U.S. FOOD & DRUG ADMINISTRATION

GC/MS Headspace Method for Detection of NDMA in Valsartan Drug Substance and Drug Products

Background:
Valsartan products are used to treat high blood pressure and congestive heart failure. On July 13, 2018, FDA announced a recall of valsartan tablets because of the potential for certain products to contain an impurity, N-nitrosodimethylamine (NDMA). This impurity is classified as a probable human carcinogen and is believed to have been introduced into the finished products as a result of the manufacturing process of the drug substance. OTR has been asked to develop a gas chromatography-mass spectrometry (GC/MS) headspace method to detect the presence of NDMA in valsartan drug substance and drug products.

Conclusions:
The OTR method was developed on **drug substance** samples. The method details are reported below. A separate report including full method validation will follow.

Impurity	LOD (ppm)	LOQ (ppm)
N-nitrosodimethylamine (NDMA)	0.05	0.3

N-Nitrosodimethylamine (NDMA) Impurity Assay in Valsartan Drug Substance and Drug Products by GC/MS-HS

Equipment/Instrument:
Gas Chromatography System with a Quadrupole Mass Spectrometry Detector and Headspace Auto-sampler
DB-Wax GC Column, 30 m x 0.25 mm, 0.5 µm, or equivalent
Analytical Balance
Wrist Action Mechanical Shaker
Vortex Mixer
Tablet Cutter
20 mL Headspace Vials
HS vial caps with Teflon/Silicone septa

N-Nitrosodimethylamine (NDMA) Reference Standard:
Use commercially available NDMA standard solution in methanol. Alternatively, prepare a 100 µg/mL standard solution in DMSO from a NDMA reference standard. Correct for purity.

Diluent: Dimethyl sulfoxide (DMSO), > 99.5%

Standard Solution Preparations (0.15 – 20 µg/mL):
Transfer the appropriate aliquot volume of the designated standard solution into separate volumetric flasks and dilute to volume with DMSO. Refer to the table below for a suggested standard preparation scheme.

Standard Solution Preparation Scheme:

Standard	Aliquot Vol. (mL)	NDMA Std. Solution (µg/mL)	Total Vol. (mL)	NDMA Conc. (µg/mL)
1	1.0	100 µg/mL	5.0	20.0
2	1.0	100 µg/mL	10.0	10.0
3	1.0	100 µg/mL	20.0	5.0
4	1.0	5 µg/mL	5.0	1.0
5	1.0	5 µg/mL	10.0	0.50
6	1.0	5 µg/mL	20.0	0.25
7	3.0	0.50 µg/mL	10.0	0.15

Working Standard Preparations (0.15 – 100 µg):
Transfer a 1.0 mL aliquot volume of the standard solutions into separate 20 mL headspace vials containing 4.0 mL of DMSO. Immediately cap and crimp the headspace vials. Refer to the table below for the working standard preparation scheme.

Working Standard Preparation Scheme:

Working Standard	NDMA Std. Solution (µg/mL)	Aliquot Vol. (mL)	DMSO Vol. (mL)	Total Vol. (mL)	NDMA Amount (µg)
1	0.15	1.0	4.0	5.0	0.15
2	0.25	1.0	4.0	5.0	0.25
3	0.5	1.0	4.0	5.0	0.5
4	1.0	1.0	4.0	5.0	1.0
5	5.0	1.0	4.0	5.0	5.0
6	10.0	1.0	4.0	5.0	10.0
7	20.0	1.0	4.0	5.0	20.0
8	100	1.0	1.0	5.0	100

Sample Preparation:

Drug Substance
Accurately weigh 500 mg of Valsartan drug substance into a 20 mL headspace vial. Add 5 mL of DMSO to the vial and immediately cap and crimp the vial. Mix the sample solution using a vortex mixer. Drug substance weight could be increased or decreased, depending on the amount of NDMA impurity in the drug substance.

Drug Product
Depending on the size, cut the tablet at least in half and accurately weigh into a 20 mL headspace vial. Add 5 mL of DMSO to the vial and immediately cap and crimp the vial. Let the vial sit for about 10 minutes and shake the vial using a mechanical wrist action shaker for at least 30 minutes or until the contents of the tablet are dispersed into the solution. Two or more tablets can be combined in a vial depending on the labeled strength and size of the tablet. The total weight of the tablet(s) should be around 1 gram.

GC/MS-HS Parameters:
Note: The method was validated and optimized using an Agilent 7890B GC System with an Agilent 5977A MSD and an Agilent 7697A Headspace Auto-sampler.

GC/MS - HS Parameters	
Instrument:	Agilent 7890B GC with Agilent 5977A MSD and Agilent 7697A HS Auto-sampler
Column:	DB-WAX, 30 m x 0.25 mm, 0.5 µm (PN: 122-7033), or equivalent
Inlet Temperature:	220 °C
Column Flow:	3 mL/min
Split Ratio	5:1
Oven Program:	70 °C for 4 min.; 20 °C/min to 240 °C, Hold for 3.5 min.
GC Run Time	16 min.
GC Cycle Time:	23 min.
HS Auto-sampler Parameters	
Oven Temperature:	120 °C
Loop Temperature:	125 °C
Transfer Line Temperature:	130 °C
Vial Equilibration Time:	15 min
Injection Time:	1.0 min
Vial Size:	20 mL
Vial Shaking:	Level 9 (250 shakes/min)
Fill Pressure:	15 psi
Loop Size:	1 mL
MS Parameters	
MS Source Temperature:	230 °C
Quad Temperature:	150 °C
Acquisition Type:	SIM
Gain Factor	1
Solvent Delay:	4.0 min.
SIM Ion	m/z 74.0
Dwell Time:	200 ms

System Suitability:
The correlation coefficient (R) of the linear calibration curves should be ≥ 0.995.
The S/N ratio of the 0.25 µg working standard should be ≥ 10.

Calculations:
Plot the NDMA peak areas against the standard concentration (µg). Plot two calibration curves – one from 0.15 – 20 µg and the other from 0.15 – 100 µg. Determine the intercepts, slopes and correlation coefficients of the linear curves. NDMA peaks ≤ the 20 µg working standard peak should be quantitated using the 0.15 – 20 µg calibration curve. NDMA peaks > the 20 µg working standard peak should be quantitated using the 0.15 – 100 µg calibration curve. Calculate the

NDMA impurity (ppm) using the formula below:

$$\text{NDMA (ppm)} = [(y - b) / m] \div \text{wt.}$$

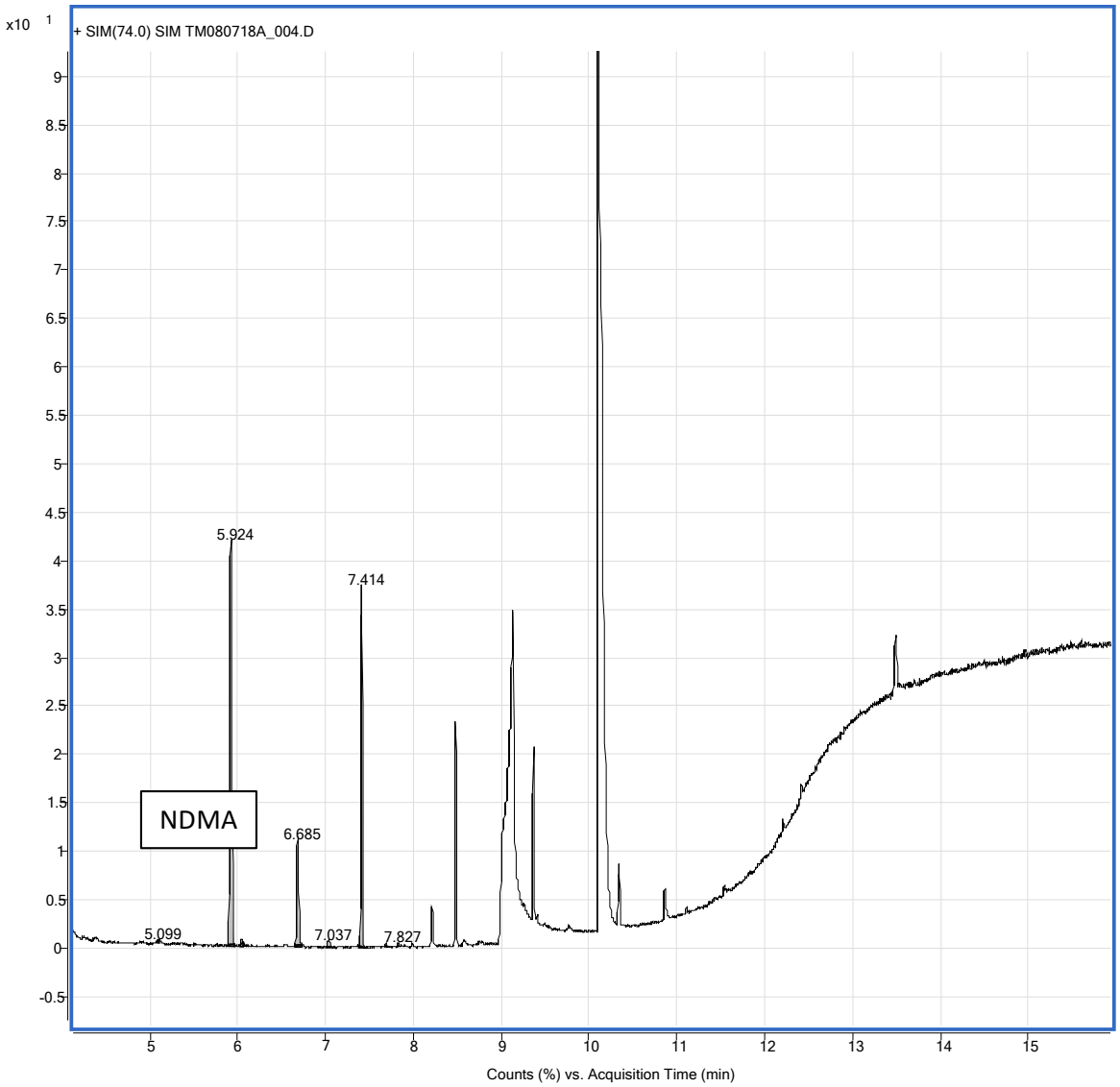
where: y = NDMA peak area
b = intercept of the linear curve
m = slope of the linear curve
wt. = Valsartan API weight (g)

Report any NDMA peak ≥ 0.3 ppm (LOQ)

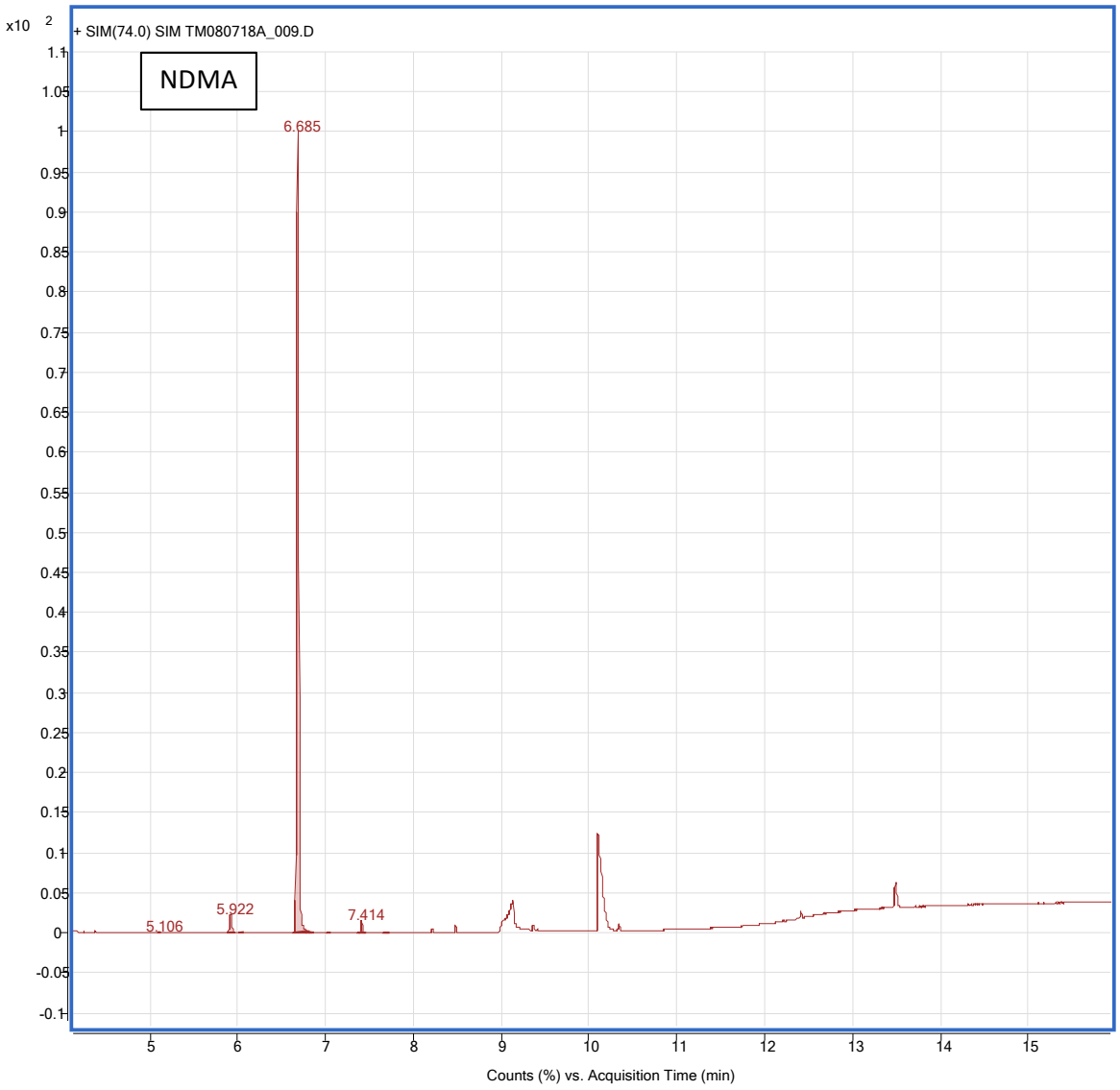
Limit of Quantitation / Limit of Detection:
Limit of detection (LOD) was determined by preparing standards of known concentrations and calculating the signal to noise ratio. The lowest standard concentration with a S/N of ≥ 3 was designated as the method LOD. Limit of Quantitation (LOQ) was determined by spiking known amount of standard at different levels into replicate samples (n = 3) of Valsartan drug substance. Spiked sample level with recoveries of 80 – 120% and a % RSD of ≤ 10 was designated as the method LOQ.

Example Chromatograms:

0.25 µg NDMA Working Standard



20 µg NDMA Working Standard



Valsartan Drug Substance