

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



# **Nitrosamine impurities**

## **Current Status & Expectations**

*5<sup>th</sup> India Pharmaceutical Forum,  
Mumbai, 27-28 February 2020*

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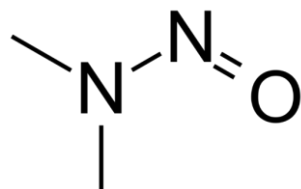
# Background

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This presentation reflects the experience of the European Directorate for the Quality of Medicines & HealthCare (EDQM) with nitrosamine contamination for substances covered by CEP applications

# Recap: Valsartan

- June 2018: information that Valsartan manufactured by Zhejiang Huahai Pharmaceutical (ZHP) was contaminated with NDMA (*N*-Nitrosodimethylamine)



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

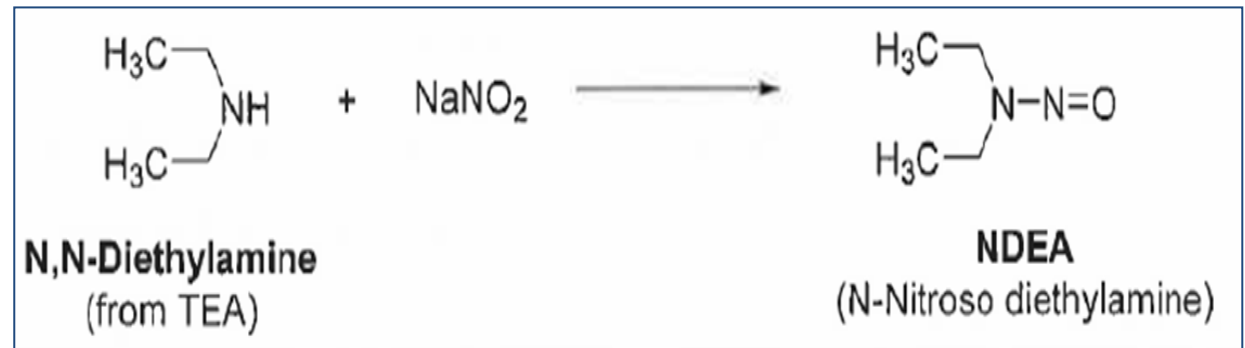
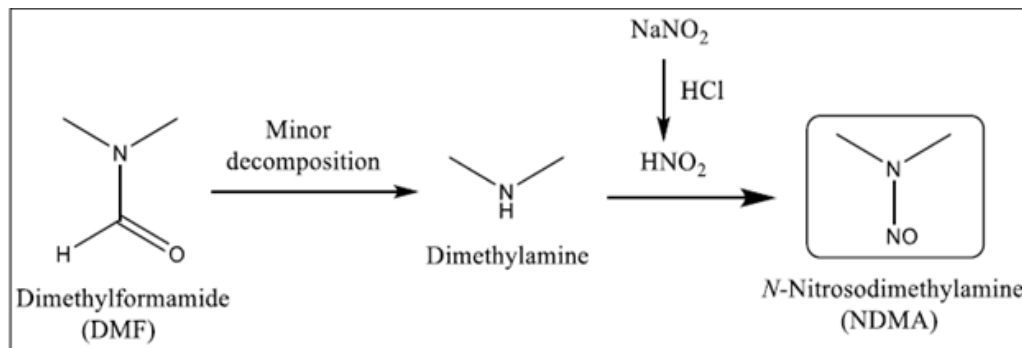
Nitrosamines are part of ICH M7 “cohort of concern”

- very low acceptable amounts, requiring sensitive analytical methods

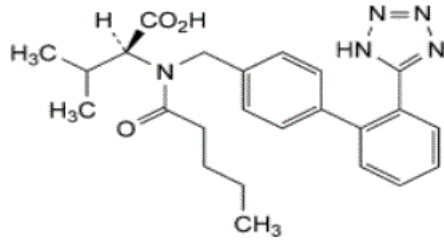
<i>Classification of NDMA</i> <sup>[4]</sup>	
American Conference of Governmental Industrial Hygienists (ACGIH)	<b>A3:</b> Animal carcinogen. “Available evidence suggests that the agent is not likely to cause cancer in humans except under uncommon or unlikely routes or levels of exposure.”
International Agency for Research on Cancer (World Health Organization) (IARC)	<b>2A:</b> 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)	<b>2:</b> Reasonably anticipated to be carcinogens

# Formation of nitrosamines

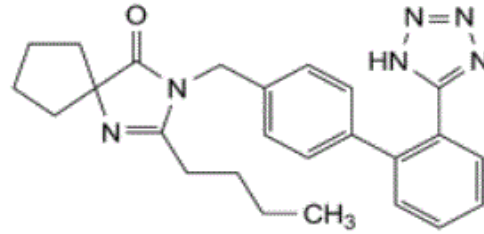
- The review of the reaction conditions quickly suggested that the issue could be more widespread:
  - other nitrosamines may be generated, e.g. NDEA (from the use of triethylamine), NDBA, NMBA, NDIPA, EIPNA etc.;
  - presence of nitrosating agent (e.g.  $\text{NaNO}_2$ ) + secondary or tertiary amine in acidic conditions;



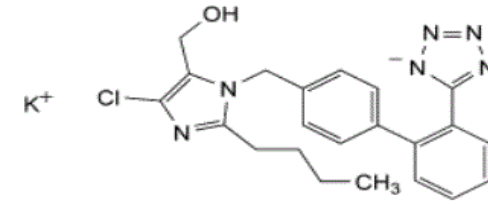
# Sartans with a tetrazole ring structure in the Ph. Eur.



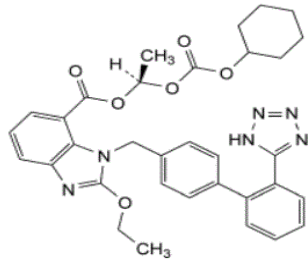
Valsartan



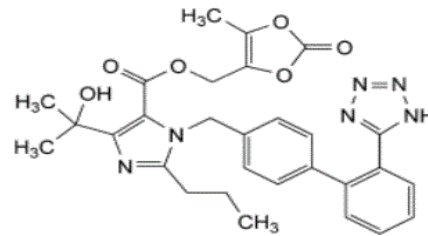
Irbesartan



Losartan potassium



Candesartan cilexetil



Olmesartan medoxomil

# Actions taken by EDQM

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- All CEP applications reviewed
- Sampling & testing of APIs and medicinal products by OMCLs
- GMP Inspections, related CEP suspensions/restorations where applicable
- 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 (e.g. Recalls)
  - Harmonisation of policies & decisions
- Regular updates published on EDQM website
  - CEP, OMCL, Ph. Eur. webpages

# Implementation of the EU Art. 31 Referral outcome (sartans)

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- 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 sartan 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)** irrespective of sartan API
  - 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](https://www.ema.europa.eu/en/documents/referral/sartans-article-31-referral-chmp-assessment-report_en.pdf)



# 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

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

If levels are above, or if **both** impurities present → reject batch

# Limits for other nitrosamines

Active substance (max daily dose)	DIPNA ( <i>N</i> -nitrosodiisopropylamine)		EIPNA ( <i>N</i> -nitrosoisopropylethylamine)		NMBA ( <i>N</i> -nitrosomethylaminobutanoic acid)	
	Maximum daily intake (ng)	Limit in API (ppm)	Maximum daily intake (ng)	Limit in API (ppm)	Maximum daily intake (ng)	Limit in API (ppm)
<b>Candesartan (32 mg)</b>	26.5	<b>0.820</b>	26.5	<b>0.820</b>	96.0	<b>3.000</b>
<b>Irbesartan (300 mg)</b>	26.5	<b>0.088</b>	26.5	<b>0.088</b>	96.0	<b>0.320</b>
<b>Losartan (150 mg)</b>	26.5	<b>0.177</b>	26.5	<b>0.177</b>	96.0	<b>0.640</b>
<b>Olmesartan (40 mg)</b>	26.5	<b>0.663</b>	26.5	<b>0.663</b>	96.0	<b>2.400</b>
<b>Valsartan (320 mg)</b>	26.5	<b>0.082</b>	26.5	<b>0.082</b>	96.0	<b>0.300</b>

Source: EMA/351053/2019 rev 1, August 2019:

[https://www.ema.europa.eu/en/documents/other/temporary-interim-limits-nmba-dipna-eipna-impurities-sartan-blood-pressure-medicines\\_en.pdf](https://www.ema.europa.eu/en/documents/other/temporary-interim-limits-nmba-dipna-eipna-impurities-sartan-blood-pressure-medicines_en.pdf)

# Impact on the Ph. Eur.

- Update of the Ph. Eur. monographs for 5 sartans with a tetrazole ring: addition of a Production section + Test section

## PRODUCTION

As *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) are classified as probable human carcinogens, manufacturers must ensure that their manufacturing process does not generate such impurities and develop appropriate control strategies. To allow manufacturers to make the necessary changes to their process, a transition period has been agreed by competent authorities and strict temporary limits on levels of these impurities introduced in the Test section.

## TESTS

**Nitrosamines.** Carry out the test by a suitable method<sup>(4)</sup>

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>

- Some CEP applications updated (again) to align with revised Ph. Eur. monographs, published in 10<sup>th</sup> Ed. and implemented on 1<sup>st</sup> January 2020
  - CEP holders contacted and asked to provide data as needed
  - CEPs subsequently revised with test method appended

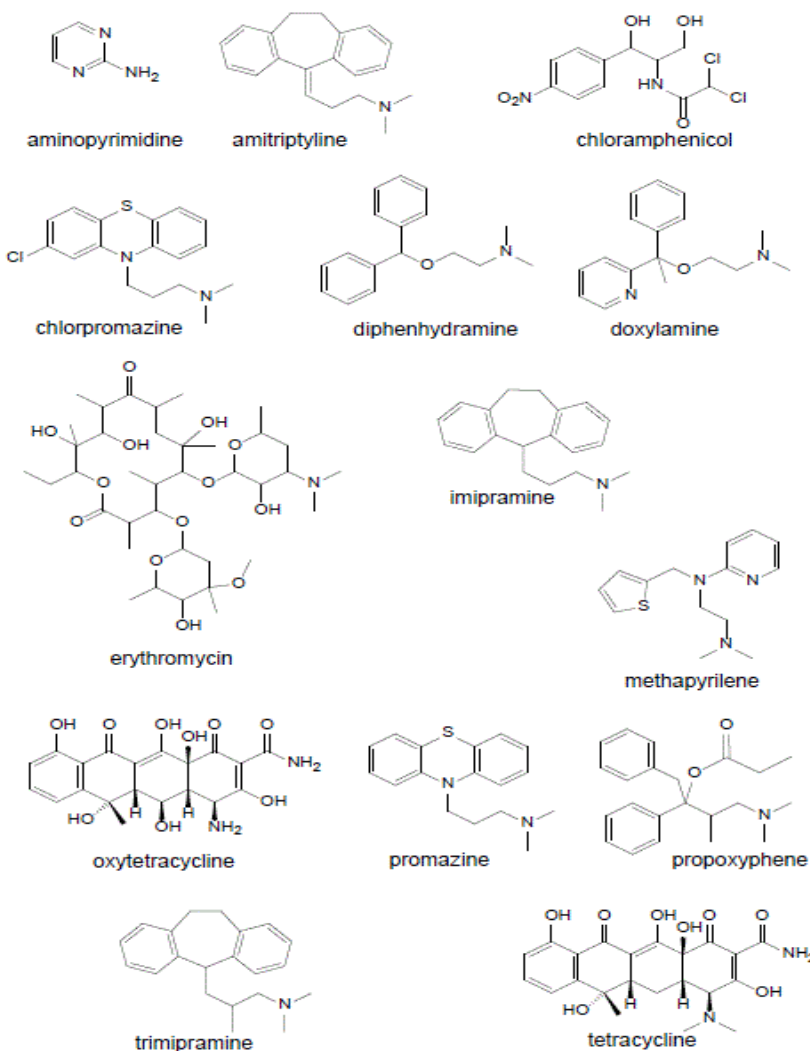
# Impact on the Ph. Eur. (ongoing)

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- After transition period:
  - New revisions of 5 sartan monographs expected by April 2021
- New updates of CEPs foreseen within 2 years, to meet the concept of “nitrosamine free” substances
  - 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>

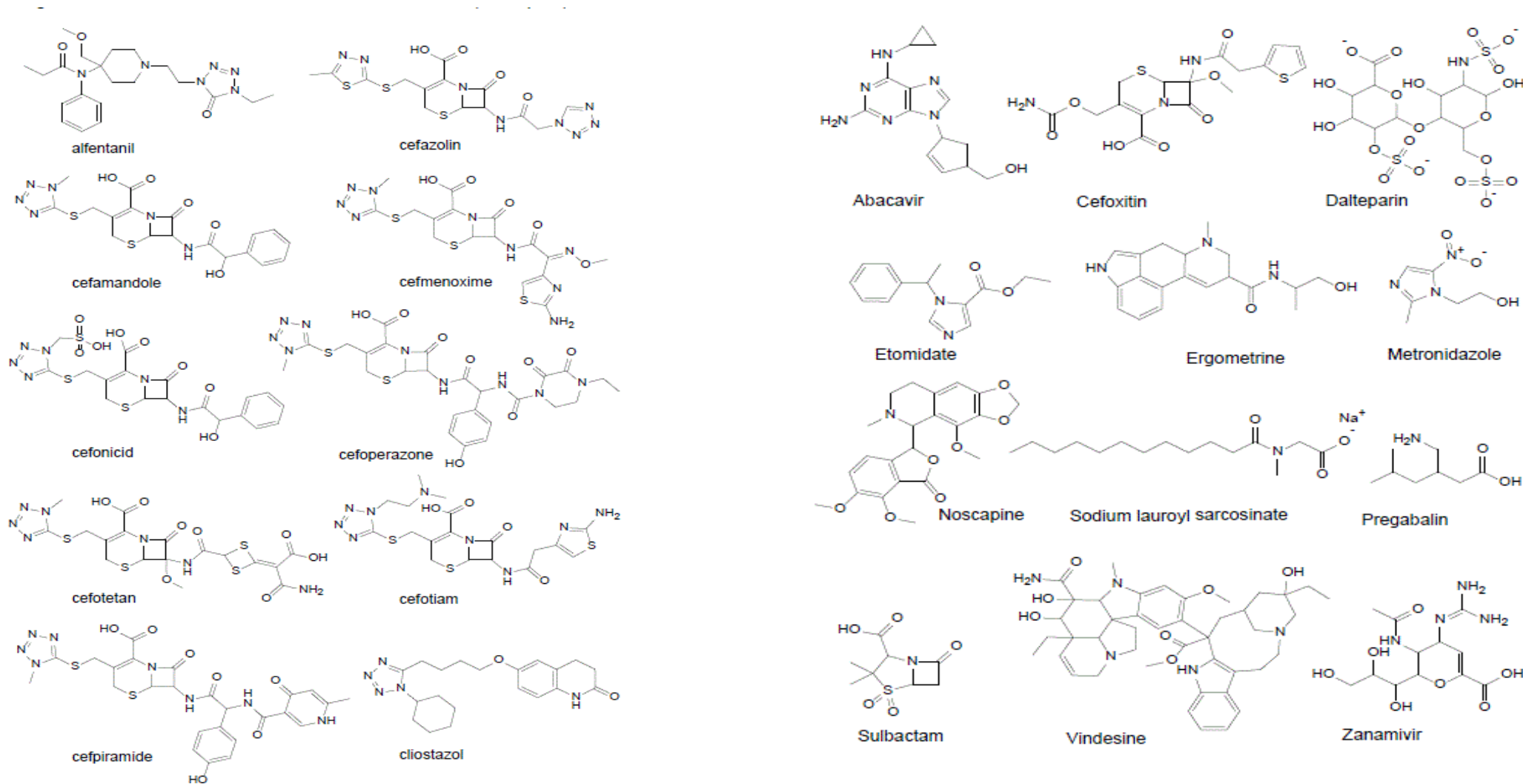
# Case closed?



## Chemical structures of APIs reported in literature<sup>2</sup> to contain NDMA

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

# APIs for which azide or nitrite is used in synthesis



# Nitrosamines in (all) APIs

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- Some findings:
  - NDMA in pioglitazone API → reaction conditions
    - CEP applications reviewed and issue addressed as necessary
  - NDMA in ranitidine HCl API & FP → root cause under continued investigation, current information suggests degradation of the API during storage rather than generation during the synthetic process
    - Article 31 referral ongoing in the EU
    - CEP applications reviewed
    - All CEPs suspended, corrective actions necessary before CEPs can be restored
- MAH and API manufacturers to conduct appropriate investigations & risks assessments and inform authorities/EDQM (CEP holders) in case nitrosamines are detected:
  - Scope: products for human use containing chemical substances
  - <https://www.ema.europa.eu/en/news/ema-advises-companies-steps-take-avoid-nitrosamines-human-medicines>
  - [https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-information-nitrosamines-marketing-authorisation\\_en.pdf](https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-information-nitrosamines-marketing-authorisation_en.pdf)

# Nitrosamines in (all) APIs (2)

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- Stepwise approach for CEPs:

- Evaluate risks of formation of nitrosamines, based on routes of synthesis, materials used, recovery, etc. (prioritise work, deadline March 2020)
- If there is a risk, inform EDQM with a testing plan and timelines
- Provide test results to EDQM, and if needed a corrective actions plan with timelines
- Send revision application to EDQM as needed (for finalisation by end of September 2022)

<https://www.edqm.eu/en/news/announcement-all-cep-holders-synthesised-apis-regarding-presence-nitrosamines>

- CEP holders should be supportive to MAHs and provide them with relevant information!
- Harmonised limits/thresholds currently being discussed



# Impact on Ph. Eur. (ongoing)

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- Elaboration of a General chapter on control of nitrosamines (NDMA, NDEA) (with support of OMCLs for the analytical method)
- Proposed revision of General monograph 2034 « Substances for pharmaceutical use »  
Draft text published in Pharmeuropa 32.1, deadline for comments 31 March 2020!

## *NOTE ON THE MONOGRAPH*

**Production:** further to the EU referral (2019)2698 of 2 April 2019 (here), and to the detection of NDMA in batches of ranitidine hydrochloride, the Ph. Eur. Commission proposes to add a requirement to perform a risk assessment of the manufacturing process and implement a control strategy for the detection and control of N-nitrosamine impurities.

The Ph. Eur. Commission would especially like to seek the opinion of users on the application of those requirements to all substances for pharmaceutical use, whether they are:

- active substances (or intermediate, if justified) or excipients;
- substances for human use or for veterinary use;
- produced by chemical synthesis or obtained from natural sources, or produced by extraction from raw materials or fermentation.

*If no response is received, it will be understood that this approach is acceptable.*

- Final decisions to be taken by the Ph. Eur. commission

# What next?

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## Lessons Learned Exercise (LLE)

- Participation of EDQM
- Co-ordinated by the EMA
- Involvement of international partners and other stakeholders

## Considerations

- Quality aspects
- Supply chain
- GMP

# Quality aspects

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- Process development and process understanding by API manufacturers is often lacking
- Risk assessment is consequently deficient:
  - nitrosating agents (sodium nitrite, organic nitrites,  $N_2O_3$ , etc.)
  - sources of amines ( $2^\circ/3^\circ$  amines, impurities, degradants (e.g. DMF))
  - reaction conditions, carryover of nitrites/amines from other steps or starting materials
  - recycling of materials/solvents as a source of nitrites/amines
- Root cause/risk assessment relies on careful consideration & understanding of the manufacturing process, degradation pathways etc. to at least rule out possibilities

# Supply chain

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- Finished product manufacturers are ultimately responsible for the quality of APIs used and should get the information they need to take this responsibility
  - In practice it does not work well
  - Lack of information sharing between API manufacturers and FP manufacturers
  - 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)

- Deeper review of process development and risk assessments during GMP inspections
- Deeper review of recycling operations
  - recycling processes that are applied
  - outsourcing of recovery operations
  - cross-contamination
- Risk-based inspection of API manufacturers sufficient?
- For FP manufacturers, more attention to qualifying/auditing suppliers?

# Communication

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- Communication amongst authorities worldwide to share knowledge, findings and avoid duplication of work
- Alignment of decisions
- Regular communication on updates

New EDQM web page for all news/updates relating to nitrosamines:

<https://www.edqm.eu/en/edqms-response-nitrosamine-contamination>

# Conclusions

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- After more than 1 year, issue still on-going, with new findings
- Actions taken by EDQM on various levels (review of CEP dossiers, GMP inspections, analytical testing, Ph. Eur., communication etc.)
- Has fostered international collaboration
- Issue expanded to other non-sartans substances !
- Communication between API manufacturer and FP manufacturer to be improved
- On-going reflection on lessons learnt and on changes for the future, with international partners

# Thank you for your attention

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