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

edqm

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Current Challenges in the field of quality control of medicines

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EDQM/Council of Europe

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The Council of Europe

Intergovernmental organisation

Core values:

- human rights
- pluralist democracy
- rule of law

The EDQM

- Council of Europe Directorate

- Convention on the Elaboration of a European Pharmacopoeia (1964)
- General OMCL Network

OMCL = Official Medicines Control Laboratory

- OMCLs are public institutions which support (or are part of) regulatory authorities in controlling the quality of medicinal products for human and veterinary use (available on the market / intended to be placed on the market).
- OMCLs test medicinal products independently from manufacturers (no conflicts of interest, guarantee of impartiality, respecting confidentiality)

- **OMCL is a recognised term in the EU legislation**

General European OMCL Network (GEON)

- **1994:** the Commission of the EU and the Council of Europe decided to create a **Network of OMCLs**, to promote the collaboration in the area of quality control of marketed medicinal products for human and veterinary use.

General European OMCL Network

- **1995:** EDQM sets up the OMCL Network and acts as Secretariat => responsible for co-ordinating the Network activities and joint programmes, with the financial support from the EU.
  Work programmes are decided on an annual basis in collaboration with the National Authorities and, where applicable, the European Medicines Agency (EMA).

=> aims at avoiding duplication of testing and mutual recognition of results

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Composition of the OMCL Network

➢Currently 71 OMCLs from 41 countries

- Members to the European Pharmacopoeia Convention
  - 27 out of the 28 EU countries (except Malta)
  - Norway (EEA)
  - Switzerland (MRA)
  - Bosnia & Herzegovina, Serbia, North Macedonia, Ukraine
- Associated members (observers to Ph. Eur. Convention)
  - Australia, Belarus, Canada, Israel, Kazhakhstan, Morocco Russian Federation, Singapore

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Impurity control in APIs (1)

- ICH Q3A(R2) Impurities in New Drug Substances
- Implemented by Ph.Eur. in

  General monograph Substances for pharmaceutical use (2034)

➢ Related substances

- Unless otherwise prescribed, organic impurities in active substances are to be reported, in Table 2034.-1. identified wherever possible, and qualified as indicated
- Specific thresholds may be applied for impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects.

Impurity Control in APIs (2)

Use	Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
Human or human and veterinary	≤ 2 g /day	>0.05 per cent	**>0.10 per cent** or daily intake >1.0 mg (whichever lower)	>0.15 per cent or daily intake >1.0 mg (whichever lower)
Human or human and veterinary	> 2 g/day	>0.03 per cent	**>0.05 per cent**	> 0.05 percent
Veterinary only	Not applicable	>0.10 per cent	**0.20 per cent**	>0.50 per cent

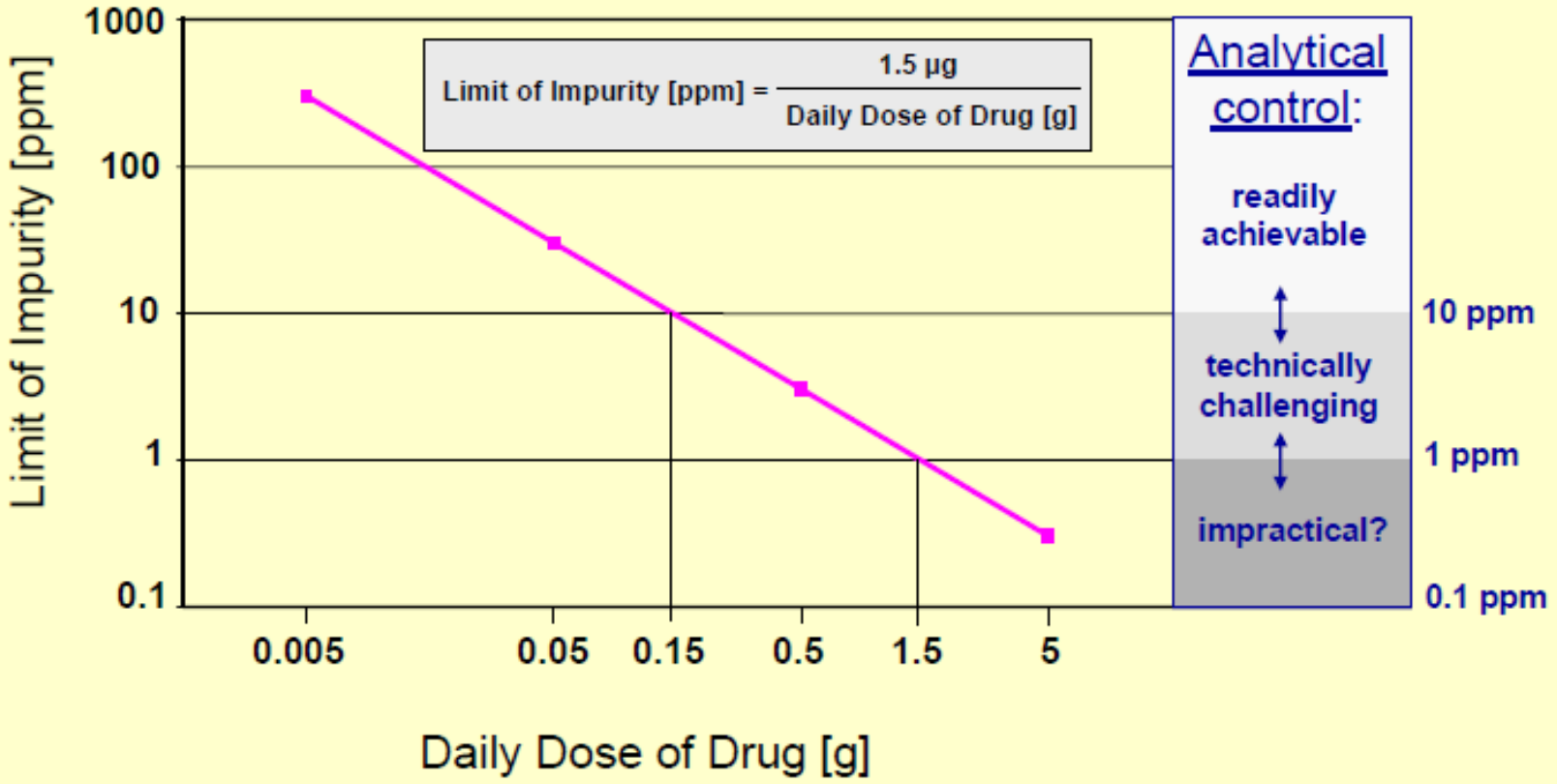
A special case: DNA reactive impurities

- 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
  - 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

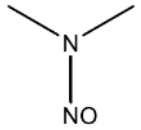
Analytical control can be a challenge!



Source: Peter Kasper, BfArM, Impurities Forum 2009

The Valsartan 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



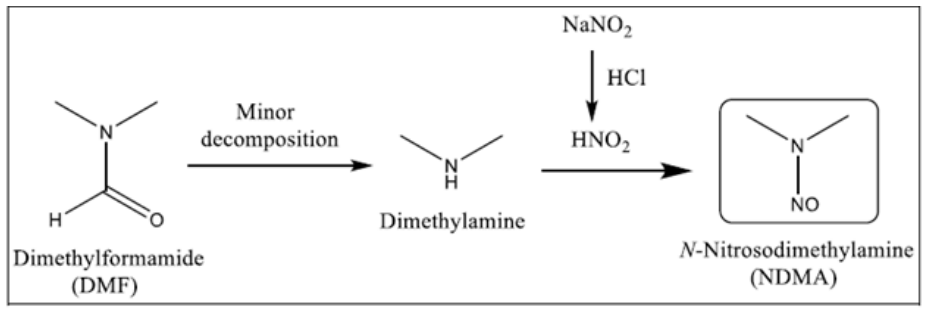
N-Nitrosodimethylamine
(NDMA)

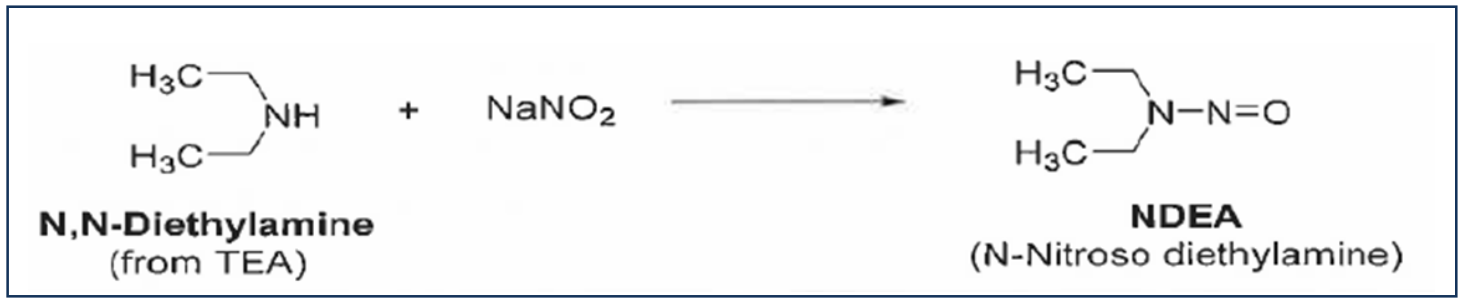
- EDQM Certification of Substances Department and regulatory authorities worldwide have taken action
- Review of ASMFs and marketing autorisation applications by EU authorities
- Review CEPs by EDQM (reliance on the work done, not only in Europe!)
- EMA: CHMP Article 31 referral was started and later extended to other Sartans
- Sampling & testing for APIs and medicinal products coordinated by EDQM
- GMP Inspections

The Valsartan issue - 2

- Origin of nitrosamines:

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

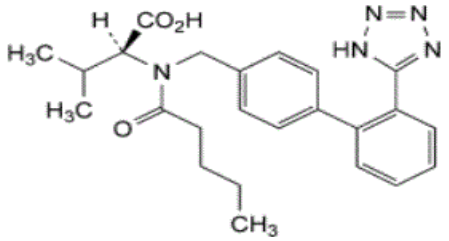




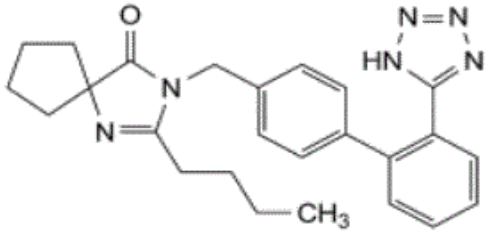
  - A number of synthetic processes use NaNO2 for quenching excess of azide or cyanide after forming tetrazol structure -> potential risk to form N-Nitrosamines

  - Cross-contaminations - processes running in parallel on same lines
  - Contaminations by other factors e.g. recycling of solvents

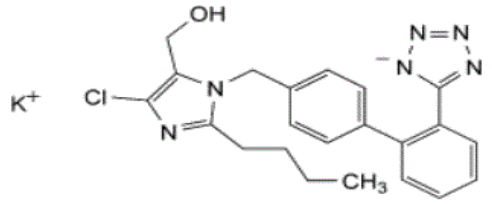
Sartans with tetrazole ring structure



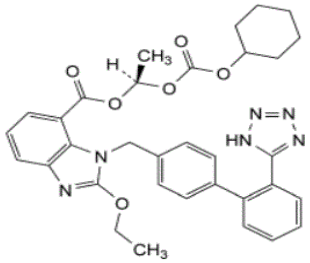
Valsartan



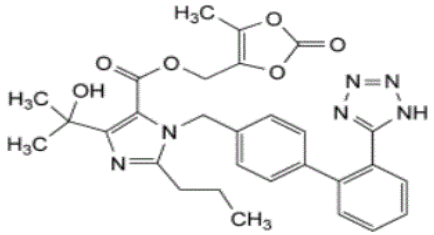
Irbesartan



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?

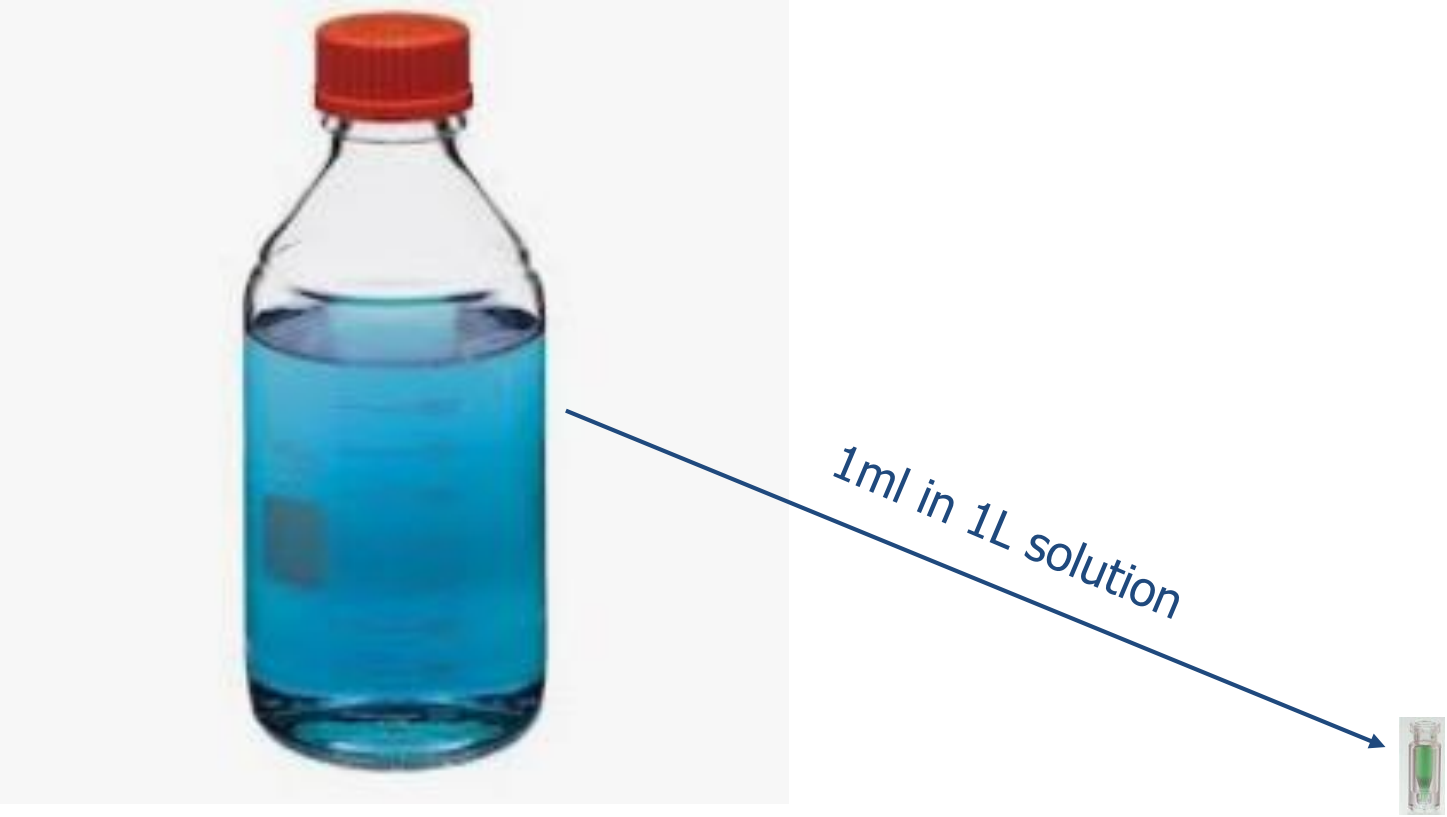
- In the EU, a referral under article 31 (of directive 2001/83/EC) was triggered by the European Commission
- In this referral, based on toxicological data and in line with ICH M7 (R1) the EMA CHMP decided on acceptable intakes (AI) for an interim period of 2 years
- These interim limits were harmonised with 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: work in ppm range

- To put everything in context, here are some figures on what an 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 (DI)

GC-MS (HS)

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)

…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 OMCLs

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	-

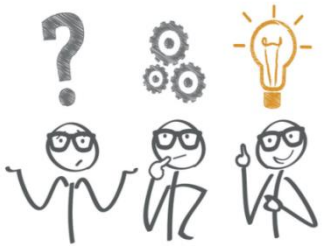
NDEA

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 – eg. Australia, Brazil, Canada, China, Europe, Japan, Korea, Taiwan, USA, etc



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

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
  - After implementation of appropriate corrective action, CEPs may be restored
- Ph. Eur. Monographs Valsartan, Losartan K, Irbesartan, Candesartan cilexetil, Olmesartan medoxomil have been revised with the interim limits and will be further updated.
- It is intended to update the General monograph «Substances for Pharmaceutical use»

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 processed to be reviewed for the potential risk of formation of N-Nitrosamines and changed as necessary to minimise nitrosamine contamination

NDMA and NDEA must be below 0.03ppm (LOQ)

Details are available here

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

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)
- Some OMCLs are active in the method development for future Ph.Eur. General Method(s)
- Main challenges:
  - sensitivity
  - broad coverage of N-Nitrosamines
  - applicability to different APIs

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 » under the auspices of the EMA
- Potentially wider action needed to review non-Sartan substances

Thank you for your attention

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