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

edqm

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The (Val)sartan incident –EDQM experience

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Introduction to EDQM activities and the CEP procedure

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 rights: access to good quality medicines and healthcare.

CEP = Certificate of Suitability to the monographs of the European Pharmacopoeia

European Pharmacopoeia
OMCL
Healthcare
Certification

National Authorities
EU

Licensing Authorities
Inspectorates
Control Laboratories
Pharmacopoeia Authorities

National Authorities
EU & non-EU

Introduction to EDQM activities and the CEP procedure

CEP Procedure

Provides centralised assessment of the quality of a source of pharmaceutical substance (mainly APIs):

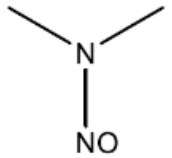
- Compliance with European regulatory requirements with regards quality
- Demonstrates that the substance can be controlled by the Ph. Eur. monograph, with additional tests if needed. Ensures that possible impurities are suitably controlled
- Provides information on the need to revise Ph. Eur. Monographs
- Provides easier management of marketing autorisation applications and their variations – A CEP replaces main part of 3.2.S of CTD

➔ Saving of resources/costs

CEPs are increasingly accepted by regulatory authorities worldwide

The Valsartan issue; when it all started...

- June 2018: information that Valsartan manufactured by Zhejiang Huahai Pharmaceutical (ZHP) was contaminated with NDMA (Nitrosodimethylamine)
  - ➢ NDMA is known as possible carcinogen for humans (well-known in food area, may be present in water, smoked meat, beer...)
  - ➢ NDMA was unexpected and therefore not controlled
- Source covered by a CEP
- CEP suspended immediately by EDQM



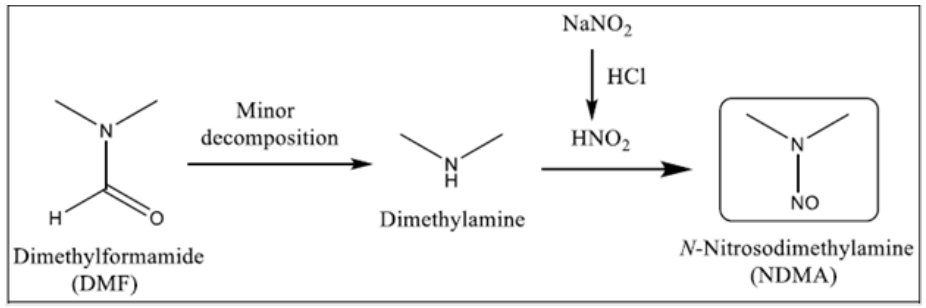
N-Nitrosodimethylamine
(NDMA)

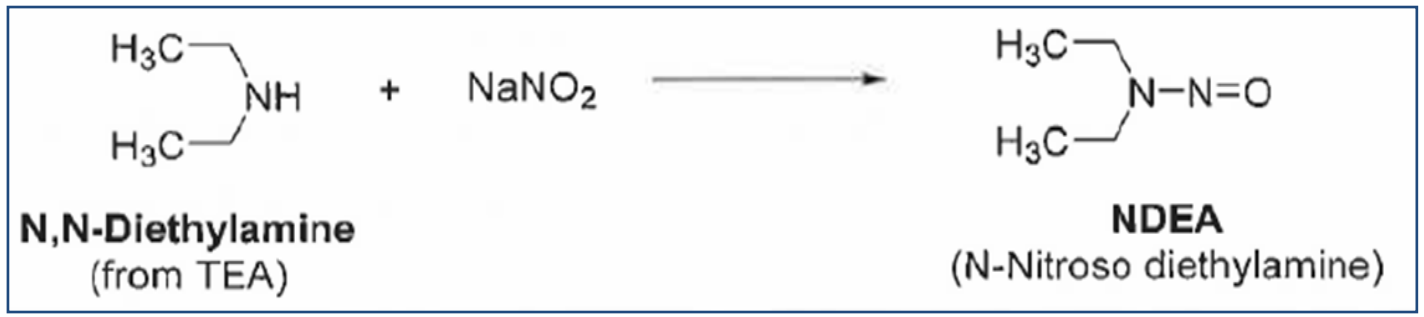
Formation of nitrosamines

- The review of the root cause and reaction conditions suggested quickly that the issue could be broader than initially considered
  - Other sources of valsartan
  - Other sartans with a tetrazole structure
  - Not only CEP applications, also ASMFs & Marketing Authorisation Applications
  - Other nitrosamines may be generated, eg. NDEA, NDBA, NMBA, NDIPA, EIPNA etc
  - And possibly other active substances beyond sartans...
- Nitrosamines are part of ICH M7 “cohort of concern”
  - Very low acceptable amounts – require sensitive analytical methods (< ppm)

Formation of nitrosamines (2)

- Origin of nitrosamines:
  - Simultaneous presence of sodium nitrite (NaNO2) + primary or secondary amine in acidic conditions

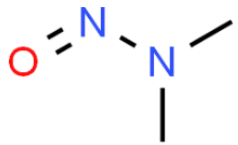




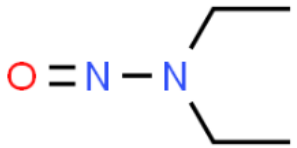
  - A number of synthetic processes for sartans use NaNO2 for quenching excess of azide after forming the tetrazole structure -> potential risk to form N-Nitrosamines
  - Various sources of amines, eg. heated DMF, impurity in triethylamine, etc (list not exhaustive)

Nitrosamines

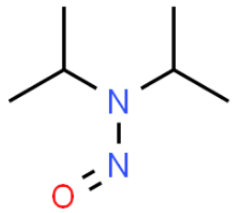
- NDMA = N-nitrosodimethylamine



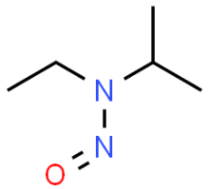
- NDEA = N-nitrosodiethylamine



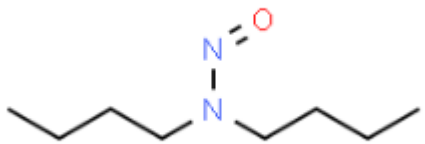
- NDIPA = N-nitrosodiisopropylamine



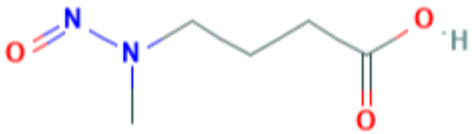
- NIPEA = N-nitrosoisopropylethylamine



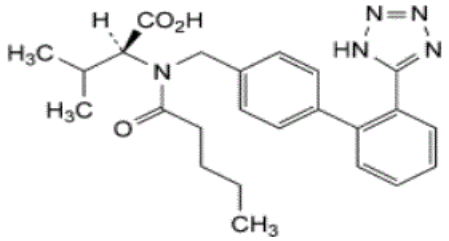
- NDBA = N-nitrosodibutylamine



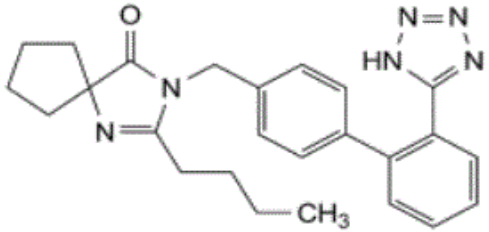
- NMBA = N-nitrosomethylamino butyric acid



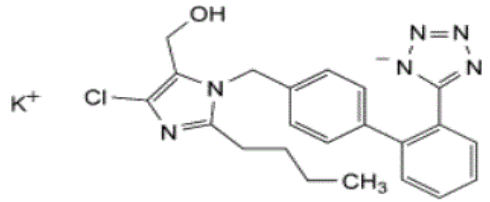
Sartans with tetrazole ring structure in the Ph. Eur



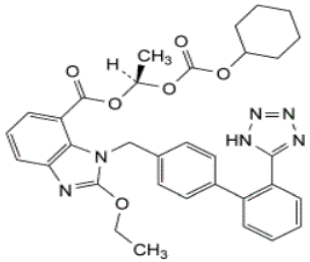
Valsartan



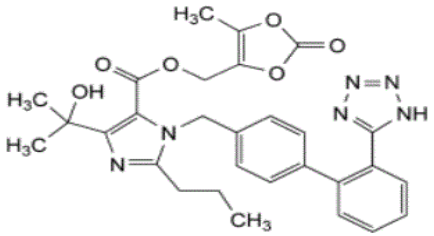
Irbesartan



Losartan potassium



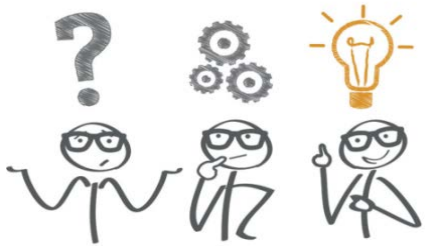
Candesartan cilexetil



Olmesartan medoxomil

Impact of the issue

- Many API manufacturers and Finished Products manufacturers affected
- Worldwide issue – eg.
  Australia, Brazil, Canada, China, Japan, Korea, Switzerland, Taiwan, US A
  - ➢Regular recalls of medicinal products due to contaminations
- EU initiated referral (Article 31) on Valsartan, extended in October 2018 to other sartans with a tetrazole ring
- Situation evolving quickly and constantly, with new information. new findings, decisions etc



Actions taken by EDQM

- Review of CEP applications
- Sampling & testing of APIs and medicinal products by OMCLs
- GMP Inspections
- Revision of Ph. Eur requirements

- And also, due to high interest of media in Europe, regular communication and updates

Review of CEP dossiers

- About 125 applications concerned (incl. history of dossiers)
  - Data requested from API manufacturers (CEP holders) and evaluated (risk assessments, test results, analytical specification, etc)
  - Additional controls, changes of process submitted by API manufacturers
  - Information received from API manufacturers, international partners & OMCLs

- Science was not enough ! Other factors contributed to contaminations with nitrosamines:
  - Reaction conditions (reagents, solvents, their quality, degradation of materials)
  - Cross-contaminations between processes (running on same line)
  - Recovery of solvents (incl. contamination at 3rd party)

Review of CEP dossiers (2)

- In total, 11 CEPs suspended
  - Valsartan sources contaminated with NDMA, NDEA, NDIPA
  - Irbesartan contaminated with NDEA
  - Losartan K sources contaminated with NDEA, NMBA

- Exercise completed in June 2019
  - Confirmation of “no risk” for the vast majority of CEP sources
  - Letters of approval or revised CEPs granted
  - A couple of CEPs restored already (corrective actions + assessment)

Limits for NDMA and NDEA

- Based on toxicological data and in line with ICH M7 (R1) the EMA CHMP decided on interim acceptable intakes (AI)
- Interim limits harmonised with international regulators and used by EDQM

	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 levels are above, or if both impurities present ➔ reject batch

Sampling and testing in the OMCL Network

EDQM:

- Coordinated network of European Official Medicines Control Laboratories (OMCLs) – “Sartan testing group”, 13 European labs + 3 associated labs involved
- Supported method development & validation
- Sourced samples & materials for validation
- Common format for reporting of plans and results
- Exercise focused on detection of NDMA, NDEA or both, in APIs and/or drug products

➔A number of methods available, published on the EDQM website : https://www.edqm.eu/en/ad-hoc-projects-omcl-network

Sampling and testing in the OMCL Network (2)

- Testing purposes:
  - ➢ Confirm levels of NDMA in contaminated products, already recalled (Art. 31 referral request, verification of MAH results, confirm patient exposure)
  - ➢Market surveillance of products
  - ➢Market surveillance of other sartans than valsartan
  - ➢Analysis of samples from GMP inspections

  ➔# 2000 medicinal products and 600 APIs batches tested for NDMA and/or NDEA

  ➔ Triggered/supported batches recalls & suspension of CEPs

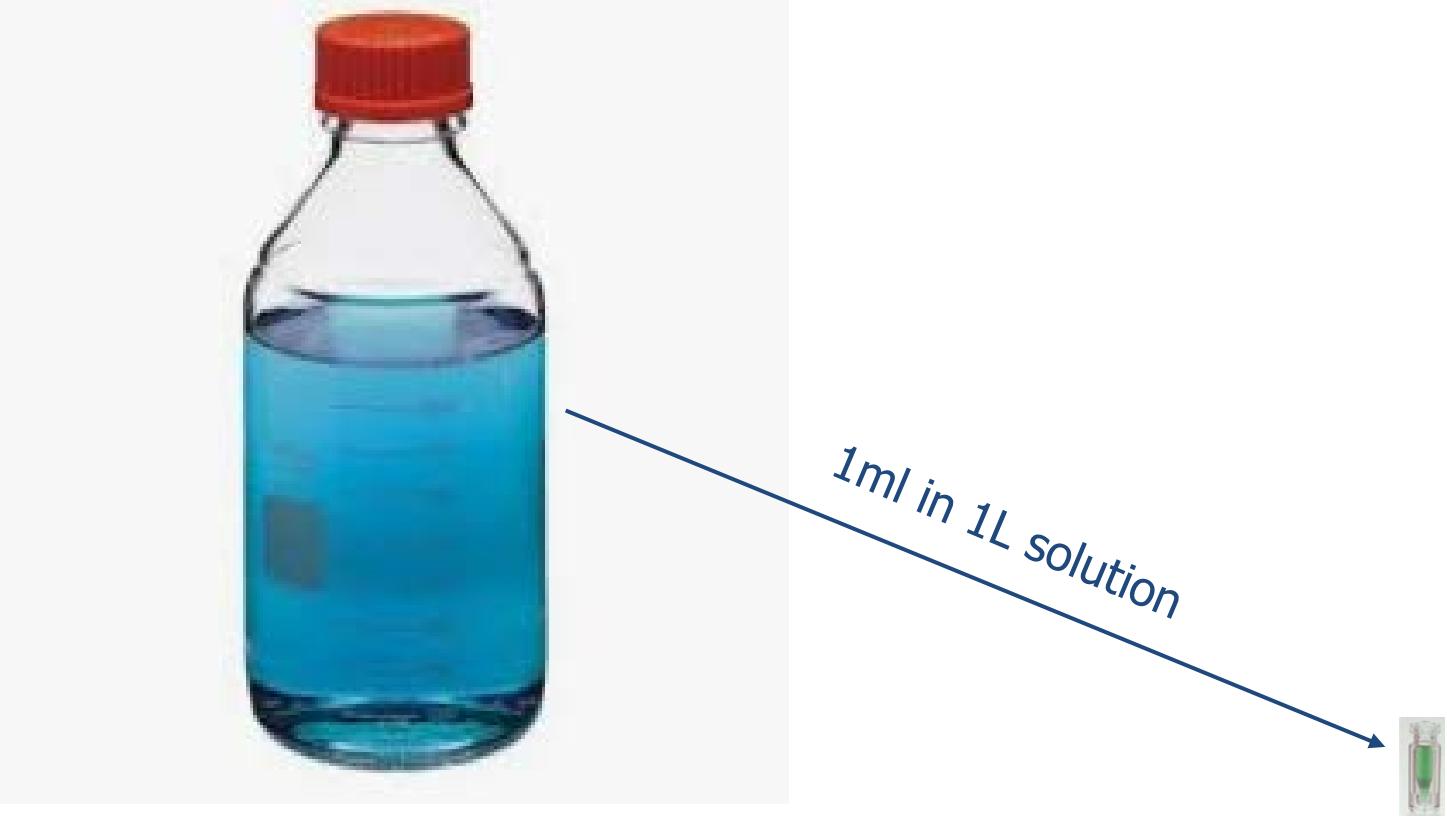
Analytical methods used

	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

DS: drug substance DP: drug product

Analytical challenges: ppm-ppb

To put everything in context, this is what a «usual» impurity level looks like (0.05 to 0.1% = 500 to 1000 ppm):



Analytical challenges: 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

GMP inspections of API manufacturers

- Joint inspection EMA/EDQM of ZHP in 2018
  - ➢A number of major deficiencies to GMP
  - ➢Statement of Non Compliance to GMP issued for ZHP for Valsartan
    - Published in EudraGMDP website (http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPNonCompliance.do)
    - ZHP was intermediate manufacturer for other manufacturers of valsartan covered by CEPs ➔ Impact on these sources: 4 CEPs for Valsartan revised in October 2018 to remove this site
  - ➢USFDA inspection of ZHP➔ same findings, broader actions
  - ➢Re-inspection of ZHP in March 2019 (joint EDQM/EU/US/AU)
- Other USFDA, EU, EDQM, and joint inspections of other manufacturers
- Samples taken, for testing by OMCLs

Information sharing & communication

- Close cooperation with EMA and within the EU network (regular TCs)
- 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
- Regular updates published on EDQM website
  - CEP, OMCL, Ph. Eur webpages

Implementation of the EU Art.31 referral

- CHMP opinion endorsed by EU commission and published on 2 April 2019
- Transition period:

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

  ➔Specifications must include the interim limits for NDMA & NDEA
- After transition period (2 April 2021):

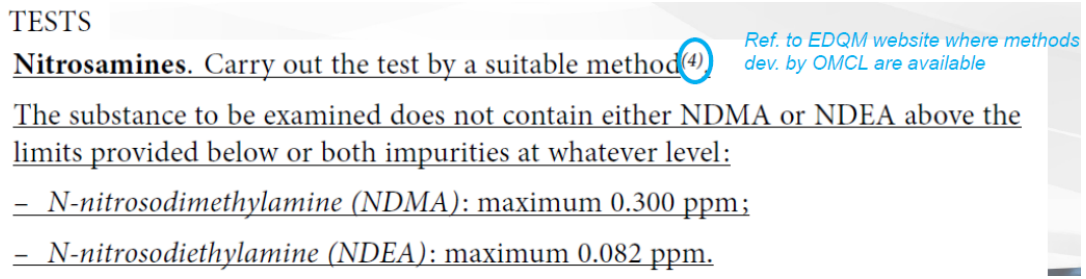
  "No nitrosamines" concept ➔NDMA and NDEA below 0.03ppm (LOQ)

  Manufacturing processes to be reviewed for the potential risk of nitrosamines and changed as necessary

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

Impact on the Ph. Eur

- Update of the Ph. Eur monographs for 5 sartans with tetrazole ring: addition of a Production section + Test section
  - ➢Published in Ph. Eur 10th ed, implementation in January 2020


TESTS

Nitrosamines. Carry out the test by a suitable method (4).

Ref. to EDQM website where methods dev. by OMCL are available

The substance to be examined does not contain either NDMA or NDEA above the limits provided below or both impurities at whatever level:

– *N-nitrosodimethylamine (NDMA)*: maximum 0.300 ppm;

– *N-nitrosodiethylamine (NDEA)*: maximum 0.082 ppm.

https://www.edqm.eu/en/news/control-nitrosamine-impurities-sartans-revision-five-ph-eur-monographs

Next steps

- On CEPs:
  - Restorations of suspended CEPs, after implementation of corrective actions (eg. control strategy, etc) and their evaluation (on-going)
  - Some CEP applications to be updated (again) to align with revised Ph. Eur monographs
    - CEP holders contacted and asked to provide data as needed
    - Revised CEPs with test method appended, by January 2020
  - New updates of CEPs foreseen within 2 years, to meet the “nitrosamine free” concept
    - Revisions to be submitted by CEP holders if changes to processes are needed
    - Some CEPs may be revised (again) by April 2021

https://www.edqm.eu/en/news/update-edqm-review-cep-applications-sartans-and-next-steps-june-2019

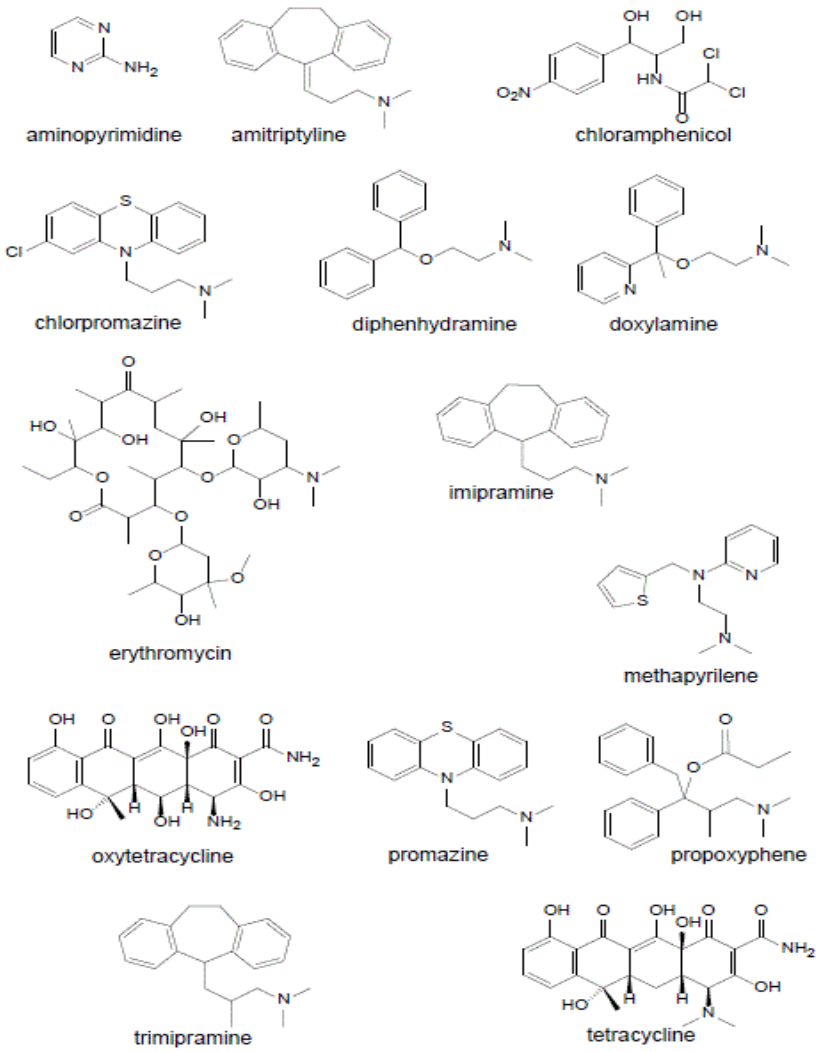
Next steps (2)

- Sampling & Testing by OMCLs:
  - Testing other APIs than sartans
  - Testing other nitrosamines than NDMA & NDEA
  - Development of «universal» method for NDIPA, EIPNA, NDBA, NDMA and NDEA

- On the Ph. Eur:
  - New revisions of 5 sartans monographs expected by April 2021
  - Elaboration of a General Chapter on control of nitrosamines (NDMA, NDEA) (with support of OMCLs for the analytical method)
  - Revision of General Monograph « Substances for pharmaceutical use »

- Participation of EDQM in on-going “Lessons learnt exercise”, co-ordinated by the EMA
  - Involvement of international partners

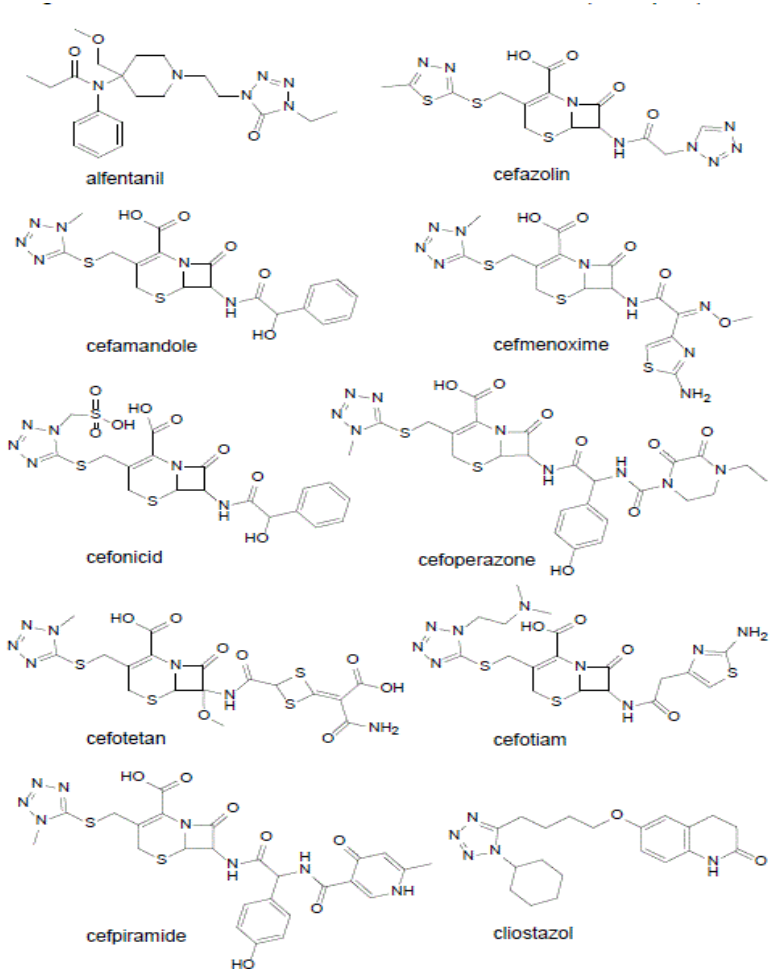
Nitrosamines may be everywhere!

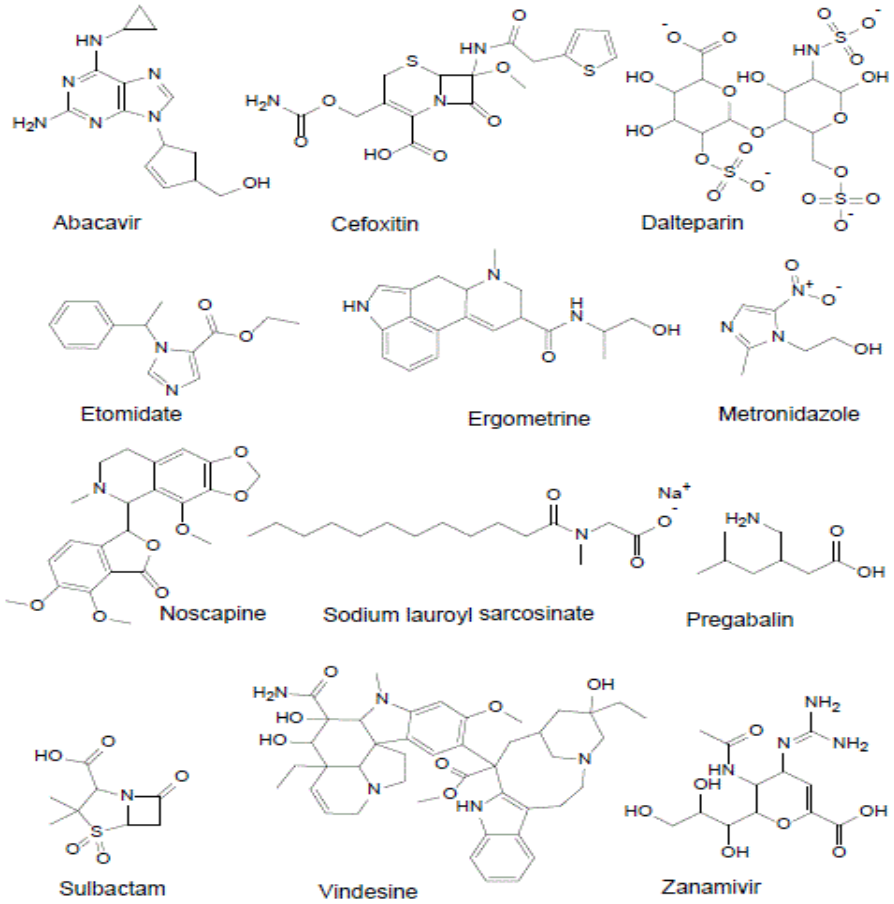


Chemical structures of APIs reported in literature[2] to contain NDMA

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

APIs for which azide or nitrite is used in synthesis





Conclusion

- After more than 1 year, issue still on-going
- Actions taken by EDQM on various levels (review of CEP dossiers, GMP inspections, analytical testing, Ph. Eur., communication etc)
- Has fostered international collaboration
- On-going reflection on lessons learnt and on future actions to avoid such an event, with international partners
- Consider other non-sartans substances !

Thank you for your attention

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