THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Nitrosamine Contamination of Sartans – Actions taken by the EDQM -

2019 Training Session
"The European Pharmacopoeia"
Dr Susanne Keitel
EDQM Director

10 – 11 September 2019, Iselin, New Jersey, USA

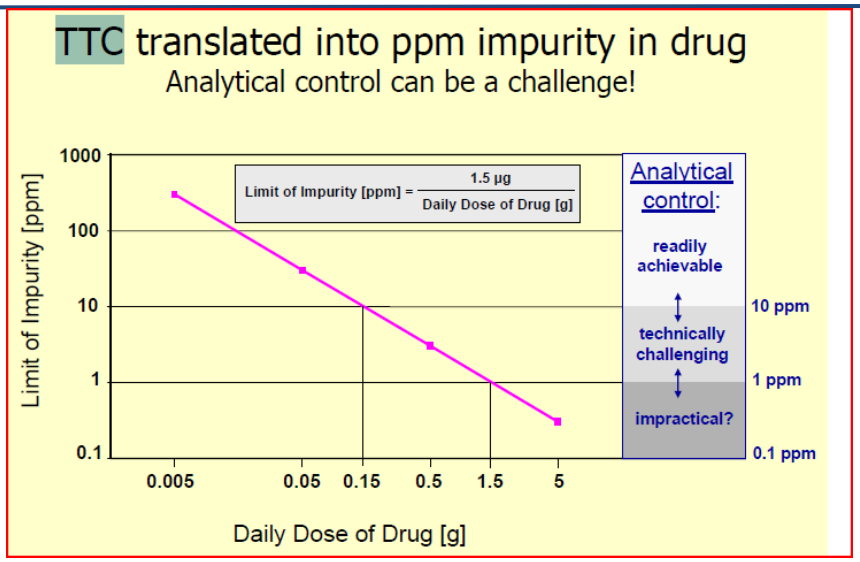
A special case: DNA reactive impurities

- Require control according to the ICH Guideline M7 (R1)
- Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- Following hazard assessment acceptable intakes are assigned e.g.
  - ➢ based on TTC-principle (1.5 µg /per person per day) or
  - ➢ based on compound-specific risk assessments
  - ➢ Extrapolation when carcinogenicity data are available
- Special cohort of concern:
  Aflatoxin-like-, N-nitroso or alkylazoxy structures

- Often this implies control of the impurities in the low ppm range

TTC translated into ppm impurity in drug

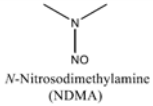
Analytical control can be a challenge!



Source: Peter Kasper, BfArM, Impurities Forum 2009

The (Val)sartan issue - 1

- June 2018: information that Valsartan manufactured by Zhejiang Huahai Pharmaceutical (ZHP) was contaminated with NDMA (Nitrosodimethylamine)
  - NDMA is known as possible carcinogen for humans
  - NDMA was unexpected and therefore not controlled

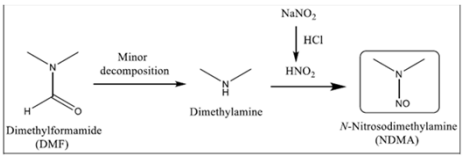


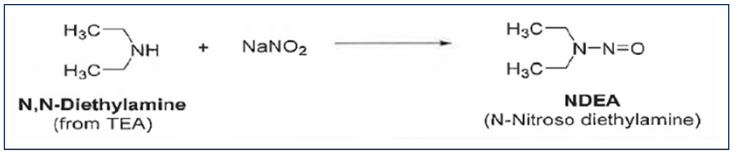
N-Nitrosodimethylamine
(NDMA)

- EDQM Certification of Substances Department and regulatory authorities worldwide have taken action
- Review of ASMFs and marketing authorisation applications by EU authorities
- Review of CEPs by EDQM (reliance on the work done, not only in Europe!)
- European Commission: initiated CHMP Article 31 referral (of directive 2001/83 EC) and later extended to other Sartans
- Sampling & testing of APIs and medicinal products coordinated by EDQM
- GMP Inspections

The (Val)sartan issue - 2

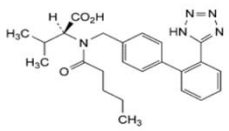
- Origin of nitrosamines:
  - Process conditions (sodium nitrite + amine, acidic conditions) – direct introduction or degradation/by-product



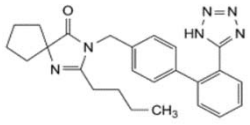


  - Cross-contaminations - processes running in parallel on same lines
  - Contaminations by other factors e.g. recycling of solvents
  - A number of synthetic processes use NaNO2 for quenching excess of azide or cyanide after forming tetrazol structure -> potential risk to form N-Nitrosamines

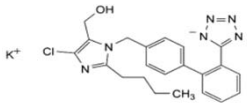
Sartans with tetrazole ring structure



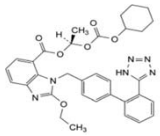
Valsartan



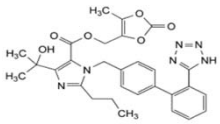
Irbesartan



Losartan potassium



Candesartan cilexetil



Olmesartan medoxomil

Nitrosamines are known as possible carcinogens for humans, part of ICH M7 "cohort of concern" - **Very low amounts acceptable – require highly sensitive analytical methods**

Sampling and testing in the OMCL Network

EDQM coordinated

- Sartan testing group of 13 OMCLs
- Supported method development and validation
- Sourced contaminated material for validation
- Developed a common format for communication of sampling plans and testing results
- Developed a risk-oriented sampling plan in discussion with EMA, NCA, inspectorates and CMDh representative

Testing purposes:

- Confirming levels of NDMA in contaminated products (Art. 31 referral request), already recalled (verification of MAH results, confirm patient exposure)
- Market surveillance of products theoretically of low concern (route of synthesis)
- Market surveillance of other sartans
- Analysing samples from several GMP inspections

What are applicable interim limits for NDMA and NDEA?

- In referral under article 31 (of directive 2001/83/EC), based on toxicological data and in line with ICH M7 (R1), EMA CHMP recommended limits for acceptable intakes (AI) for an interim period of 2 years
- Interim limits harmonised between international regulators

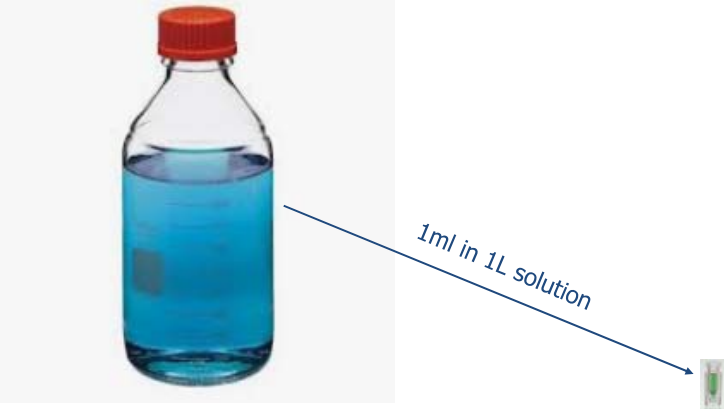
	NDMA		NDEA	
Active substance (max daily dose)	Maximum daily intake (ng)	Limit in API (ppm)	Maximum daily intake (ng)	Limit in API (ppm)
Candesartan (32 mg)	96.0	**3.000**	26.5	**0.820**
Irbesartan (300 mg)	96.0	**0.320**	26.5	**0.088**
Losartan (150 mg)	96.0	**0.640**	26.5	**0.177**
Olmesartan (40 mg)	96.0	**2.400**	26.5	**0.663**
Valsartan (320 mg)	96.0	**0.300**	26.5	**0.082**

➢If both of the above impurities present, reject batch

Analytical challenge: ppm-ppb

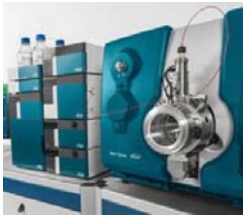
To put things into context, this is what a usual «impurity» level looks like

(0.05 to 0.1% = 500 to 1000 ppm):



Which method is suitable?

- Several techniques have been tested:



LC-MS/MS

GC-MS (HS)

GC-MS (DI)

HPLC-UV

Analytical methods used

	DE_BW CVUA	IE_PAL PALG	CH_Swissmedic	DE_BY LGL	DE_BY LGL	FR_ANSM
Analytical technique	LC-MS/MS	GC-MS (HS)	GC-MS (liquid DI) limit test	GC-MS (DI)	LC-MS/MS	HPLC-UV
Analytes(s)	NDMA, NDEA	NDMA, NDEA	NDMA, NDEA	NDMA, NDEA	NDMA, NDEA	NDMA, NDEA
Sample (DS and/or DP)	DS and DP	DS and DP	DS and DP	DS	DS and DP	DS and DP

- Methods published on EDQM website:

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

LOQs for NDMA

	DE_BW CVUA LC-MS/MS (DP)	CH_Swissmedic GC-MS (liquid DI) limit test (DS and DP)	DE_BY LGL GC-MS (DI) (DS)	DE_BY LGL LC-MS/MS (DS and DP)	FR_ANSM HPLC-UV (DS)	Health Canada GC-MS/MS (DI)
Valsartan limit: 0.300 ppm / day	0.10 ppm	0.03 ppm	0.10 ppm	0.236 ppm	0.04 ppm	0.005 ppm (DS and DP)
Irbesartan limit: 0.320 ppm / day	0.10 ppm	0.03 ppm	0.10 ppm	0.079 ppm	0.04 ppm	0.005 ppm (DS and DP)
Losartan limit: 0.640 ppm / day	0.10 ppm	0.03 ppm	0.10 ppm	0.492 ppm	0.05 ppm	0.005 ppm (DS and DP)
Candesartan limit: 3.000 ppm / day	0.10 ppm	0.03 ppm	0.10 ppm	-	0.25 ppm	0.005 ppm (DS)
Olmesartan limit: 2.400 ppm / day	0.10 ppm	0.03 ppm	0.10 ppm	-	0.25 ppm	0.005 ppm (DS)

HS: Head Space; DI: Direct Injection; DP: Drug Product; DS: Drug Substance

In green: suitable sensitivity
In black: borderline sensitivity
In red: insufficient sensitivity

LOQs for NDEA

	DE_BW CVUA LC-MS/MS (DP)	CH_Swissmedic GC-MS (liquid DI) limit test (DS and DP)	DE_BY LGL GC-MS (DI) (DS)	DE_BY LGL LC-MS/MS (DS and DP)	FR_ANSM HPLC-UV (DS)	Health Canada GC-MS/MS (DI)
Valsartan limit: 0.082 ppm / day	0.04 ppm	0.03 ppm	0.08 ppm	0.061 ppm	0.08 ppm	0.007 ppm (DS and DP)
Irbesartan limit: 0.088 ppm / day	0.04 ppm	0.03 ppm	0.08 ppm	0.0195 ppm	0.09 ppm	0.007 ppm (DS and DP)
Losartan limit: 0.177 ppm / day	0.04 ppm	0.03 ppm	0.08 ppm	0.149 ppm	0.10 ppm	0.007 ppm (DS and DP)
Candesartan limit: 0.820 ppm / day	0.04 ppm	0.03 ppm	0.08 ppm	-	0.40 ppm	0.007 ppm (DS)
Olmesartan limit: 0.663 ppm / day	0.04 ppm	0.03 ppm	0.08 ppm	-	0.50 ppm	0.007 ppm (DS)

HS: Head Space; DI: Direct Injection; DP: Drug Product; DS: Drug Substance

In green: suitable sensitivity
In black: borderline sensitivity
In red: insufficient sensitivity

Samples tested by OMCLs (by 15/04/19)

...for NDMA

	DP	DS
Valsartan	612	141
Losartan	312	16
Olmesartan	313	13
Candesartan	434	10
Irbesartan	260	20
Telmisartan	69	49
Total	**2000**	**249**

...for NDEA

	DP	DS
Valsartan	246	200
Losartan	188	149
Olmesartan	194	43
Candesartan	204	85
Irbesartan	175	160
Total	**1007**	**637**

The testing was carried out by 10 European OMCLs + 3 associated members of the European OMCL Network

OMCL OOS Findings by 15/4/2019

NDMA

VALSARTAN	API	DP
Manufacturer A	55	240
Manufacturer B	14	10
Manufacturer C	-	3
Manufacturer D	1	-

NDEA

VALSARTAN	API	DP
Manufacturer E	38	22
Manufacturer F	14	9
Manufacturer A	1	5
LOSARTAN		
Manufacturer G	-	2
Manufacturer A	1	-
Irbesartan		
Manufacturer F	25	28
Manufacturer A	1	1

OMCL testing triggered/supported batch recalls and suspension of CEPs

Impact of the issue

- Regular recalls of products due to contaminations
- Many API manufacturers and Finished Products manufacturers affected
- Worldwide issue – e.g. Australia, Brazil, Canada, China, Europe, Japan, Korea, Taiwan, USA….

- Joint GMP inspections (EMA/EDQM/nat. authorities) carried out at concerned facilities confirmed GMP non-compliance
- Efficient exchange of information between regulatory authorities worldwide

Final CHMP Assessment Report

Conditions to the MA	Due date
The MAH must ensure that the manufacturing processes of the drug substances used for their drug products are reviewed for the potential risk of formation of *N*-nitrosamines and changed as necessary to minimise nitrosamine contamination as much as possible.	Within 2 years after Commission Decision.
For all *N*-nitrosamines, the MAH must ensure a control strategy is in place in drug substance batches used for their drug products.	At the time of Commission Decision.
For *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA), the MAH must introduce the following specifications for the drug substance: 1) Limits for NDMA and NDEA outlined below should be implemented for a transitional period of 2 years:	At the time of Commission Decision

Drug substance*	Max. daily dose (mg)	NDEA Limit in ng/day	NDEA Limit in ppm in API	NDMA Limit in ng/day	NDMA Limit in ppm in API
Valsartan	320	26.5	0.082	96.0	0.300
Losartan	150	26.5	0.177	96.0	0.640
Olmesartan	40	26.5	0.663	96.0	2.400
Irbesartan	300	26.5	0.088	96.0	0.320
Candesartan	32	26.5	0.820	96.0	3.000

** These limits are not applicable for batches where more than one of the above N-nitrosamines has been identified simultaneously; such batches should be rejected.*

2) After the transitional period of 2 years, a limit for NDMA and NDEA of maximum 0.03 ppm should be implemented.	Within 2 years after Commission Decision.

Outcome of the Art.31 referral

1) With immediate effect:

For all N-nitrosamines, the MAH must ensure a control strategy is in place in drug substance batches used for their drug products

Specifications must include the interim limits

2) Within 2 years (as of 1/4/2021):

Manufacturing processes to be reviewed for the potential risk of formation of N-Nitrosamines and to be changed as necessary to minimise nitrosamine contamination as much as possible

NDMA and NDEA below 0.03ppm (LOQ)

Details available here

https://www.ema.europa.eu/en/documents/referral/sartans-article-31-referral-chmp-assessment-report_en.pdf

Current status

- Review of CEPs: New information received on a regular basis, either from manufacturers, or from international partners
- Confirmation of « No risk » for the vast majority of CEP dossiers
- 11 CEPs suspended:
  - Valsartan contaminated with NDMA
  - Valsartan contaminated with NDEA
  - Valsartan source contaminated with NDIPA
  - Other sartans contaminated with NDEA: Losartan K, Irbesartan
  - Losartan K contaminated with NMBA
- Ph. Eur. Monographs Valsartan, Losartan K, Irbesartan, Candesartan cilexetil, Olmesartan medoxomil revised with interim limits, published in 10th edition,
- Will be further updated in line with end of transition period
- Intention to revise general monograph «Substances for Pharmaceutical use»

Impact on Ph. Eur.

April 2021

We're here! **We need to prepare for that!**

Phase 1 ✦ **Phase 2a** **Phase 2b**

Elaboration of a general chapter on control of nitrosamines

5 individual monographs on sartans revised for publication in the Ph. Eur. 10.0 (impl.: 01/01/2020)

- Valsartan
- Candesartan cilexetil
- Irbesartan
- Losartan potassium
- Olmesartan medoxomil

Done!

Alignment with final stage of EC decision
- General monograph 2034 to be revised
- 5 individual monographs on sartans changed as part of Phase 1 to be revised

All revised texts to be published in Suppl. 10.4 ideally

Confirmed at 163rd session

General chapter on control of nitrosamines ready and published in the Ph. Eur. Suppl. 10.X
Impacted monographs revised and published in Ph. Eur. Suppl. 10.X

Another challenge: ppm-ppb

… and here is what we are looking for:
e.g. 1ml in 33'000 L tank (0.03 ppm = 30 ppb):

1ml in 33'000 L solution

Ongoing work in the OMCL network/EDQM

- OMCLs now testing other APIs than sartans from «suspect» production sites
- Additional N-nitrosamines considered now:
  - NDIPA = N-nitrosodiisopropylamine
  - NIPEA = N-nitroso-isopropylethylamine
  - NDBA = N-nitrosodibutylamine
  - NMBA = N-nitrosomethylamino butyric acid (derived from the use of N-methylpyrrolidone)
- OMCLs collaborating on universal method for NDIPA, EIPNA, NDBA, NDMA and NDEA
- NMBA requires a different method (meanwhile developed and published on EDQM website)
- Some OMCLs are active in the method development of MG subgroup for future Ph. Eur. General Method(s)
- Main challenges:
  - sensitivity
  - broad coverage of N-Nitrosamines
  - applicability to different APIs

Lessons learnt – EDQM's initial thoughts

On quality aspects:

- Not all root causes are yet fully understood (e.g. impact of raw materials) !
- Lack of process knowledge & process development by API manufacturers
- Some manufacturers don't perform an adequate risk assessment
- ICH M7 principles on mutagenic impurities do not seem to be sufficient for nitrosamines

For regulatory dossiers:

- Need for data on process development & validation for known active substances?
- More requirements on recycling of materials and a respective risk analysis?

Lessons learnt – EDQM's initial thoughts (2)

On the supply chain:

- Finished products manufacturers ultimately responsible for quality of APIs used and legally obliged in the EU to get the information they need to take this responsibility
  - Apparently not sufficiently done in practice
  - Lack of information sharing between API manufacturers and FP manufacturers
- Most API manufacturers supply the same quality in many regions
- Many sources of APIs are covered by CEPs
- Difficulties for authorities to trace back which batch of API is in which medicinal product on which market (IDMP)

Lessons learnt – EDQM's inital thoughts (3)

- On GMP aspects:
  - Deeper review of process development and risk assessments during GMP inspections of API manufacturers
  - Deeper review of recycling operations
  - Is the current system sufficient (risk-based inspections)?
- Opportunities:
  - Communication amongst authorities worldwide to share knowledge, findings and avoid duplication of work
  - Alignment of decisions

➔Need to reflect further on different levels with international partners

Conclusions

- Issue still on-going
- Actions on various levels (review of dossiers, GMP, analytical testing, communication etc.)
- EDQM CEP department had a leading role
- OMCL Network provided strong and efficient support for regulators
- In EU, the Art. 31 referral has defined the way forward for industry
- Sartan-Case has fostered international collaboration
- Further development of sensitive (and if possible universal) methods needed
- « Lessons learnt exercise » initiated by the EMA ongoing
- Potentially wider action needed to review non-Sartan substances

Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: **https://go.edqm.eu/Newsletter**
LinkedIn: **https://www.linkedin.com/company/edqm/**
Twitter: **@edqm_news**
Facebook: **@EDQMCouncilofEurope**