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


• 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
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 authorisation 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
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, NDI PA, EI PNA 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, NDI PA
  - 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

<table>
<thead>
<tr>
<th>Active substance (max daily dose)</th>
<th>NDMA</th>
<th>NDEA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum daily intake (ng)</td>
<td>Limit in API (ppm)</td>
</tr>
<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 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:
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

<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></td>
<td>LC-MS/MS</td>
<td>GC-MS (HS)</td>
<td>GC-MS (liquid DI) limit test</td>
<td>GC-MS (DI)</td>
<td>LC-MS/MS</td>
<td>HPLC-UV</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>

**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

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.

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.

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

Next steps (2)

• Sampling & Testing by OMCLs:
  ➢ Testing other APIs than sartans
  ➢ Testing other nitrosamines than NDMA & NDEA
  ➢ Development of «universal» method for NDIPA, EI PNA, 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

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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