL of the control water were pipetted into a series of 16-mL glass test tubes.
2. 40 µL of 1.0 N hydrochloric acid was added to the sample tube.
3. For preparing fortified samples, 40 µL of the 0.05-µg/mL standard solution was dispensed into the sample tube.
4. 50 µL of the 1.00-µg/mL mixed internal standard solution was added into the sample vial.
5. The sample tube was capped with a PTFE-lined cap and then mixed for 1-2 seconds.
6. The samples were filtered with a Whatman syringeless 0.45-µm filter device.
7. The samples were analyzed by LC/MS/MS with positive-ion electrospray tandem mass spectrometry.

Analysis Procedure With SPE Purification

1. Ten mL of the control water were pipetted into a series of 16-mL glass test tubes.
2. One hundred µL of 1.0 N hydrochloric acid was added to each sample tube.
3. For preparing amples fortified at 0.05 µg/mL, 100-µL aliquots of the 0.005-µg/mL spiking solutions were dispensed into the sample tube.
4. The sample tube was capped with a PTFE-lined cap and then mixed on Vortex for 1-2 seconds.
5. The sample was purified using the following SPE procedure:
    a. An OASIS® HLB SPE cartridge (3-mL, 60 mg) was placed on the vacuum manifold and conditioned with 1 mL of acetonitrile. The cartridge was dried using full vacuum for approximately 5 seconds. The cartridge was subsequently conditioned with 1 mL of 0.01 N hydrochloric acid. The eluate was discarded.
    b. The sample was transferred to the SPE cartridge using a disposable pipette. The flow rate was controlled at approximately 1 mL/min.
    c. The sample tube was rinsed with 1 mL of 0.01 N hydrochloric acid and transferred to the SPE cartridge. After the eluate eluted through the cartridge, the cartridge was dried under full vacuum for approximately 60 seconds.
    e. XDE-208 and metabolites were eluted from the SPE column with two 500-µL aliquots of an acetonitrile/water solution (80:20) containing 0.10% formic acid. The eluate was collected into a graduated test tube.
6. Twenty-five µL of the 1.00-µg/mL mixed internal standard solution was added into the sample vial.
7. The sample volume was adjusted to 2.0 mL with a solution of water/acetonitrile solution (95:5) containing 0.01% formic acid.
8. The sample was transferred to a 2-mL autosampler vial for LC/MS/MS analysis.

Analytical Instrumentation and Equipment

Prior to initiation of the first ILV trial, the JRFA laboratory used calibration standard solutions for establishing the instrumental parameters that would be used for the LC/MS/MS system. These preliminary assessments included optimizing the mass spectrometer, establishing adequate HPLC retention times, and testing the sensitivity and linearity of the standards.

Liquid Chromatography Operating Conditions

Instrumentation:	Waters Acquity UPLC system
Column:	Agilent Zorbax SB-C8 4.6 x 75 mm, 3.5-µm
Column Temperature:	Ambient
Injection Volume:	10 µL
Mobile Phase:	A – water containing 0.01% formic acid B – acetonitrile containing 0.01% formic acid
Run Time	14 minutes
Flow Rate:	400 µL/min

Gradient:

Time, min	A, %	B, %
0.00	100	0
3.00	100	0
8.00	0	100
10.00	0	100
11.00	100	0
14.00	100	0

Mass Spectrometry Operating Conditions

Instrumentation:	Applied Biosystems QTRAP 4000 MS System Applied Biosystems Analyst 1.4.2 data system
Ionization Mode:	Turbospray
Polarity:	positive
Scan Type:	MRM
Resolution:	Q1 – unit, Q3 – unit
Curtain Gas (CUR)	40 psi
Collision Gas (CAD):	2.0
Ion Source Gas 1 (GS1)	80 psi
Ion Source Gas 2 (GS2)	10 psi
Temperature (TEM):	475 °C
Entrance Potential (EP):	10 volts
IonSpray Voltage (IS):	5200 volts
Acquisition Time Delay:	0.00 minutes
Period Duration:	14.0 minutes
Dwell Time:	50 ms

Analytes:	Precursor Ion, Q1	Product Ion, Q3	Declustering Potential, v	Collision Energy, v	Cell Exit Potential, v
X11422208					
Quantitation	278.0	174.1	41	13	15
Confirmation	278.0	154.0	41	41	8
X11719474					
Quantitation	296.1	174.0	41	17	10
Confirmation	296.1	154.0	41	47	8
X11519540					
Quantitation	254.0	175.0	61	27	10
Confirmation	254.0	154.0	61	59	8
X11579457					
Quantitation	253.1	174.0	26	11	10
Confirmation	253.1	154.0	26	37	8
X11843864 (M+3 ISTD) (XDE-208 stable isotope)					
Quantitation	281.0	177.0	41	15	10
Confirmation	281.0	156.0	41	41	8
X11944782 (M+4 ISTD) (X11719474 stable isotope)					
Quantitation	300.0	177.9	46	17	10
Confirmation	300.0	157.1	46	47	8

Calculations

Linear regression equations were generated using 10 different concentration levels of calibration standards interspersed throughout the run. Linear regression calculation was performed by the Analyst software, with 1/x weighting, using the residue concentration ratio (analyte)/(internal standard), in (µg/L)/(ng/mL), for the X-axis, versus the peak area ratio (analyte peak area)/(internal standard peak area) for the Y-axis. For compounds X11519540 and X11579457, the regression was performed by the Analyst software, with 1/x weighting, using the residue concentration for the X-axis, versus the peak area for the Y-axis.

Calibration standards (see Figure 1 to Figure 4 for examples) consisted of 0.075, 0.125, 0.25, 0.625, 1.25, 2.50, 6.25, 12.5, 25.0 and 62.5 ng/mL of XDE-208 and its major metabolites X11519540, X11579457, X11719474, all containing 12.5 ng/mL of internal standards X11843864 and X11944782.

Concentrations (µg/L) of XDE-208 and its major metabolites in samples were determined by substituting the peak area ratios into the linear regression equation as shown below:

Y = aC + b

Y: Ratio: (Analyte peak area / IS peak area) or peak area

C: Ratio: (Analyte concentration/ IS concentration) or residue concentration in final extract

a: slope

b: intercept

Thus:

C = ((Y – b) x Conentration of IS / a

C = ((Y – b) / a for X11519540 and X11579457

ppb (µg/L) in sample = C x Final volume (mL)/ (initial sample volume mL)

For the samples prepared without SPE, the final volume = initial sample volume

Recoveries (Rec.) were calculated for the fortified specimens as follows:

Recovery = (ppb in sample – ppb in control) / $ppb_{fortified}$ x 100 %

Example for Calculation

The calculation is exemplified with the tap water specimen Tap UTC+0.05ppb-1.

10 mL of tap water were fortified at 0.05 µg/L by dosing with 0.1 mL of the 0.005-µg/mL XDE-208 and three metabolites mixed solution. After sample preparation, the final volume was adjusted to 2.0 mL.

The final extract was analyzed by LC/MS/MS, resulting in a X11519540 peak area of 45111 counts for the quantitation transition ion *m/z* 254->175. A concentration of 0.276 ng/mL was obtained in the final extract using the analyst software.

ppb (µg/L) in the sample = 0.276 x 2.0/ 10.0 = 0.055

No residues were detected in the control

Recoveries (Rec.) were calculated for the fortified specimens as follows:

Rec. = (ppb in spiking– ppb in control) / $(ppb)_{fortified}$ x 100 %

= (0.055 µg/L / 0.050 µg/L) x 100 %

= 110 %

Statistical Treatment of Data

The mean recoveries for the fortified samples were calculated using the "AVERAGE" function of the Microsoft Excel spreadsheet computer program, which divides the sum of the selected cells by the number of determinations. The standard deviation of the recoveries for a fortification level of one matrix type was calculated using the "STDEV" function of the same spreadsheet program, which sums the squares of the individual deviations from the mean, divides by the number of degrees of freedom, and extracts the square root of the quotient. Percent relative standard deviation, % RSD, was calculated by dividing the standard deviation by the mean, and then multiplying by 100.

Confirmatory Evaluation

As presented in the instrument condition section, two ion transitions were monitored for each compound, and the peak area ratio of the two ion transitions was computed. The presence of XDE-208 and its metabolites X11519540, X11579457, X11719474 was confirmed by calculating the difference between the ratios found for each individual sample and the overall average ratios found for the calibration standards.

Determination of Isotopic Crossover

The experiments for investigation of potential crossover between stable-isotope labeled internal standards and the unlabeled compounds were conducted. The standards prepared in the section "Preparation of XDE-208 mixed Internal Standards to Determine Isotopic Crossover" were injected using the same instrument methods as used for sample analysis. The peak area ratios for isotopically labeled and unlabeled compounds in each standard solution were examined.
For compound XDE-208 and its internal standard X11843864, the crossover factors were listed as the average of two injections.

$$\text{Crossover Factor (analyte} \rightarrow \text{ISTD)} = \frac{\text{peak area at } m/z \text{ 281/177}}{\text{peak area at } m/z \text{ 278/174}} = 0$$

$$\text{Crossover Factor (ISTD} \rightarrow \text{analyte)} = \frac{\text{peak area at m/z 278/174}}{\text{peak area at m/z 281/177}} = 0.0003$$

For compound X11719474 and its internal standard X11944782

$$\text{Crossover Factor (analyte} \rightarrow \text{ISTD)} = \frac{\text{peak area at m/z 300/178}}{\text{peak area at m/z 296/174}} = 0$$

$$\text{Crossover Factor (ISTD} \rightarrow \text{analyte)} = \frac{\text{peak area at m/z 296/174}}{\text{peak area at m/z 300/178}} = 0.0007$$

Problems Encountered, Changes or Modifications Made, and Critical Steps

ILV studies are meant to show that an independent lab can follow the method as written and obtain results similar to those shown in the validated method. The different instrumentation employed in this ILV study required that the chromatographic and spectroscopic parameters be modified for the equipment used. Because the instrumentation used in this ILV study was of lower sensitivity than that described in the method, the effluent flow from the column was not split prior to mass spectral analysis and a flow rate of 0.4 ml/minute was determined to be optimum for use in the analysis. No problems were encountered with the methodology, nor were other necessary changes made for the successful execution of this study.

REFERENCES

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