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Incident Management

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Sartans with N-nitrosamine impurities - Lessons Learnt Exercise

Interested Parties Meeting, EMA, 4 November 2019

How the incident was triggered and managed – EMA & Rapid Alert Network

- **June 25 2018** - EMA became aware of Zhejiang Huahai Pharmaceuticals' notifications to its customers re. presence of an unknown genotoxic impurity in valsartan API.
- Rapid Alert Network informed by EMA on June 26th - the issue was managed in the EEA as a **quality defect case**
  - *Well-defined and agreed **procedures** in place at EEA level for Competent Authorities to manage quality defects, in term of risk assessment, risk communication, risk control.*
  - *These address the **key steps** to be followed when assessing the risks presented by quality defects, overseeing company investigations into quality defect issues and making risk-based decisions on any required risk mitigating actions (e.g. batch recalls).*

The Incident Review Network (IRN)

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- **June 28th 2018:** as the defect was considered to represent a **potential major impact to public health**, the case was escalated to *the Incident Review Network (IRN)*.
- **July 5th 2018** IRN triggered a **Referral** under Article 31 of Directive 2001/83/EC (a scientific assessment of the issue):
  - Investigate the levels of the N-nitrosamine impurities present in the distributed valsartan-containing medicines;
  - Evaluate the **potential risks for patients** who had been taking concerned medicines;
  - Identify the required risk minimisation measures;
  - Evaluate the **measures needed** to reduce or eliminate the impurity from future batches produced by the company - Consultation with the Safety Working Party (SWP) and Quality Working Party (QWP).

Initial Response & Risk-Based Decision-Making (June-August 2018)

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REGULATORY ACTIONS

- **Product recalls** (mainly at pharmacy level) **or quarantine actions** and **increase market surveillance** activities depending on market criticality in each Member State.
- Advice to patients to consult their pharmacist or doctor **not to stop taking their medicines**, as the risk of doing so was considered to be higher than the risks presented by the N-nitrosamine impurities.
- The **advice for patients was harmonised** to a large extent across the EEA but it allowed for national provisions and other factors to be taken into account.

Initial Response & Risk-Based Decision-Making (cont'd)

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- A major part of the initial response focused on identifying whether **any other medicines** containing valsartan from other API manufacturers (and other sartan APIs from any other manufacturer) could also have the impurity.
  - **EDQM** reviewed the process chemistry associated with the active substances used in a large number of sartan medicines in order to identify manufacturing processes and related medicinal products **potentially at-risk of generating the impurity**.
  - The work done by EDQM was pivotal for Competent Authorities during their **decision making** re. the market actions required to safeguard public health in their markets.
  - August 2018: NDEA, **another nitrosamine compound** identified in valsartan and losartan products. All affected batches were recalled from the EEA market.

Evolving Situation (August/Sept 2018 onwards)

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- As the case evolved, **new information came to light** in relation to impacted products (across other MAHs and API manufacturing sites), root causes of the issues, and new impurities (e.g. NDEA).
  - The Rapid Alert Network ensured **continuous exchange of information** on ongoing actions required to protect patients across the EU
  - It also helped ensure that **harmonised actions** were generally being taken
  - **Additional products were recalled** from the EEA market by the Competent Authorities, as needed, with coordination via the Rapid Alert Network

Evolving Situation cont'd

- **Starting in September 2018**: Several **for-cause GMP inspections** were conducted at manufacturing sites of sartan APIs by EU Authorities on behalf of the EMA and EDQM.
  - Three inspections were requested as part of the Referral procedure and were performed by GMP inspectors accompanied by quality assessors.

- **December 2018** - due to the growing nature of the issue, the EMA and the national Competent Authorities requested all MAHs of sartan products to conduct **precautionary NDMA and NDEA testing** before use of API batches in manufacture of finished product.

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How effective was the response by the Competent Authorities?

Effectiveness of Response

- There was substantial **coordination, cooperation and harmonisation** across the EEA:
  - Quick mobilization of resources at EEA level;
  - Quick availability of risk assessments and **product criticality assessments** with consequent initiation of risk mitigating actions (e.g. product recalls)**.**
- The actions taken were considered **effective and proportionate** to the level of risk presented by the quality defect issue to patients.

However, a number of **challenges** were encountered in managing the incident, and in some cases these represent certain shortcomings in the current regulatory processes and framework that need to be addressed.

Challenges Experienced & Lessons Learnt

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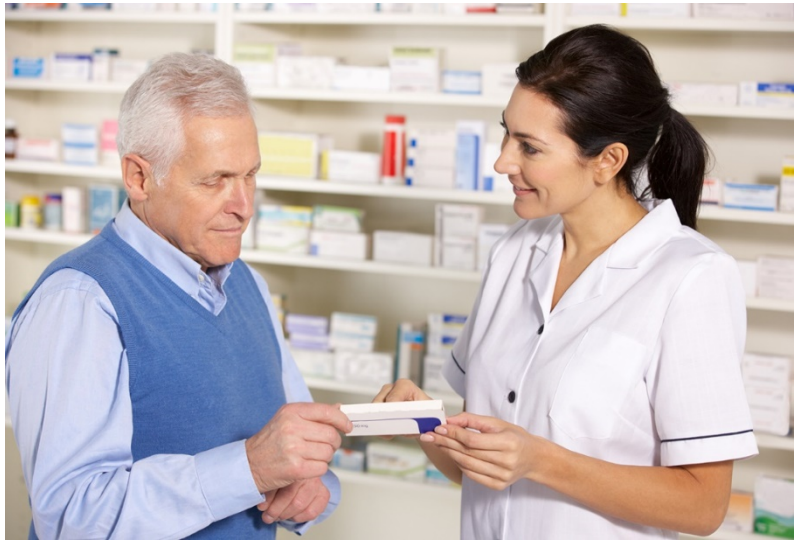
- The nitrosamine incident was **complex**, **global** in nature, emotive and alarming by virtue of the fact that it related to probable human carcinogens in widely used medicines.



Challenges & Lessons Learnt cont'd…

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Compiling an exhaustive list of impacted APIs, products and batches in a timely manner was a challenge…

- Lack of centralised **database** containing marketing authorisation information that linked API manufacturers to the finished medicinal products for products registered via different authorization procedures.
- Lack of **readily available information from MAHs and medicinal product manufacturers** about which finished product batch was manufactured with a specific concerned API batch, and the distribution
- **Added complexity** reviewing APIs registered via different routes: **Active Substance Master Files (ASMFs)** and **Certificates of Suitability with the European Pharmacopoeia (CEPs)**
- The presence of **parallel imported versions** of the affected and unaffected medicinal products on some markets

Overall…was public health protected in a timely and effective manner?

- Despite various challenges, the **actions** taken were considered **effective and proportionate to the level of risk** presented by the quality defect issue to patients.
- It is believed that public health was protected in an effective way.
- The lessons learnt here will be analysed to make the necessary improvements to the regulatory framework.

But we are interested in your opinions on this question!

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Thank you for your attention!

Questions / Discussion