

EDQM update on the Valsartan incident and lessons learned

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Background

This presentation reflects the experience and opinion of the EDQM with nitrosamines contamination for substances covered by CEP applications

Summary

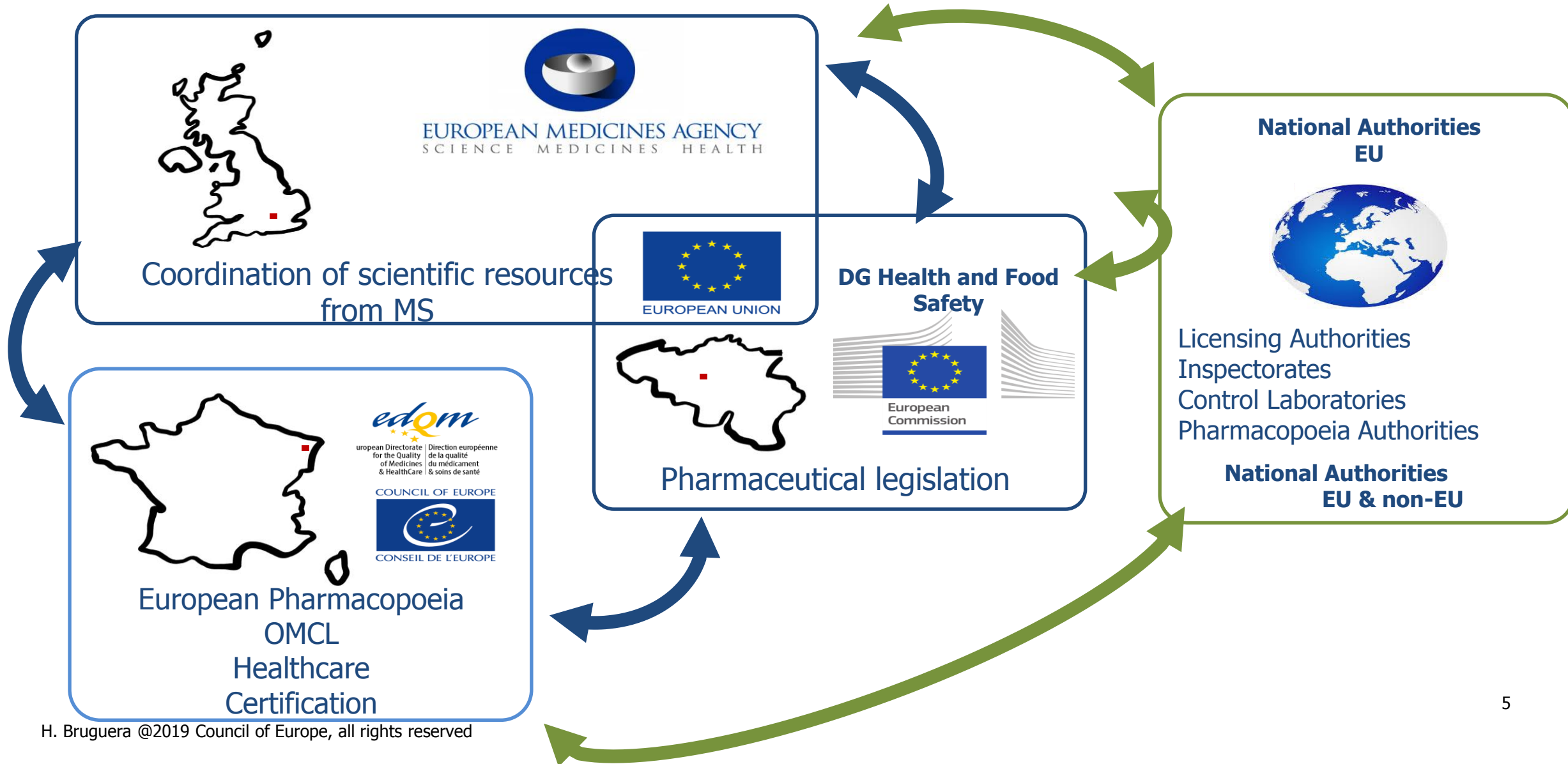
- ✓ Introduction to EDQM activities and the CEP procedure
- ✓ The Valsartan issue
- ✓ Lessons learned
- ✓ Conclusions

The EDQM

European Directorate for the Quality of Medicines & HealthCare

- A **Council of Europe Directorate**, based on the Convention on the Elaboration of a European Pharmacopoeia (1964)
- Located in Strasbourg, France
- Mission: to contribute to a basic human right: access to good quality medicines and healthcare

Key players for the quality of medicines in Europe



The CEP procedure



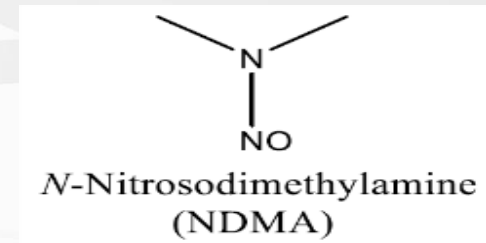
- CEP = **C**ertificate of Suitability to the monographs of the **E**uropean **P**harmacopoeia
- An international platform for:
 - Assessment of the quality of substances for pharmaceutical use (mainly APIs), with reference to monographs of the Ph. Eur.
 - Coordination and conduct of GMP inspections of API manufacturers
- Provides easier management of marketing authorisation applications and their variations → saving of time and resources for Industry and authorities
- Increasingly accepted worldwide

The Valsartan issue

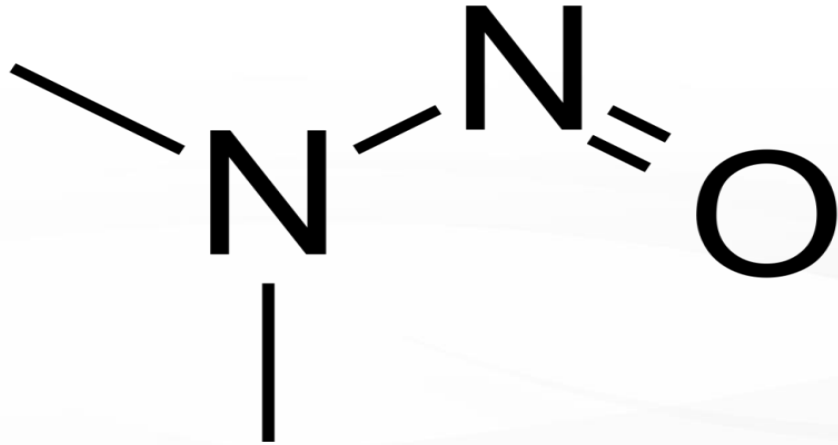
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The Valsartan issue

- June 2018: information that Valsartan manufactured by Zhejiang Huahai Pharmaceutical (ZHP) was contaminated with NDMA (Nitrosodimethylamine)
 - NDMA likely to be present in batches since 2012, when a change of process was made
 - NDMA was unexpected and therefore not controlled
 - Significant levels found
- CEP suspended immediately by EDQM



N-Nitrosodimethylamine (NDMA)



NDMA is known as **possible carcinogen for humans** (well-known in food area, may be present in water, smoked meat, BBQ...)

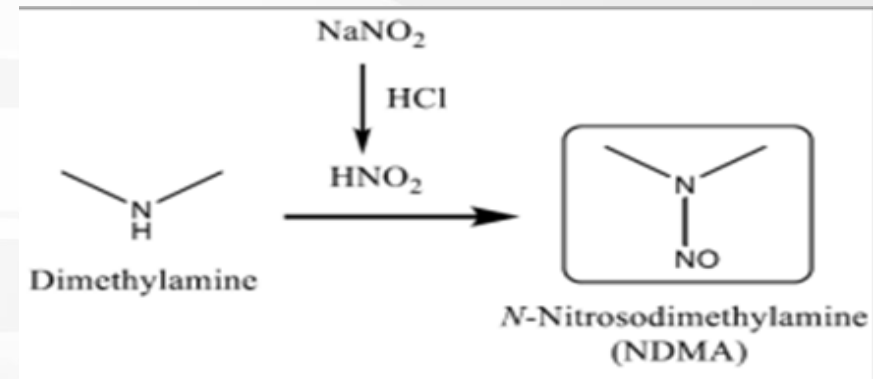
Classification of NDMA^[4]

American Conference of Governmental Industrial Hygienists (ACGIH)	A3: Animal carcinogen. "Available evidence suggests that the agent is not likely to cause cancer in humans except under uncommon or unlikely routes or levels of exposure."
International Agency for Research on Cancer (World Health Organization) (IARC)	2A: The agent (mixture) is probably carcinogenic to humans; there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals.
National Toxicology Program (Health and Human Services Dept., Public Health Service, NIH/NIEHS) (NTP)	2: Reasonably anticipated to be carcinogens

Formation of NDMA



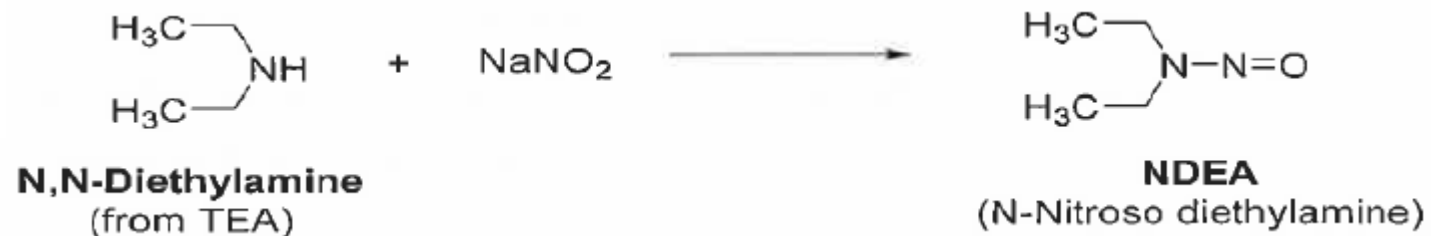
- Contamination linked to specific conditions, raised with the formation of the tetrazole ring
 - Presence of nitrous acid, from Na nitrite in acidic conditions, in order to quench the azide
 - Presence of dimethylamine (not introduced into the process)
 - Linked to the use of DMF (when heated)



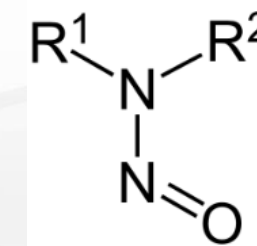
Formation of nitrosamines

- The review of the reaction conditions suggested quickly that the issue could be broader
 - Other sources of valsartan
 - Other sartans (except telmisartan)
 - Other nitrosamines may be generated, eg. NDEA (from the use of triethylamine), NDBA, NMBA, NDIPA, EIPNA etc
 - Not only CEP applications
 - And possibly other active substances beyond sartans...
- Nitrosamines are part of ICH M7 “cohort of concern”
 - Very low acceptable amounts – require sensitive analytical methods

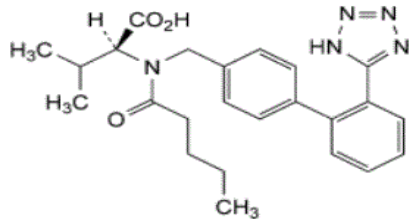
Formation of nitrosamines



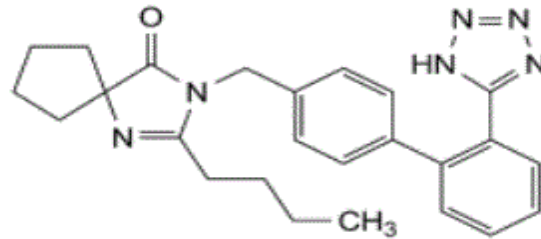
- NDIPA = N-nitrosodiisopropylamine
- NIPEA = N-nitroso-isopropylethylamine
- NDBA = N-nitrosodibutylamine
- NMBA = N-nitrosomethylamino butyric acid (derived from the use of the N-methylpyrrolidone)



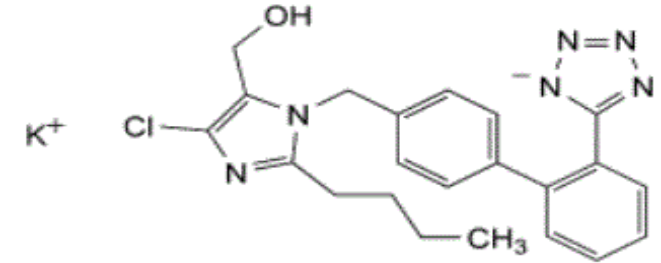
List of sartans with tetrazole ring in the Ph. Eur



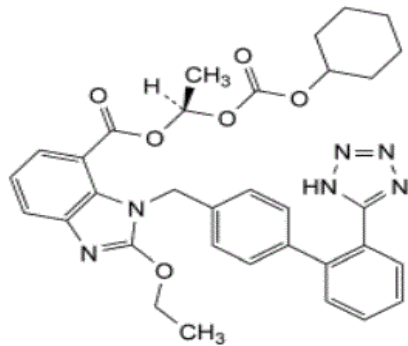
Valsartan



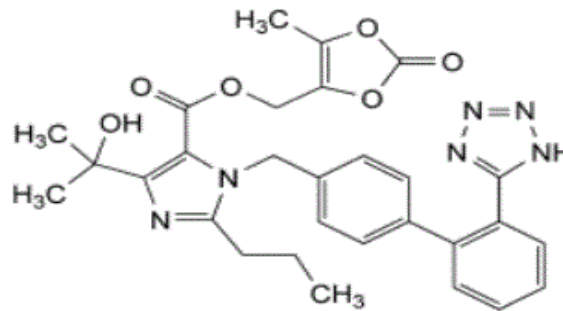
Irbesartan



Losartan potassium



Candesartan cilexetil



Olmesartan medoxomil

Limits for NDMA/NDEA

Tentatively agreed limits – based on Toxnet (TD50 studies)

Active substance (max daily dose)	NDMA		NDEA	
	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

Limits for other nitrosamines

- NDIPA: no tox data available, use the one for NDEA → 0.0265 g/day (0.08 ppm in Valsartan)
- NIPEA: no tox data available, use the one for NDEA → 0.0265 g/day (0.08 ppm in Valsartan)
- NMBA → 0,982 µg/day (3,07 ppm in Valsartan)
- NDBA → 0,691 µg/day (2,16 ppm in Valsartan)

These thresholds are still under discussion !

Actions taken

- Review of ASMFs and marketing authorisation applications by EU authorities
- Review of CEP applications by EDQM (reliance on the work done, not only in Europe!)
- Sampling & testing for APIs and medicinal products
- GMP Inspections
- Decisions on contaminated products already on the market (impact on patients and recalls)
- High interest for some media in Europe, regular communication on updates

Impact of the issue

- Many API manufacturers and Finished Products manufacturers affected
- Worldwide issue – eg. Australia, Brazil, Canada, China, Japan, Korea, Taiwan, USA
 - Regular recalls of products due to contaminations
- EU initiated referral (Article 31) on Valsartan, extended in October 2018 to other sartans having a tetrazole ring



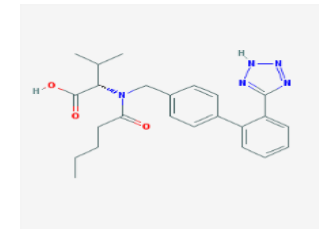
Initial actions taken by EDQM

- In July 2018, review of **all** sartans CEP applications (including history of revisions) – about 125 dossiers
 - CEP holders contacted in 3 waves in July & August 2018:
 - ✓ CEPs for Valsartan considered at risk for NDMA
 - ✓ CEPs for other sartans considered at risk for NDMA
 - ✓ All CEP holders not already contacted
- ➔ Requests to address the presence of nitrosamines

Initial results

- July 2018: other sources of valsartan contaminated with NDMA, or lack of information from companies → a couple of CEPs for valsartan suspended
- August 2018: EDQM was informed of detection of NDEA in Valsartan due to the use of triethylamine (source of diethylamine) → CEP suspended

Further findings



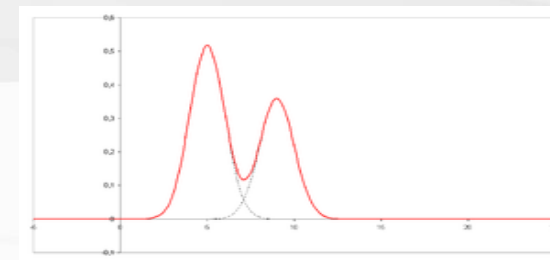
- New information received on a regular basis, either from manufacturers following requests for information, or from international partners
 - Other sartans contaminated with NDEA: losartan K, irbesartan
 - A valsartan source contaminated with NDIPA
 - A source of losartan K contaminated with NMBA
- ➔ CEPs suspended

Further findings - 2

- Science is not enough ! Other factors contribute to contaminations with nitrosamines:
 - cross-contaminations due to use of different processes on identical lines
 - recycling of solvents (cross-contamination at 3rd party)
 - ➔ CEPs suspended

Sampling & testing

- EDQM coordinating sampling and testing by the network of European Official Medicines Control Laboratories (OMCLs)
 - Risk-based testing plans
 - Common format for communication of sampling plans and test results
 - Methods developed by several labs
 - Detection of NDMA, NDEA or both
 - In APIs and/or finished products



Sampling & testing - 2

- A number of methods published on the EDQM website (GC/MS, HPLC-UV, LC/MS/MS, GC/MS/MS):
<https://www.edqm.eu/en/ad-hoc-projects-omcl-network>
- Duly validated
- OMCLs provide official results:
 - to confirm patient exposure for products on the market
 - for samples taken from the GMP inspections
 - to verify data given by manufacturers
 - Market surveillance for various sartans

Analytical challenges

	Limit in Valsartan	Limit in Losartan
NDMA	0.3 ppm	0.64 ppm
NDEA	0.08 ppm	0.18 ppm

LOQs achieved for Valsartan tablets

	UHPLC/MS/MS	GC/MS/MS
NDMA	0.2 ppm	0.08 ppm
NDEA	0.04 ppm	0.04 ppm

GMP inspections



- Joint inspection EMA/EDQM of ZHP
 - A number of major deficiencies to GMP
 - Statement of Non Compliance to GMP issued for ZHP for Valsartan
 - ZHP is intermediate manufacturer for other manufacturers of valsartan → Impact on these sources: 4 CEPs for Valsartan revised in October 2018
- FDA inspection of ZHP → same findings, broader actions
- Joint inspection EMA/EDQM of Zh. Tianyu
- FDA, EU inspections of other manufacturers

Information sharing

- Close cooperation with EMA and within the EU networks
- Close cooperation with other authorities worldwide
 - Sharing test results and data from manufacturers under confidentiality agreements, including with the USFDA, HC, TGA, HSA, TFDA, etc
 - EDQM information used by competent authorities to decide on products (eg. Recalls)
 - Harmonisation of policies, decisions, worldwide



Current status – CEPs review

- As of today:
 - Confirmation of « No risk » and data for nitrosamines for the vast majority of CEP dossiers
 - 11 CEPs suspended
 - A number of applications still under review (requests for info)
- After review of the data, confirmation letters or revised CEPs sent to CEP holders (with limits and a test appended)
- Restoration of suspended CEPs where applicable in the near future
- Regular information on the EDQM website

Current status – EU opinion

- Since January 2019, all batches (APIs/FP) put on the market in EU should have been tested and found compliant with tentative limits
- Outcome of the EU Article 31 referral available since end January 2019 → CHMP opinion

<https://www.ema.europa.eu/en/news/sartan-medicines-companies-review-manufacturing-processes-avoid-presence-nitrosamine-impurities>

- Opinion in line with position of other authorities (US, Switzerland, Singapore etc)

Current status - What to do

- Transition period of # 2 years:
 - Use tentative limits for nitrosamines (cf. slide 14-15)
 - Batches containing higher levels cannot be put on the market
 - Only **1** nitrosamine allowed

Current status – What to do - 2

- In the future, only nitrosamine free materials will be allowed
 - Manufacturing processes to be changed so they do not produce any nitrosamine impurities, for example:
 - Use different solvents (no amides such as DMF, DMA, NMP), no amines (e.g. inorganic bases)
 - Remove sodium nitrite, replace by other quenching agents, or quench azide outside the process
 - Change order of steps
 - Introduce controls for raw materials that may introduce nitrite
 - Be extra-careful with recycling of solvents
- Introduce routine testing of the API: levels of nitrosamines should be « **not measurable (< 0.03 ppm)** », **irrespective of nitrosamine and API**

CEPs in the future

- CEP applications to be updated according to EU decision
- EDQM will contact CEP holders and give instructions
 - Requests for revisions to be submitted in due time
 - Process change + changes to specification

In the European Pharmacopoeia

- On-going work:
 - Update of the Ph. Eur monographs for sartans with tetrazole ring ==> different options based on the CHMP opinion
 - Development and validation of a general method that may be used as reference
 - Final decision to be taken at the Ph. Eur commission meeting in March 2019

➔ Watch the space !

Communication by EDQM

- Regular communication on the EDQM website

- CEP page (new findings):

<https://www.edqm.eu/en/news/update-edqm-review-cep-applications-sartan-substances-4-february-2019>

<https://www.edqm.eu/en/news/update-review-cep-applications-sartans-18-january-2019>

<https://www.edqm.eu/en/news/update-review-cep-applications-sartans> (November 2018)

<https://www.edqm.eu/en/news/update-detection-nitrosamines-valsartan-and-validated-testing-method> (September 2018)

<https://www.edqm.eu/en/news/update-edqms-actions-following-detection-impurity-valsartan> (August 2018)

- OMCL page (new methods and validation):

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

Lessons learned

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Lessons learned

Initial thoughts:

- On quality aspects
 - Not all root causes are yet fully understood (impact of raw materials, etc) !
 - Lack of process development & process understanding by API manufacturers
 - Risk assessments not sufficiently performed by some companies
 - 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 for data on recycling of materials?

Lessons learned - 2

- On the supply chain:
 - Finished products manufacturers are ultimately responsible for the quality of APIs used and are legally obliged to get information they need to take this responsibility
 - In practice it does not work well
 - 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)

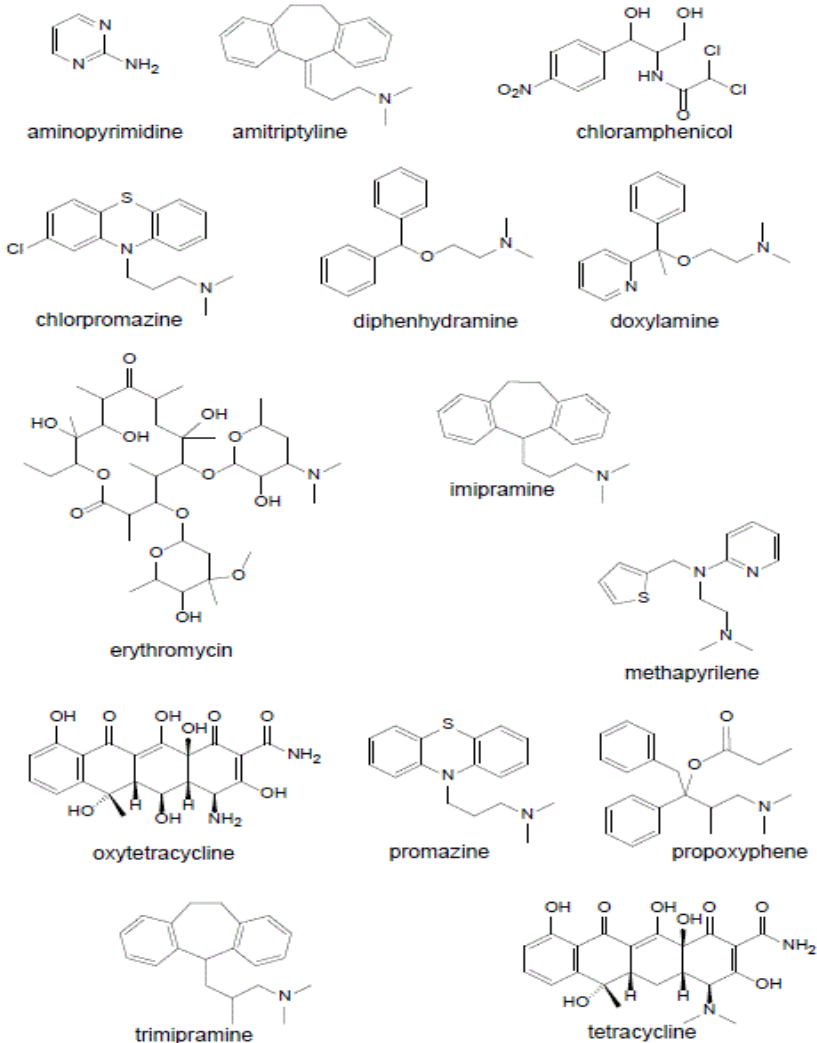
Lessons learned - 3

- On GMP aspects:
 - Deeper review of process development and risk assessments during GMP inspections
 - Deeper review of recycling operations
 - Is the current system sufficient ?
 - risk-based inspections of API manufacturers
 - during inspections of FP manufacturers, check more in depth auditing and risk assessment for supplier qualification

Lessons learned - 4

- Opportunities:
 - Communication amongst authorities worldwide to share knowledge, findings, test results and avoid duplication of work
 - Alignment of decisions
- ➔ Need to reflect further on different levels with international partners

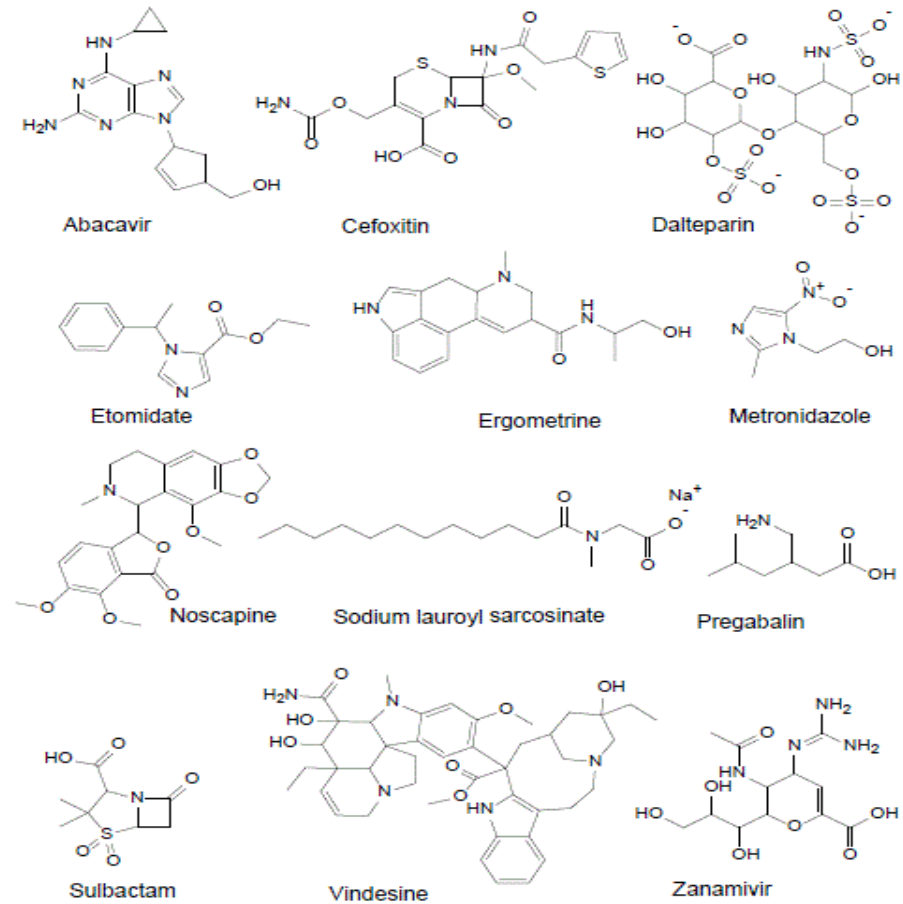
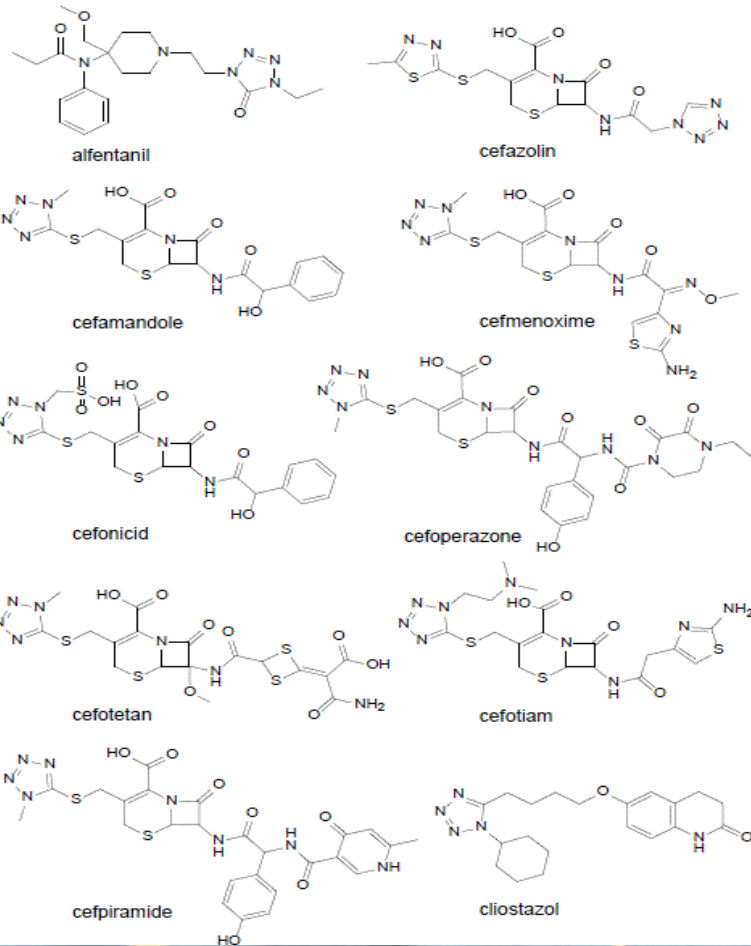
Nitrosamines may be everywhere !



Chemical structures of APIs reported in literature² to contain NDMA

²M.K. Parr, J.F. Joseph, J Pharm Biomed Anal., 2019; 164:536-549

Chemical structures of APIs using azide or nitrile in synthesis



Conclusions



- Issue still on-going – will take some time
- Actions on various levels (review of dossiers, GMP, analytical testing, communication etc)
- Has fostered international collaboration
- Need to reflect on lessons learnt and on future actions to avoid such an event, with international partners
- Changes of process for sartans required within max 2 years for several markets
- Consider other non-sartans substances !

THANK YOU
FOR YOUR ATTENTION