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
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

- 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

<table>
<thead>
<tr>
<th>Active substance (max daily dose)</th>
<th>NDMA</th>
<th>NDEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan (32 mg)</td>
<td>96.0</td>
<td>3.000</td>
</tr>
<tr>
<td>Irbesartan (300 mg)</td>
<td>96.0</td>
<td>0.320</td>
</tr>
<tr>
<td>Losartan (150 mg)</td>
<td>96.0</td>
<td>0.640</td>
</tr>
<tr>
<td>Olmesartan (40 mg)</td>
<td>96.0</td>
<td>2.400</td>
</tr>
<tr>
<td>Valsartan (320 mg)</td>
<td>96.0</td>
<td>0.300</td>
</tr>
</tbody>
</table>

- 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 (DI)
  - GC-MS (HS)
  - HPLC-UV

### Analytical methods used

<table>
<thead>
<tr>
<th>Analytical technique</th>
<th>DE_BW CVUA</th>
<th>IE_PAL PALG</th>
<th>CH_Swissmedic</th>
<th>DE_BY LGL</th>
<th>DE_BY LGL</th>
<th>FR_ANSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>DE_BW CVUA</td>
<td>LC-MS/MS</td>
<td>GC-MS (HS)</td>
<td>GC-MS (DI)</td>
<td>LC-MS/MS</td>
<td>HPLC-UV</td>
<td></td>
</tr>
<tr>
<td>Analytes(s)</td>
<td>NDMA, NDEA</td>
<td>NDMA, NDEA</td>
<td>NDMA, NDEA</td>
<td>NDMA, NDEA</td>
<td>NDMA, NDEA</td>
<td>NDMA, NDEA</td>
</tr>
<tr>
<td>Sample (DS and/or DP)</td>
<td>DS and DP</td>
<td>DS and DP</td>
<td>DS and DP</td>
<td>DS</td>
<td>DS and DP</td>
<td>DS and DP</td>
</tr>
</tbody>
</table>

➢ Methods published on EDQM website:
### LOQs for NDMA

<table>
<thead>
<tr>
<th></th>
<th>DE_BW CVUA</th>
<th>CH_Swissmedic</th>
<th>DE_BY LGL</th>
<th>DE_BY LGL</th>
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<th>Health Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LC-MS/MS (DP)</td>
<td>GC-MS (Liquid Di) limit test (DS and DP)</td>
<td>GC-MS (DS)</td>
<td>LC-MS/MS (DS and DP)</td>
<td>HPLC-UV (DS)</td>
<td>GC-MS/MS (DS)</td>
</tr>
<tr>
<td>Valsartan limit</td>
<td>0.03 ppm</td>
<td>0.03 ppm</td>
<td>0.10 ppm</td>
<td>0.236 ppm</td>
<td>0.04 ppm</td>
<td>0.005 ppm (DS and DP)</td>
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<tr>
<td></td>
<td>0.10 ppm</td>
<td>0.03 ppm</td>
<td>0.10 ppm</td>
<td>0.679 ppm</td>
<td>0.04 ppm</td>
<td>0.006 ppm (DS and DP)</td>
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<tr>
<td>Irbesartan limit</td>
<td>0.03 ppm</td>
<td>0.03 ppm</td>
<td>0.10 ppm</td>
<td>0.492 ppm</td>
<td>0.05 ppm</td>
<td>0.006 ppm (DS and DP)</td>
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<tr>
<td></td>
<td>0.10 ppm</td>
<td>0.03 ppm</td>
<td>0.10 ppm</td>
<td>-</td>
<td>0.25 ppm</td>
<td>0.006 ppm (DS)</td>
</tr>
<tr>
<td>Losartan limit</td>
<td>0.03 ppm</td>
<td>0.03 ppm</td>
<td>0.10 ppm</td>
<td>-</td>
<td>0.25 ppm</td>
<td>0.005 ppm (DS)</td>
</tr>
<tr>
<td>Olmesartan limit</td>
<td>0.03 ppm</td>
<td>0.03 ppm</td>
<td>0.10 ppm</td>
<td>-</td>
<td>0.50 ppm</td>
<td>0.007 ppm (DS)</td>
</tr>
</tbody>
</table>

**Legend:**
- 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

<table>
<thead>
<tr>
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<th>DE_BW CVUA</th>
<th>CH_Swissmedic</th>
<th>DE_BY LGL</th>
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<th>Health Canada</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>LC-MS/MS (DP)</td>
<td>GC-MS (Liquid Di) limit test (DS and DP)</td>
<td>GC-MS (DS)</td>
<td>LC-MS/MS (DS and DP)</td>
<td>HPLC-UV (DS)</td>
<td>GC-MS/MS (DS)</td>
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<tr>
<td>Valsartan limit</td>
<td>0.03 ppm</td>
<td>0.03 ppm</td>
<td>0.08 ppm</td>
<td>0.061 ppm</td>
<td>0.08 ppm</td>
<td>0.007 ppm (DS and DP)</td>
</tr>
<tr>
<td></td>
<td>0.04 ppm</td>
<td>0.03 ppm</td>
<td>0.08 ppm</td>
<td>0.0195 ppm</td>
<td>0.09 ppm</td>
<td>0.007 ppm (DS and DP)</td>
</tr>
<tr>
<td>Irbesartan limit</td>
<td>0.03 ppm</td>
<td>0.03 ppm</td>
<td>0.08 ppm</td>
<td>0.149 ppm</td>
<td>0.10 ppm</td>
<td>0.007 ppm (DS and DP)</td>
</tr>
<tr>
<td></td>
<td>0.04 ppm</td>
<td>0.03 ppm</td>
<td>0.08 ppm</td>
<td>-</td>
<td>0.40 ppm</td>
<td>0.007 ppm (DS)</td>
</tr>
<tr>
<td>Losartan limit</td>
<td>0.03 ppm</td>
<td>0.03 ppm</td>
<td>0.08 ppm</td>
<td>-</td>
<td>0.50 ppm</td>
<td>0.007 ppm (DS)</td>
</tr>
<tr>
<td>Olmesartan limit</td>
<td>0.03 ppm</td>
<td>0.03 ppm</td>
<td>0.08 ppm</td>
<td>-</td>
<td>0.50 ppm</td>
<td>0.007 ppm (DS)</td>
</tr>
</tbody>
</table>

**Legend:**
- 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)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td><strong>DP</strong></td>
<td><strong>DS</strong></td>
</tr>
<tr>
<td>Valsartan</td>
<td>612</td>
<td>141</td>
</tr>
<tr>
<td>Losartan</td>
<td>312</td>
<td>16</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>313</td>
<td>13</td>
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<tr>
<td>Candesartan</td>
<td>434</td>
<td>10</td>
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<tr>
<td>Irbesartan</td>
<td>260</td>
<td>20</td>
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<tr>
<td>Telmisartan</td>
<td>69</td>
<td>49</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2000</strong></td>
<td><strong>249</strong></td>
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</table>

...for NDMA

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<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td><strong>DP</strong></td>
<td><strong>DS</strong></td>
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<tr>
<td>Valsartan</td>
<td>246</td>
<td>200</td>
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<tr>
<td>Losartan</td>
<td>188</td>
<td>149</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>194</td>
<td>43</td>
</tr>
<tr>
<td>Candesartan</td>
<td>204</td>
<td>85</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>175</td>
<td>160</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1007</strong></td>
<td><strong>637</strong></td>
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...for NDEA

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

OMCL OOS Findings by 15/4/2019

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<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td><strong>API</strong></td>
<td><strong>DP</strong></td>
</tr>
<tr>
<td>VALSARTAN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturer A</td>
<td>55</td>
<td>240</td>
</tr>
<tr>
<td>Manufacturer B</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Manufacturer C</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Manufacturer D</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

NDMA

<p>| | | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>API</strong></td>
<td><strong>DP</strong></td>
</tr>
<tr>
<td>Manufacturer E</td>
<td>38</td>
<td>22</td>
</tr>
<tr>
<td>Manufacturer F</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Manufacturer A</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

LOSARTAN

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer G</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Manufacturer A</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

Irbesartan

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer F</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Manufacturer A</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug Substance* Max. Daily Dose (mg)</th>
<th>NDA Limit in ng/day</th>
<th>NDMA Limit in ppm in API</th>
<th>NDMA Limit in ng/day</th>
<th>NDMA Limit in ppm in API</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valenzartan                          320</td>
<td>26.5</td>
<td>0.032</td>
<td>96.0</td>
<td>0.300</td>
</tr>
<tr>
<td>Lisinopril                           450</td>
<td>26.5</td>
<td>0.177</td>
<td>66.0</td>
<td>0.646</td>
</tr>
<tr>
<td>Olmesartan                           40</td>
<td>26.5</td>
<td>0.063</td>
<td>96.0</td>
<td>2.400</td>
</tr>
<tr>
<td>Moxidartan                           300</td>
<td>26.5</td>
<td>0.048</td>
<td>66.0</td>
<td>0.320</td>
</tr>
<tr>
<td>Candesartan                          32</td>
<td>26.5</td>
<td>0.031</td>
<td>66.0</td>
<td>0.308</td>
</tr>
</tbody>
</table>

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

1) After the transitional period of 2 years, a limit for NDMA and NDGA of maximum 0.05 ppm should be implemented.
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

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)
  - Valsoatin
  - Candesartan cilexetil
  - Losartan
  - Losartan potassium
  - Olmesartan medoxomil

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
All revised texts to be published in Suppl. 10.4 ideally

Confirmed at 163rd session

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 initial 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

需 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

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Twitter: @edqm_news
Facebook: @EDQMCouncilofEurope