THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)
EDQM experience of collaboration between assessors and inspectors in the frame of quality defect investigations

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Overview

A. The certification procedure: occasions for assessor's request for inspection

B. Collaboration related to nitrosamines contamination
The certification procedure: occasions for assessor's request for inspection

Evaluation report (part A, B and C)

<table>
<thead>
<tr>
<th>Report A</th>
<th>Report B</th>
<th>Report C</th>
</tr>
</thead>
<tbody>
<tr>
<td>• exhaustive critical review of the dossier</td>
<td>• request for monograph update</td>
<td>• reference of applied GMP or QA-system</td>
</tr>
<tr>
<td>• confidential, copy may be given to national authority</td>
<td>• to be drafted only when necessary</td>
<td>• comments/questions/suspicion for inspectors</td>
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</tbody>
</table>
The certification procedure: occasions for assessor's request for inspection

Appropriate occasions to issue a request for inspection

**Sterile Grade**
- Inspection is routinely performed for any sterile grade substance
- should only be issued for requesting the inspection prior granting the CEP
- Draw attention to a specific point; e.g. tray lyophilisation

**Suspicion regarding the submitted dossier**
- Inconsistencies in the data
- Suspicion of fake data

**Process-related or specification-related potential weak points**
- Starting material close to the final step is not prepared by the manufacturer itself and lack of information
- Complex or badly explained process steps
- Subcontracting some steps of the manufacturing process

**Site-related potential weak points**
- Suspicion of low awareness and knowledge of the GMP principles, i.e. When the applicant has first provided a commitment to GMPs which are not recognized as equivalent to the requested GMPs
- Suspicion of risk of cross-contamination
The certification procedure: occasions for assessor's request for inspection

- Tropicamide is a racemic mixture (2RS) and the optical purity is controlled by the Ph.Eur monograph by optical rotation (-0.1° to +0.1°). Batch data given show optical rotation between -0.005° and +0.002°.

The synthesis starts from tropic acid and in the original dossier no information on the stereochemistry of the reaction was available, it wasn’t clear if the racemization occurred after the introduction of tropic acid + enantiomeric purity of tropic acid was not controlled. In the 1st response to deficiency letter the Company confirmed that tropic acid is a racemic mixture and submitted a very detailed scientific discussion on the fact that their synthesis is stereo selective and leads to intermediate (R)-tropicamide. As the substance is a racemic mixture, clarification was asked. In response they claimed that a mistake was made.

Inspection is requested because the traceability of the several starting material sources is doubted. Initially, 4 manufacturers of the starting material were included, but during the validation phase one of them ( ) was deleted due to discontinuation of . The correspondence between EDQM and applicant showed that the understanding of our request for data of the starting material manufacturers and willingness to provide this requested data was unsatisfactory. As, for instance, no discussion on comparability of the impurity profiles of the several sources is provided and the starting material specification as applied by the applicant does not cover all three sources, it is questioned whether the applicant has a good overview on the source of starting material used in the different batches of the active substance.
The certification procedure: occasions for assessor's request for inspection

*Example: query from Assessors related to Flunarizine and Cinnarizine*

Trigger for report C: OOS results for impurity cis-cinnamic alcohol in Certificate of Analysis (CoA) of starting material cinnamic alcohol

Inspection outcome:
- wrong impurity peak assignment leading to the non-identification of a number of OOS with regard the content of cis-cinnamic alcohol; regarded as unknown impurity.
- handling of this incident by the company was inadequate: no retrospective OOS/deviation investigation; no systematic approach on the retrospective analysis/evaluation of all batches of cinnamic alcohol; no risk assessment to evaluate the impact on manufactured API batches.
- CAPA/dossier update review on-going
The « Corridor Effect »

DCEP
Overview

A. The certification procedure: occasions for assessor's request for inspection

B. Collaboration related to nitrosamines contamination
The Valsartan issue

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

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

N-Nitrosodimethylamine (NDMA)
Formation of NDMA and other nitrosamines

- Contamination linked to specific process (a tetrazole ring) and specific conditions

- Presence of nitrous acid, from sodium nitrite in acidic conditions, in order to quench the azide

- Presence of secondary amine: dimethylamine (not introduced into the process). Other nitrosamines may be generated, eg. NDEA (from the use of triethylamine), NDBA, NMBA, NDIPA, NIPEA etc.

- Linked to the use of DMF (when heated)

\[
\begin{align*}
\text{DMF} & \quad \text{NaNO}_2 \quad \text{HCl} \\
\triangle & \quad \rightarrow \\
\text{H}_3\text{C}^\text{N} - \text{CH}_3 & \quad \rightarrow \\
\text{HNO}_2 & \quad \rightarrow \\
\text{H}_3\text{C}^\text{N} - \text{CH}_3 & \quad \text{NDMA}
\end{align*}
\]
List of sartans with tetrazole ring

- High risk due to formation of tetrazole ring in the last synthetic step and high MDD of substance
  
  - Valsartan
  - Irbesartan
  - Losartan potassium

- Lower risk due to formation of tetrazole ring in early stages and low MDD of substance
  
  - Candesartan cilexetil
  - Olmesartan medoxomil
Actions

• Review of ASMFs and marketing autorisation applications by EU authorities

• EDQM review of CEP applications :
  In July 2018, review of all sartans CEP applications (including history of revisions) – about 125 dossiers

• 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

• EU initiated referral (Article 31) on Valsartan, extended in October 2018 to other sartans having a tetrazole ring
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 potassium, irbesartan
  • A valsartan source contaminated with NDIPA
  • A source of losartan potassium contaminated with NMBA

• 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
GMP inspections related to nitrosamine contamination

• Joint for-cause inspection EMA/EDQM of Zhejiang Huahai (ZHP) with assessors on site
  - A number of major deficiencies to GMP and ICH guidelines
  - Statement of Non Compliance to GMP issued for Valsartan only
    • ZHP is intermediate manufacturer for other manufacturers of valsartan ➔
      Impact on these sources: 4 CEPs for Valsartan revised in October 2018
      - Recent re-inspection was carried out (evaluation of CAPA-on-going)

• Joint for-cause inspection EMA/EDQM of Zhejiang Tianyu (ZTP) with assessors on site

• Joint full GMP inspection EDQM/Swissmedic of Lantech Pharmaceuticals Ltd.

• FDA, EU inspections of other manufacturers
Assessor's role: the nitrosamine risk assessment (case 1)

Preparation of Valsartan

NDMA risk factors:
- DMF decomposition to dimethylamine (DMA) and sodium nitrite presence
- recovery of solvents/materials (sodium nitrite for azide quenching)
- solvents interchangeability between different processes for the same substance
- second crops from mother liquors (sodium nitrite used for azide removal)

*Tributyl tin chloride could be used instead of zinc chloride
Assessor's role: The nitrosamine risk assessment (case 2)

Preparation of Irbesartan

**NDEA/NMBA risk factors:**
- NMP degradation to secondary amine
- TEA presence during tetrazole formation
- Usage of recovered solvents and second crops (sodium-nitrite for azide removal during recovery procedures)
- Cross contamination between different processes for the same substance with recovered solvents
GMP inspections related to nitrosamine contamination

Synergistic approach allowed inspectors to cover areas that are usually not covered during a regular GMP inspection, such as:

- Process development
- Thorough check of impurity profiles

Synergistic approach allowed assessors to cover areas that are usually not covered during assessment of regulatory filings, such as:

- Full access to analytical source data
- QC data check
- Unknown peaks identification
- In depth impact of recovery procedures

Inspector / Assessor collaboration in the context of sartan inspections

- Extraction of relevant information from dossiers
- Support during CAPA review
- Active participation in the inspection
- Preparatory meeting ahead of the inspections
Collaboration with OMCLs: Sampling and testing

• EDQM coordinating sampling and testing by the European Official Medicines Control Laboratories (OMCLs) - *collaboration with Swissmedic*
  • 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

• OMCLs provide official results:
  • for samples taken from the GMP inspections
  • to verify data given by manufacturers
  • Market surveillance for various sartans
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

• Inspection findings sharing
Lessons learned from nitrosamine contamination

- Deeper review of process development and risk assessments
  - Ensure sufficient process knowledge—the assessment of impurity profiles during development phase
  - In depth risk assessment related to new process change/technology transfer

- Deeper review of recycling operations

- Is the current system sufficient (risk-based inspections)?

- More requirements on recycling of materials (dossier content)?

• Opportunities:
  - Communication amongst authorities worldwide to share knowledge, findings and avoid duplication of work
  - Alignment of decisions

➤ Need to reflect further on different levels with international partners/foster international collaboration

• Actions on various levels (review of dossiers, GMP, analytical testing, etc.)
Conclusions

The collaboration between assessment and inspection at EDQM demonstrates several benefits:

- Most sustainable assessment of certification dossiers in combination with an inspection scheme, and vice versa
- Effective discussion and communication of issues and appropriate feedback (i.e. team meetings)
- Establishment of working groups to combine knowledge in certain areas
- Embedded in a common QA System (ISO 9001)
- Positive feedback of close cooperation with assessors during inspection
Thank you for your attention

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