Current analytical testing methodology and capacity

Session 3: Prevention Part 1

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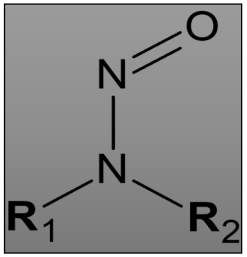
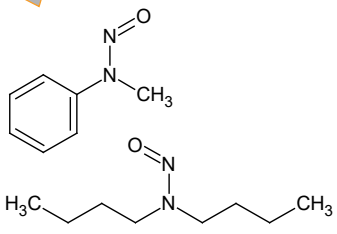
EMA Sartans with N-nitrosamine impurities
Lessons Learnt Exercise - Interested Parties Meeting
Amsterdam, 04. November 2019

Background
-Stop Press



R_1	R_2	Compound	C…ment
Me	Me	ND	…ethylamine from
Et	Et		…ine from
IPA			…mine
Et			…pyl amine
Me		NM	…(methyla…no) …tanoic acid from NMP



Initial cause- change in synthesis around Tetrazole functionality in 'pseudo-generic' Valsartan

July 2018 Valsartan recalled by Bfarm-EMA, FDA (NDMA)

August 2018 Valsartan, Losartan, Irbesartan- (NDEA)

EMA Article 31 triggered July 2018 ,extended in August– 'Nitrosamine free synthesis (30ppb LOQ) .Finalised April 2019 - phased in over 2 years

FDA 'non-detected' –currently at c.5ppb , SwissMedic 30ppb all Bx from May

Pharm Eur monograph adopted for Nitrosamine testing in 5 Sartans- released in July 2019

Health Canada mandates NDMA, NDEA,NMBA NDIPA and NDEIPA- co-ordinate with FDA and EMA July 2019

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The Challenges

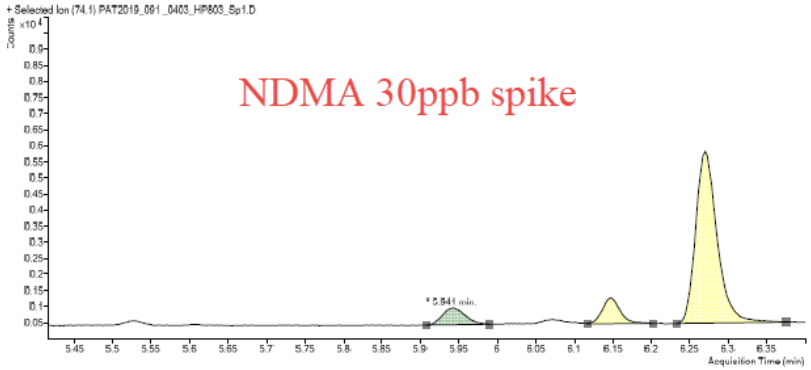
Status of Methods

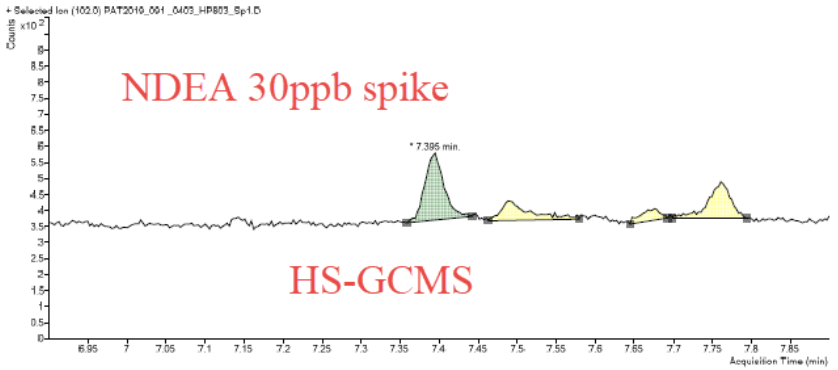
- **It is good to have analytical methodology available and regulatory efforts to support suitable methods being available is appreciated.**
- **Currently ~ 20 published methods (September 2019) developed by OMCLs.**
  - 9 European (including 1 from Swissmedic) and 6 FDA
  - Canada, Taiwan and Korea have also published methods

- **It would be good to rationalise to a limited number of sample prep and introduction, chromatography and then detection**
  - limits set for sartans challenge current technology, and almost 50% of the OMCL don't meet the required sensitivity

FALSE POSITIVES

- **In the current situation appropriate specificity best achieved by MS/MS data**
- **Trade off between sensitivity and specificity**
  - False positives described in official methods and literature
  - Impact of false positive results is very high
- **Small m/z ions prone to chemical interference from the matrices**
  - Small target molecules falls into the region of chemical background
    - In GCMS EI Single Ion Monitoring m/z 74 >10,100 library hits as top 30%





Analytical Capacity

- **It will be important to focus analytical testing capacity on the most important / highest priority testing**
  - Risk assessment should be capable of focusing the analytical testing needed
  - Universal blanket testing of APIs (and for what?) should not be necessary and Is there sufficient analytical capacity in contract labs to conduct such testing on a routine basis?

- **When addressing the analytical effort necessary to measure trace levels of nitrosamines, it is critical to focus testing based probability of presence of certain risks.**

  - It is unlikely that any reasonable testing capacity would allow finished product manufacturers / MAH to routinely test every batch of API, solvent, excipient or even drug products by GC-MS/MS or HPLC-MS/MS

Assessment of actual risk

- **In order to perform a full evaluation of the underlying risk, regulators should grant finished product manufacturers / MAH access to all necessary information (e.g. closed part of DMF).**
  - Here the industry needs support by regulators / legislators as the existing rules are not sufficient.
- **Another key aspect is to arrive at an internationally-accepted limit,**
  - Increasing number of authorities, as a limit below which products can be regarded as 'nitrosamine free'.

Summary

- **Very conservative transitional limits set by health authorities:**
  - nmt 5 ppb (LoD) expectation from FDA by HS-GCMS (5ppb NDMA and 1ppb NDEA, or 2ppb /1ppb Canada by GC-MS/MS)
  - EMA/Pharm. Eur./ Swissmedic 30ppb LOQ with nmt 10ppb expectation for >1 nitrosamine
  - limits were for sartans and may not be fully right for every other situation …

- **We are operating at the edge of analytical capability and this has significant consequences in terms of capacity**

- **Testing needs to be focused and based on risk**

Official Methods of Analysis

OMCL Methods

- **Currently 19 published methods (September 2019)- linked from EDQM website**
  - 9 European (including 1 from Swissmedic) and 6 FDA
  - Canada, Taiwan and Korea remaining 3 methods
- **8 UHPLC or LC-MS/MS methods, using APCI in positive mode**
  - Including FDA LC-HRMS method
- **5 HS-GCMS , 1 DI GCMS, 2 DI GC-MS/MS with liquid extraction**
- **2 HPLC-UV methods**
- **1 Automated SPE (RapidFire®)-MS/MS**

https://www.edqm.eu/en/ad-hoc-projects-omcl-network

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OMCL Methods

- **Majority of small polar n-Nitrosamines of interest are GC amenable**
- **NMBA not optimal for direct trace GCMS analysis – LC-MS/MS**
- **Majority of methods are for NDMA alone or NDMA plus NDEA, and now NMBA**
  - FDA LC-MS/MS method NDMA, NDEA, NDIPA, NEIPA, NDBA and NMBA
  - FDA GC-MS/MS method NDMA, NDEA, NDIPA, NEIPA, NDBA
  - FDA HS-GCMS method NDMA, NDEA, NDIPA, NEIPA
- **Sample preparation**
  - Ultrasonic extraction- varying organic content
  - Swissmedic and FDA liquid/liquid extraction for GCMS and GC-MS/MS
- **Sample loading can be increased to maximise sensitivity !**

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NDMA and NDEA methods from Article 31

	Health Canada	US FDA		European OMCL Network							Taiwan FDA
				CVUA	CVUA	PALG	Swissmedic	LGL	LGL	ANSM	
Analytical technique	GC-MS/MS (DI)	GC-MS (HS)	GC-MS/MS (DI)	LC-MS/MS	LC-MS/MS	GC-MS (HS)	GC-MS (liquid DI) limit test	GC-MS	LC-MS/MS	HPLC-UV	LC-MS/MS
Analyte(s)	NDMA, NDEA	NDMA, NDEA	NDMA, NDEA	NDMA, NDEA	NDMA	NDMA	NDMA, NDEA	NDMA, NDEA	NDMA, NDEA	NDMA	NDMA, NDEA
Sample (DS and/or DP)	DS and DP	DS and DP	DS and DP	DP	DP	DS and DP	DS and DP	DS	DS and DP	DS and DP	DS and DP
Which ARB?	various (DS: valsartan, irbesartan, losartan, candesartan, olmesartant) (DP: valsartan, irbesartan and losartan)	valsartan	valsartan	various	valsartan	various	Various (valsartan, irbesartan, losartan, candesartan, olmesartan)	various (valsartan, irbesartan, losartan, candesartan, olmesartan)	various (valsartan, irbesartan and losartan)	valsartan	various
NDMA – LOD	0.002 ppm	0.005 ppm	0.015 ppm (DP), 0.010 ppm (API)	0.08 ppm	0.08 ppm	0.04 ppm	0.01 ppm	0.01 ppm	Irb: 24 ppb Val: 71 ppb Los: 148 ppb	0.1 ppm	--
NDMA – LOQ	0.005 ppm	0.10 ppm	0.08 ppm (DP), 0.05 ppm (API)	0.2 ppm	0.2 ppm	--	[0.03 ppm]	0.10 ppm	Irb: 79 ppb Val: 236 ppb Los: 492 ppb	0.3 ppm	0.1 ppm
NDEA – LOD	0.002 ppm	0.02 ppm	0.015 ppm (DP), 0.010 ppm (API)	0.02 ppm	--	N/A	0.01 ppm	0.02 ppm	Irb: 6 ppb Val: 18 ppb Los: 45 ppb	N/A	--
NDEA – LOQ	0.007 ppm	0.05 ppm	0.04 ppm (DP), 0.03 (API)	0.04 ppm	--	N/A	[0.03 ppm]	0.080 ppm	Irb: 19.5 ppb Val: 61 ppb Los: 149 ppb	N/A	0.05 ppm
Version / reference	20/12/2018	--	FY19-006-DPA-S	10/10/2018	13/09/2018	3/30, issue 1.1	31_PV_163	16/01/2019	16/01/2019	18A0399-02	Nov. 14, 2018

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Highest sensitivity Methods

Technique	NDMA	NDEA	NEIPA	NDIPA	NDBA	NMBA	Prep.
LC-HRMS FDA	5	16	3	8	5	10	100mg/5mL
HS-GCMS FDA	10	10	25	25	—	—	500mg/5mL
GC-MS/MS FDA	5	1	1	1	10	—	500mg/5mL
GC-MS/MS Canada	2	1	—	—	—	—	250mg/5mL
LC-MS/MS LGL (DE)	—	—	—	—	—	8.6	50mg/10mL

LOD wrt API , *LLOQ (RSD at S/N >5) for DP

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