EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Background on cases of sartans with N-nitrosamine impurities

Sartans with N-nitrosamine impurities Lessons Learnt Exercise Interested Parties Meeting

EMA, Amsterdam, 4 November 2019

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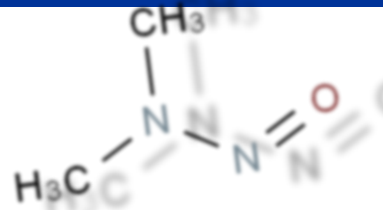
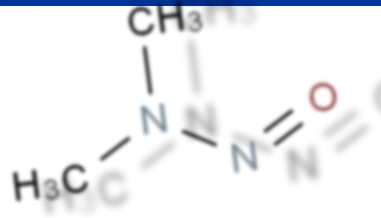
Background - Nitrosamine contaminations (1)



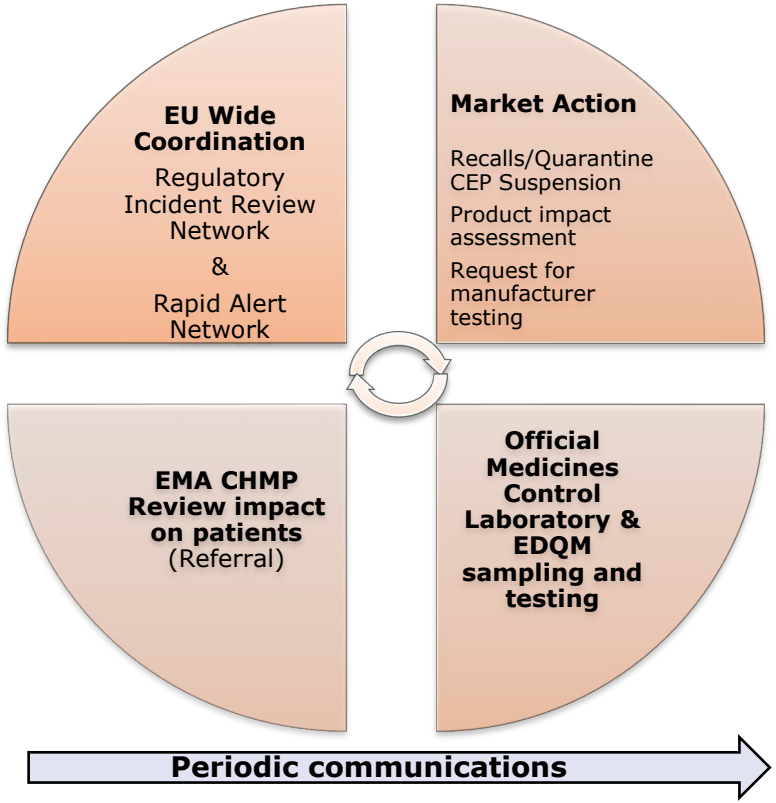
- Starting with June 2018, there have several notifications of APIs (e.g. '**sartans**' e.g. *valsartan, losartan, irbesartan, pioglitazone, ranitidine*) with N-Nitrosamines impurities (*NDMA, NDEA, NMBA*, etc)
- ICH-M7, all ***N-nitroso-*** substances are included in the "***cohort of concern***" as probable human carcinogens on the basis of animal studies
- Root Cause related to **route of synthesis** (choice of materials and reaction steps and conditions) as well as **cross-contamination, or potential degradation** of API/starting material
- **Significant impact to worldwide markets** – API used by many finished product manufacturers in many products

Background - Nitrosamine contaminations (2)

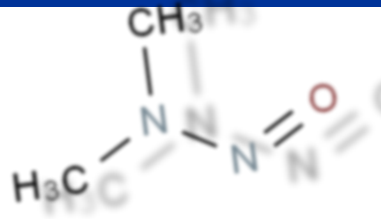


- Dynamic case - expanding to include **other impacted manufacturers, other nitrosamine impurities** (NMBA, EIPNA, etc) **other APIs** (pioglitazone, ranitidine)
- Health Authorities around the world have been:
  - conducting **reviews** and taking **regulatory actions** as necessary to protect public health (*recalls, interruption of supply, inspections, GMP statements of non-compliance, suspension of API certification, etc*)
  - sharing information on **manufacturers/impurities**, **assessment**, **inspection** to ensure a rapid and harmonised responses

EU Regulatory Network Actions



Potential Root Causes for N-nitrosamine formation



- **Main cause** identified to date:

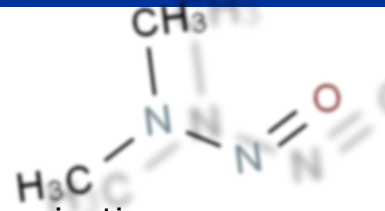
  $NaNO_2$ reacting in same step or carried over multiple steps with a secondary amine or tertiary amine

  - Secondary amine or tertiary amine can be **starting material, degradant or impurity**
  - **NaNO2 as an impurity** in certain raw materials (e.g. used to make NaN_3) or **process water**

- **Cross contamination**

  1. **Use of NaNO2** to quench waste streams – **recovered materials** (solvents, reagents) **contaminated by N-nitrosamines** re-introduced into process
  2. API manufacturing on **shared equipment**
  3. **Solvent/reagent recycling** using the **same (shared) equipment** (on site or by 3rd party)
  4. **Transportation of materials** using same containers (3rd parties)
  5. Finished product primary **packaging material** (blister)

Review of QRM in the GMP Environment (2)



- Several **GMP inspections** of API manufacturing sites as a result of *N*-Nitrosamine contamination case
- 1 Statement of GMP Non-Compliance by EU Authorities
- In some cases inspections noted findings in area such as:
  - **Insufficient understanding** of Quality Risk Management Principles
  - Insufficient **knowledge of process development**
  - Inadequate **Out-of-Specification management**, root cause **investigations** were **superficial,** only focusing on main synthesis route without considering other potential causes (solvent recovery, raw materials, water, etc)
  - **Ineffective change management system**
  - **Communication not transparent**, company did not provide all or complete requested documentation

Official Laboratory Testing

- Several laboratories from the **European OMCL network** coordinated by **EDQM**
    1. Development of testing methods for API and FP testing
    2. Risk based sampling and testing strategy to make best use of available resources
    3. Evaluate manufacturer testing method reliability
- **Objectives**
    - Confirm or exclude potential nitrosamine presence in products on the market or collected during inspections
    - OMCL method development and publication by EDQM as reference for manufacturers
- **Points to consider**
    - Surveillance exercise cannot replace need for manufacturer testing
    - Method development (depending on set limits based on toxicological assessment and on different APIs/matrices) and testing of high number of samples is a time limiting step
    - Collaboration with inspection team to sample APIs during inspection
    - Coordination at EEA level but also with international partners on method harmonization, sharing and cross checking results

International Collaboration

- **Regular exchanges** with US FDA, Health Canada, MHLW & PMDA Japan, Swissmedic, TGA Australia, HSA Singapore

- **Exchange information and harmonization** of:
  - Market actions
  - Inspection outcomes and planning
  - Scientific assessments and harmonisation of requirements
  - Communications

- Ad Hoc confidentiality arrangements with other international regulatory authorities (e.g. South Korea, Taiwan)

- Dialogue with Chinese Authorities

EU Review of Sartans with Nitrosamine impurities

- **EMA review** (referral acc. art. 31 of Dir. 2001/83 EC) of sartans at risk of containing N-nitrosamines concluded:

1. *Manufacturers must review and if necessary change their manufacturing processes to minimise nitrosamine impurities as much as possible*
   - Possible root causes of N-nitrosamine formation and contamination as well as recommendations for steps to take to avoid such impurities

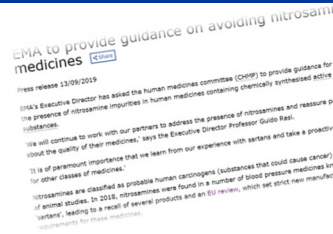
2. *Implement a control strategy to detect and control N-nitrosamine in sartans*
   - Strict interim and long term limits were set for N-nitrosamines in sartan APIs
     - https://www.ema.europa.eu/en/documents/referral/sartans-article-31-referral-chmp-assessment-report_en.pdf
     - https://www.ema.europa.eu/en/documents/other/temporary-interim-limits-nmba-dipna-eipna-impurities-sartan-blood-pressure-medicines_en.pdf

EU Review of Sartans with Nitrosamine impurities

Lifetime risk based on of ZH contaminated valsartan (worst case):

- partially combined exposure to the highest levels of NDEA for 4 years (2011 – 2015) and to NDMA for 6 years (2012 – 2018), resulting in a theoretical excess cancer risk of 29.5:100,000 (0.03%)
- Low in comparison with lifetime cancer risk (1:2)
- No need for invasive procedures to follow up patients – also target organ in humans not clear

Ongoing EU Reviews of Nitrosamine impurities


EMA to provide guidance on avoiding nitrosami
medicines
Press release 13/09/2019

1. CHMP scientific opinion under **Article 5(3) of Regulation (EC) No 726/2004**

   a. Phase I: to provide guidance on avoiding presence of nitrosamine impurities to MAHs to consider alongside their knowledge of the manufacturing processes of their products

   b. Phase II: evaluate all available scientific knowledge on the presence of nitrosamines in medicines and advise regulatory authorities on actions to take if companies find nitrosamines in their medicines

2. Referral according to **Art. 31 of Directive 2001/83/EC** to review **ranitidine** medicines that may contain N-nitrosodimethylamine (NDMA) to look at the potential root causes and assess whether there patients using ranitidine are at any risk

EMA request to evaluate risk of nitrosamine impurities

- **Precautionary measure**:

  MAHs for human medicines containing chemically synthesised APIs together with API manufacturers and Finished product manufacturers to review risk of nitrosamine impurities presence taking into account knowledge of the manufacturing processes as well as potential sources of nitrosamine impurities as described in the assessment of the Art. 31 Referral on Sartans with a tetrazole ring

- A notice and questions-and-answers document available on EMA website

- Review **timelines**:

  - **Step 1 - Risk evaluation**: MAHs should perform risk evaluation of all products latest within 6 months of publication (i.e. March 2020) and inform concerned Competent Authorities of outcome
  - **Step 2 - Confirmatory testing**: product where a risk has been identified in Step I, should undergo confirmatory testing at the latest within 3 years of the publication (or earlier if otherwise justified by risk)

    MAHs should inform the competent authorities immediately if tests confirm the presence of an nitrosamine impurity irrespective of the amount detected
  - **Step 3 - Changes to the marketing authorisation**: variations should be submitted to introduce any required changes (e.g. changes to manufacturing process, or product specifications etc.)

Sartan Lessons Learnt Exercise

- In May 2019 **EMA and EU regulatory network** have started a **Lessons Learnt Exercise** on Sartans with N-Nitrosamine impurities case
  - To improve the way impurities in medicines are identified and handled
  - To consider how to prevent such incidents in future
  - To see if the management of such incident can be improved should they occur
- **Workshop with stakeholders**, including representatives from the pharmaceutical industry
- EMA will **publish the outcome** of the exercise

Any questions?

Further information

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