Determination of NDMA (HS-GC-MS) Method 3/30- Issue No. 1.1



1. Principle:

This method involves the use of HS-GC-MS (single quad) for the determination of N-Nitrosodimethylamine (NDMA).

2. Scope:

This method is applicable to Active Pharmaceutical Ingredients (API) and Powdered Tablets. These samples are preliminarily screened in Scan mode, **Procedure A**. If NDMA is found to be present, samples undergo a NDMA Quantification method, outlined in **Procedure B**. If no NDMA is found samples follow **Procedure C**.

3. Apparatus:

- 3.1 HS-GC-MS: Shimadzu GC-2010Plus Gas Chromatograph (Item No. 1043B), Headspace HS-20 auto-sampler (Item No. 1043A), GC-MS QP2020 Mass Spectrometer (Item No. 1043C), or equivalent.
- 3.2 Autopipettes, Gilson or equivalent: $(1,000 \mu L, 200 \mu L, 100 \mu L, 20 \mu L, 10 \mu L)$.
- 3.3 Capillary GC Column: Restek Rtx-624 (30m x 0.25 mm I.D, 1.4µm).

4. Reagents:

- **4.1 Solvent:** Dimethyl sulfoxide (DMSO), (Merck SupraSolv, Dimethyl Sulfoxide for headspace gas chromatography), Catalogue no. 101900.
- 4.2 Helium gas (CP grade), BOC supplied or equivalent.
- **4.3** Reference Standard: NDMA (N-nitrosodimethyl amine), Restek Catalog no. 31427, Concentration 1000μg/mL in Methanol (Reference Standard).
- **4.4 Quality Control Standard:** NDMA (N-nitrosodimethyl amine), Supelco Catalog no. 48670, Concentration **200**µg/mL in Methanol (QC).

Prepared solutions are protected from light prior to analysis.

5. Calibration Standards:

5.1 Stock standard Solution (NDMA) 200 µg/mL

Dilute 200 μ L of NDMA Reference Standard (4.3) to 1mL in DMSO, in a volumetric flask.

5.2 <u>1μg/mL NDMA Standard:</u>

Dilute $10\mu\text{L}$ of stock standard ($200\mu\text{g/mL}$) (5.1) to 2mL with DMSO, in a volumetric flask.

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6. Quality Control Standard:

6.1 2µg/mL NDMA QC Solution:

Dispense $10\mu L$ of Quality Control Standard, $200\mu g/mL$ (4.4) into a headspace vial, add 1.0 mL of DMSO, cap and crimp.

7. Methods of Analyses:

7.1 Procedure A - Preliminary scan*

7.1.1 2µg/mL NDMA Check Standard:

Dispense $10\mu\text{L}$ of stock standard ($200\mu\text{g/mL}$) (5.1) into a headspace vial, add 1.0 mL DMSO, cap and crimp.

(A higher concentration standard may be used to achieve a greater response).

7.1.2 Sample Preparation

Place 0.20-0.25g of powdered tablet or API in a headspace vial, add 1.0 mL of DMSO, cap and crimp.

7.1.3 Analyses

Perform a full mass scan on the standard (7.1.1) and sample (7.1.2) using the GC and Headspace conditions specified in **Procedure A** (Annex I).

Establish the retention time, and confirm that the mass spectrum obtained from the eluted peak in the standard solution is that of NDMA.

Continue with Quantification of NDMA, Procedure B (7.2), if NDMA is detected in the sample, or with Procedure C (LOD/LOQ determination, 7.3) if NDMA is not detected.

*This preliminary scan method can detect NDMA at a level of 10 μ g/g. As LOD/LOQ determination (Procedure C) has a lower detection limit of 0.04 μ g/g, if an appreciable amount of NDMA is observed when carrying out LOD/LOQ determination (Procedure C) (7.3) the sample in question will be reanalysed using Quantification of NDMA (Procedure B).

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7.2 Procedure B - Quantification of NDMA

7.2.1 Sample Preparation (Tablets)

Accurately weigh the same amount of sample (0.20-0.25g) into each of 4 Headspace vials.

- 7.2.1.1 Add 1.0mL of DMSO to Vial 1, cap and crimp.
- 7.2.1.2 Add 2μg (10μl of Stock standard solution (5.1)) of NDMA to Vial 2 and make up to 1.0mL with DMSO, cap and crimp.
- 7.2.1.3 Add 4μg (20μl of Stock standard solution (5.1)) of NDMA to Vial 3 and make up to 1.0mL with DMSO, cap and crimp.
- 7.2.1.4 Add 6μg (30μl of Stock standard solution (5.1)) of NDMA to Vial 4 and make up to 1.0mL with DMSO, cap and crimp.
- 7.2.1.5 Run all solutions using the GC and Headspace conditions described in Procedure B (Annex 1). Plot the standard addition curve and obtain the sample NDMA concentration (μg/mL) from the intercept. See calculated example in Annex 2.

7.2.2 Sample Preparation (API)

- 7.2.2.1 Accurately weigh the same amount of sample (0.05-0.2g) into each of 4 vials.
- 7.2.2.2 Add 1.0mL of DMSO to Vial 1, cap and crimp.
- 7.2.2.3 Add 2μg (10μl of Stock standard solution (5.1)) of NDMA to Vial 2 and make up to 1.0mL with DMSO, cap and crimp.
- 7.2.2.4 Add 4μg (20μl of Stock standard solution (5.1)) of NDMA to Vial 3 and make up to 1.0mL with DMSO, cap and crimp.
- 7.2.2.5 Add 6μg (30μl of Stock standard solution (5.1)) of NDMA to Vial 4 and make up to 1.0mL with DMSO, cap and crimp.
- 7.2.2.6 Run all solutions using the GC and Headspace conditions described in Procedure B (Annex 1). Plot the standard addition curve and obtain the sample NDMA concentration (μg/mL) from the intercept. See calculated example in Annex 2.
- 7.2.3 Include a 2.0μg/mL NDMA Check Standard (7.1.1), and a 2.0μg/mL NDMA QC Solution (6.1) with each analytical run.
 - The peak areas of the $2.0\mu g/mL$ standard and QC solution must correspond within $\pm 10\%$.
- 7.2.4 The correlation coefficient (r) of the calibration curve must be ≥ 0.990 .

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7.3 Procedure C - LOD/LOQ determination

7.3.1 Sample Preparation (API/ Finished products)

Accurately weigh in duplicate 0.5 g of each sample (powdered) into a headspace vial.

- 7.3.1.1 Add 1.0mL of DMSO to Vial 1, cap and crimp.
- 7.3.1.2 Add 20μl (0.02μg NDMA) of 1μg/mL NDMA Standard (5.2), and 1.0mL of DMSO to Vial 2, cap and crimp.
- 7.3.1.3 Run all solutions using the conditions described in Procedure C (Annex 1). Ensure that a peak with a S/N of at least 3 is obtained for the 0.02μg/mL NDMA standard. Examine all chromatograms and if no NDMA peak is observed, or a peak area less than that of the standard (0.02μg/mL) is observed in the samples, results are reported as <0.04μg/g. If the sample peak area is significantly greater than that of the standard, proceed with Procedure B (7.2).</p>

<u>Annex 1</u> – GC-MS conditions – Procedures A, B and C <u>Annex 2</u> – Standard Addition Plot



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Procedure A

```
[Comment]
                    Analytical Line I =
HS-20]
Oven Temp.
Sample Line Temp.
Sample Line Temp.
Transfer Line Temp.
Shaking Level
Multi Injection Count
Pressurizing Gas Pressure
Equilibrating Time.
Pressurizing Time.
Pressure Equilib. Time
Load Time
                                                                                                                                               :120.0 °C
                                                                                                                                                :150.0 °C
                                                                                                                                               :2
:1
:80.0 kPa
:10.00 min
                                                                                                                                              :10.00 min
:3.00 min
:0.10 min
:0.50 min
:0.10 min
:0.08 min
:5.00 min
:35.00 min
:ON
:45 min
Pressure Equilib.Time
Load Time
Load Equilib. Time
Injection Time
Needle Flush Time
GC Cycle Time
Check System Ready
Extended System Ready Check Limit
Check GC Ready
Extended GC Ready Check Limit
Analysis Mode
Needle Check
                                                                                                                                               :ON
:10 min
                                                                                                                                               :Constant
:Yes
 Needle Check
Action on Leak Check Error
Action with No Vial on Tray
                                                                                                                                               :Stop
[GC-2010]
Column Oven Temp.
Injection Mode
Flow Control Mode
                                                                                      :70.0 °C
                                                                                    :70.0 °C
:Split
Linear Velocity
:61.8 kPa
:23.4 mL/min
:0.97 mL/min
:36.1 cm/sec
:3.0 mL/min
:20.0
:OFF
 Pressure
 Total Flow
Column Flow
Linear Velocity
 Purge Flow
Split Ratio
 High Pressure Injection
 Carrier Gas Saver
Splitter Hold
 Oven Temp. Program
Rate
                                                                                      Temperature(°C)
70.0
100.0
                                                                                                                                                                           Hold Time(min)
    3.00
60.00
                                                                                                                                                                            2.00
                                                                                      240.0
  < Ready Check Heat Unit >
           Column Oven
HS Flow
                                                                                      : Yes
: Yes
MS : Yes

Keady Check Detector(FTD/BID) >
Ready Check Baseline Drift >
Ready Check Injection Flow >
HS Flow Carrier : Yes
HS Flow Purge : Yes
APC1 : Yes
Ready Check APC Flow >
APC1 : Yes
Ready Check Detector APC Flow >
External Wait : No
External Wait : No
Equilibrium Time : 3.0 min
Additional Flow >
APC1 Pressure : 80.0 kP
           MS
                                                                                      :No
:3.0 min
                                                                                     :80,0 kPa
 [GC Program]
[GCMS-QP2020]
IonSourceTemp
Interface Temp.
Solvent Cut Time
Detector Gain Mode
Detector Gain
                                                                                                                                                             :250.00 °C
:250.00 °C
:4.00 min
:Absolute
:0.93 kV
  Threshold
 [MS Table]
-Group 1 - Event 1-
Start Time
End Time
                                                                                                                                                             :6.00min
:22.00min
 ACQ Mode
Event Time
Scan Speed
                                                                                                                                                             :Sean
:0.30sec
:3333
:30,00
```

:800.00

Start m/z



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Procedure B

```
[Comment]
               Analytical Line 1 ===
[HS-20]
Oven Temp.
                                                                                                        :120.0 °C
:150.0 °C
Sample Line Temp.
Transfer Line Temp.
Shaking Level
Multi Injection Count
                                                                                                         :150.0 °C
Multi Injection Count
Pressurizing Gas Pressure
Equilibrating Time.
Pressurizing Time.
Pressure Equilib.Time
                                                                                                        :80.0 kPa
                                                                                                        :10.00 min
                                                                                                        :0.10 min
:0.50 min
Load Time
Load Equilib. Time
                                                                                                        :0.10 min
:0.08 min
Injection Time
Needle Flush Time
GC Cycle Time
Check System Ready
                                                                                                        :5.00 min
:25.00 min
                                                                                                        :ON
:45 min
:ON
Check System Ready
Extended System Ready Check Limit
Check GC Ready
Extended GC Ready Check Limit
Analysis Mode
Needle Check
Action on Leak Check Error
Action with No Vial on Tray
                                                                                                         :10 min
                                                                                                         :Constant
:Yes
                                                                                                         :Stop
[GC-2010]
Column Oven Temp.
                                                               :70.0 °C
                                                              :Split
:Linear Velocity
:61.8 kPa
:23.4 mL/min
:0.97 mL/min
:36.1 cm/sec
Injection Mode
Flow Control Mode
Pressure
 Total Flow
Column Flow
Linear Velocity
Purge Flow
Split Ratio
                                                               :3.0 mL/min
:20.0
:OFF
Split Ratio
High Pressure Injection
Carrier Gas Saver
Splitter Hold
Oven Temp. Program
                                                               OFF
                                                                                                                              Hold Time(min)
                                                               Temperature(°C)
   Rate
                                                               70.0
240.0
                                                                                                                              12.00
2.00
   40.00
< Ready Check Heat Unit > Column Oven
        HS Flow
MS
                                                               : Yes
MS : Yes

Ready Check Detector(FTD/BID) >
Ready Check Baseline Drift >
Ready Check Injection Flow >
HS Flow Carrier : Yes
HS Flow Purge : Yes
Ready Check APC Flow >
APC1 : Yes
Ready Check APC Flow >
 < Ready Check Detector APC Flow>
External Wait :No
Equilibrium Time :3.0 min
 <Additional Flow>
APC1 Pressure
                                                               :80.0 kPa
 [GC Program]
 [GCMS-QP2020]
                                                                                                                    :0.00 amu
 Micro Scan Width
IonSourceTemp
                                                                                                                    :250.00 °C
:250.00 °C
 Interface Temp.
Solvent Cut Time
                                                                                                                     :4.00 min
:Absolute
 Detector Gain Mode
Detector Gain
                                                                                                                     :0.93 kV
 [MS Table]
 -Group 1 - Event 1-
Start Time
                                                                                                                    :8.00min
:12.00min
 End Time
ACQ Mode
Event Time
Ch1-m/z
                                                                                                                    :SIM
:0.30sec
:74.00
:42.00
  Ch2-m/z
Ch3-m/z
                                                                                                                     :43.00
                                                                                                                     :GC
```

Sample Inlet Unit



Determination of NDMA (HS-GC-MS) Method 3/30-Annex 1 GC-MS Conditions Issue No. 1

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Procedure C

Analytical Line 1		
[HS-20]		
Oven Temp.		:145.0 °C
Sample Line Temp. Transfer Line Temp.		:150.0 °C :150.0 °C
Shaking Level		:2
Multi Injection Count		:1
Pressurizing Gas Pressure		:80.0 kPa
Equilibrating Time.		:15.00 min
Pressurizing Time. Pressure Equilib. Time		:3.00 min :0.10 min
Load Time		:0.50 min
Load Equilib. Time		:0.10 min
Injection Time Needle Flush Time		:0.08 min
GC Cycle Time		:5.00 min :15.00 min
Check System Ready	:ON	
Extended System Ready Cho	:45 min	
Check GC Ready		:ON
Extended GC Ready Check I Analysis Mode	Limit	:10 min :Constant
Needle Check		:Yes
Action on Leak Check Error		:Stop
Action with No Vial on Tray		:Stop
[GC-2010]		
Column Oven Temp.	:80.0 °C	
Injection Mode	:Split	
Flow Control Mode Pressure	:Linear Velocity :64.9 kPa	
Total Flow	:13.6 mL/min	
Column Flow	:0.96 mL/min	
Linear Velocity	:36.1 cm/sec	
Purge Flow	:3.0 mL/min	
Split Ratio High Pressure Injection	:10.0 :OFF	
Carrier Gas Saver	OFF	
Splitter Hold	:OFF	
Oven Temp. Program	T	** ****
Rate	Temperature(°C)	Hold Time(min)
50.00	80,0 240,0	8.50 1.00
	240.0	1.00
< Ready Check Heat Unit >	240.0	
< Ready Check Heat Unit > Column Oven	240.0 : Yes	
< Ready Check Heat Unit > Column Oven HS Flow	240.0 : Yes : Yes	
< Ready Check Heat Unit > Column Oven	240.0 : Yes : Yes : Yes	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Baseline Drie	240.0 : Yes : Yes : Yes : Yes O/BID) >	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Baseline Dri < Ready Check Injection Flo	240.0 : Yes : Yes : Yes ()/BID) > ft > w>	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Baseline Drit < Ready Check Injection Flo HS Flow Carrier	240.0 : Yes : Yes : Yes O/BID) > ft > w> : Yes	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Baseline Drit < Ready Check Injection Flo HS Flow Carrier HS Flow Purge	240.0 : Yes : Yes : Yes ()/BID) > ft > w>	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Baseline Dri < Ready Check Injection Flo HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1	240.0 : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Baseline Drit < Ready Check Injection Flo HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC	240.0 : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Yes : Yes	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FTI < Ready Check Baseline Dri < Ready Check Injection Flo HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait	240.0 : Yes : Yes : Yes D/BID) > ft > w> : Yes : Yes : Yes : Yes : Yes : Flow > : No	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Baseline Drit < Ready Check Injection Flo HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC	240.0 : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Yes : Yes	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Baseline Dri < Ready Check Injection Flo HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time	240.0 : Yes : Yes : Yes D/BID) > ft > w> : Yes : Yes : Yes : Yes : Yes : Flow > : No	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Injection Flo HS Flow Carrier HS Flow Purge < Ready Check APC Flow> APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow> APC1 Pressure	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FTI < Ready Check Baseline Drit < Ready Check Injection Flot HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow >	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FTI < Ready Check Injection Flot HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow > APC1 Pressure [GC Program]	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Injection Flo HS Flow Carrier HS Flow Purge < Ready Check APC Flow> APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow> APC1 Pressure	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Injection Flo HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow > APC1 Pressure [GC Program] [GCMS-QP2020] Micro Scan Width IonSourceTemp	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	:0.00 amu :250.00 °C
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FTI < Ready Check Baseline Drit < Ready Check Injection Flot HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow > APC1 Pressure [GC Program] [GCMS-QP2020] Micro Scan Width LonSourceTemp Interface Temp.	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	:0.00 amu :250.00 °C :250.00 °C
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FTI < Ready Check Baseline Drit < Ready Check Injection Flot HS Flow Carrier HS Flow Purge < Ready Check APC Flow> APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow> APC1 Pressure [GC Program] [GCMS-QP2020] Micro Scan Width IonSourceTemp Interface Temp. Solvent Cut Time	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	:0.00 amu :250.00 °C :250.00 °C :4.00 min
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FTI < Ready Check Baseline Drit < Ready Check Injection Flot HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow > APC1 Pressure [GC Program] [GCMS-QP2020] Micro Scan Width LonSourceTemp Interface Temp.	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	:0.00 amu :250.00 °C :250.00 °C
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FTI < Ready Check Injection Flo HS Flow Carrier HS Flow Purge < Ready Check APC Flow> APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow> APC1 Pressure [GC Program] [GCMS-QP2020] Micro Scan Width IonSourceTemp Interface Temp. Solvent Cut Time Detector Gain Mode Detector Gain	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	:0.00 amu :250.00 °C :250.00 °C :4.00 min :Absolute
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Baseline Drit < Ready Check Injection Floth HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow > APC1 Pressure [GC Program] [GCMS-QP2020] Micro Scan Width IonSourceTemp Interface Temp. Solvent Cut Time Detector Gain Mode Detector Gain [MS Table]	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	:0.00 amu :250.00 °C :250.00 °C :4.00 min :Absolute
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Baseline Drit < Ready Check Injection Floth HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow > APC1 Pressure [GC Program] [GCMS-QP2020] Micro Scan Width IonSourceTemp Interface Temp. Solvent Cut Time Detector Gain Mode Detector Gain [MS Table]Group 1 - Event 1	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	:0.00 amu :250.00 °C :250.00 °C :4.00 min :Absolute :0.93 kV
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FT) < Ready Check Baseline Drit < Ready Check Injection Floth HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow > APC1 Pressure [GC Program] [GCMS-QP2020] Micro Scan Width IonSourceTemp Interface Temp. Solvent Cut Time Detector Gain Mode Detector Gain [MS Table]	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	:0.00 amu :250.00 °C :250.00 °C :4.00 min :Absolute
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FTI < Ready Check Baseline Drit < Ready Check Injection Floth HS Flow Carrier HS Flow Carrier HS Flow Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow > APC1 Pressure [GC Program] [GCMS-QP2020] Micro Scan Width IonSourceTemp Interface Temp. Solvent Cut Time Detector Gain Mode Detector Gain Mode Detector Gain [MS Table]Group 1 - Event 1 Start Time	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	:0.00 amu :250.00 °C :250.00 °C :4.00 min :Absolute :0.93 kV
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FTI < Ready Check Baseline Drit < Ready Check Injection Flot HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow > APC1 Pressure [GC Program] [GCMS-QP2020] Micro Scan Width IonSourceTemp Interface Temp. Solvent Cut Time Detector Gain Mode Detector Gain [MS Table]Group 1 - Event 1 Start Time End Time ACQ Mode Event Time	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	:0.00 amu :250.00 °C :250.00 °C :4.00 min :Absolute :0.93 kV :6.00min :9.00min
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FTI < Ready Check Baseline Drit < Ready Check Injection Floth HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow > APC1 Pressure [GC Program] [GCMS-QP2020] Micro Scan Width IonSourceTemp Interface Temp. Solvent Cut Time Detector Gain Mode Detector Gain Mode Detector Gain [MS Table]Group 1 - Event 1 Start Time End Time ACQ Mode Event Time Ch1-m/z	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	:0.00 amu :250.00 °C :250.00 °C :4.00 min :Absolute :0.93 kV :6.00min :9.00min :SIM :0.30sec :74.00
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FTI < Ready Check Baseline Drit < Ready Check Injection Floth HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow > APC1 Pressure [GC Program] [GCMS-QP2020] Micro Scan Width IonSourceTemp Interface Temp. Solvent Cut Time Detector Gain Mode Detector Gain [MS Table]Group 1 - Event 1 Start Time End Time ACQ Mode Event Time Ch1-m/z Ch2-m/z	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	:0.00 amu :250.00 °C :250.00 °C :250.00 °C :4.00 min :Absolute :0.93 kV :6.00min :9.00min :SIM :0.30sec :74.00 :42.00
< Ready Check Heat Unit > Column Oven HS Flow MS < Ready Check Detector(FTI < Ready Check Baseline Drit < Ready Check Injection Floth HS Flow Carrier HS Flow Purge < Ready Check APC Flow > APC1 < Ready Check Detector APC External Wait Equilibrium Time < Additional Flow > APC1 Pressure [GC Program] [GCMS-QP2020] Micro Scan Width IonSourceTemp Interface Temp. Solvent Cut Time Detector Gain Mode Detector Gain Mode Detector Gain [MS Table]Group 1 - Event 1 Start Time End Time ACQ Mode Event Time Ch1-m/z	240.0 : Yes : Yes : Yes : Yes O/BID) > ft > w> : Yes : Yes : Yes : Flow > : No : 3.0 min	:0.00 amu :250.00 °C :250.00 °C :4.00 min :Absolute :0.93 kV :6.00min :9.00min :SIM :0.30sec :74.00
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Determination of NDMA (HS-GC-MS) Method 3/30-Annex 2 GC-MS Standard Addition Plot Issue No. 1

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Standard Addition Plot of Peak Area Vs µg/mL of added NDMA

Date:			Sample				Batch:			Data Fold	ler: GCMS	soluti	ons\NDMA
Added NDMA (μg/L)	Area	sample (g)	NDMA										
0	3918	0.19908			200	00	·····			-			y = 2605.9x + 3867.
2.0	9441	0.20165		PA									$R^2 = 0.9919$
4.0	13415	0.20004		E R	150	00 +							
6.0	19966	0.19946		A E	100	00 +		-					
	mean =	0.20006		K A	50	00							
API content of to X Intercept =		0.083 0.040 μg/mL			al val	0 + 0 ue of		2	μg/mL ND	6 MA		8	
						\Rightarrow	7.24	μg	NDMA/g	Absolute value of the intercept divided average mass (g) of sample used per value NDMA/g multiplied by average tab mass.			
					diameter and a	\Rightarrow	0.60	μg ND	OMA/tablet			average tablet	
			Equation			\Rightarrow	15.0	μg	NDMA/g Val	sartan	μg NDMA		et divided by API ablet.