Nitrosamine Impurities

How to effectively identify, communicate and mitigate risks related to nitrosamine contamination

Speakers
Dr Hiltrud Horn
Horn Pharmaceutical Consulting, Germany
Dr Ulrich Kissel
European QP Association, KisselPharmaConsulting, Germany
Dr Cornelia Nopitsch-Mai
Quality Assessor, Germany
Dr Lance Smallshaw
UCB, Belgium
Dr Andrew Teasdale
Astra Zeneca, United Kingdom
Dr Christian Trendelenburg
Novartis, Switzerland

Highlights
- Nitrosamine Impurities and the Sartan Cases
- Root causes for Nitrosamine Contamination
- Practical Approaches to Risk Assessments
- Analytical Methods for Nitrosamine Testing
- Safety Aspects of Nitrosamine Impurities in Drug Products
- Communication of Risks to Regulatory Authorities
- Nitrosamine Impurities and Supplier Qualification
- Cooperation between MAHs, finished Product Manufacturers and API Manufacturers
- Regulatory Action to be taken in Case of Nitrosamine Contamination
Objectives

During this conference the relevant aspects of risk mitigation with respect to potential Nitrosamine contamination in drug substances and drug products will be discussed. You will hear what you need to know about the required risk assessments for medicinal products containing chemically synthesized APIs. In particular you will learn:

- which root causes for Nitrosamine Impurities should be considered,
- how suppliers for raw materials, solvents and packaging materials should be qualified,
- what to take into account when risks have to be assessed and communicated to regulatory authorities,
- which safety aspects need to be considered regarding Nitrosamine Impurities in drug products,
- how supply chain quality oversight can mitigate risks of Nitrosamine contamination,
- which regulatory actions are to be taken in case of Nitrosamine impurities.

You will get advice from industry experts on how to cope with the challenge of performing risk assessments within short timelines.

Background

In June 2018 EU authorities were notified that a Chinese API manufacturer had detected the presence of N-nitrosodimethylamine, NDMA, in batches of Valsartan. NDMA is a genotoxic and carcinogenic agent in animals and is classified as a Class 2A carcinogen to humans. After a referral under Article 31 of Directive 2001/83/EC triggered by the European Commission the CHMP assessed the impact of the presence of this impurity on the benefit – risk balance of valsartan-containing drug products and issued a recommendation whether the concerning marketing authorisations can still be maintained or should be suspended.

Meanwhile different Nitrosamines (NDMA, NDEA and others) were detected in almost every drug product which contains a Sartan derivative as an API. In an EMA Questions & Answers Document various potential sources of Nitrosamine contaminations are described. In September 2019 EMA published a press release where pharmaceutical companies were advised on steps to be taken to avoid nitrosamines in human medicines. In another document which appeared at about the same time Marketing Authorisation Holders are requested to evaluate the risk of the presence of Nitrosamine impurities in human medicinal products containing chemically synthesised APIs and to submit these assessments not later than end of March 2020.

Target Audience

This conference is of interest to all personnel involved in risk assessments of drug substances and drug products regarding potential Nitrosamine contamination. Scientific staff, Laboratory Managers, Supervisors and Analysts in pharmaceutical quality assurance and quality control departments are addressed. During this event regulatory requirements will be discussed, and hence the event also is applicable to people working in the regulatory affairs area.

Programme

Nitrosamine Impurities and the Sartan cases - Background
- Initial cause of Valsartan contamination
- Other causes and their implications
- Article 31 and its implications
- Reflection on alignment with ICH M7

Root Causes for Nitrosamine Impurities – practical Approaches to assess the Risks
- Development of a systematic risk-based approach
- Key factors and the development of a decision tree
  - API
  - Drug Product
  - Packaging

Confirmatory Testing: Analytical Methods for Determination of Nitrosamines
- Current status of methodology
- Analytical challenges
  - Sensitivity
  - Specificity – risk of false positives

Safety Aspects of Nitrosamine Impurities in Drug Products
- Mutagenic and carcinogenic potential
- Safety threshold, application of ICH M7 principles
- Human carcinogenic risk assessment in drug substances

Nitrosamine Impurities and Supplier Qualification
- Supplier Qualification: Points to consider
- API-Manufacturers and Nitrosamines
- Responsibilities of the API-Manufacturer
- Potential Sources of Nitrosamines
- Responsibilities of the MAH
- Reporting
- Practical Example: Risk Assessment
Assessment and Communication of Risks – what Regulatory Authorities want to see

Ensuring Supply Chain Quality Oversight: How MAHs, finished Product Manufacturers and API Manufacturers should cooperate
- Communication between the parties involved
- Who needs to know what
- How to cope with the complexity of supply chains
- Activities to be shared between the parties involved
- The role of the Qualified Person

Regulatory Consequences in Case of a Contamination
- Mitigation of risk
- Filing a variation/change
- Is a global approach possible?

Questions, Answers, Discussion

Moderator
Dr Lance Smallshaw, UCB, Belgium

Speakers

Dr Hiltrud Horn
Horn Pharmaceutical Consulting, Germany

Dr Hiltrud Horn is managing director of HORN Pharmaceutical Consulting with focus on CMC, GMP and Regulatory Affairs. She started in pharmaceutical industry in 1990 and held several managerial positions within Hoffmann-La Roche in Basel and Knoll (Abbott) with global responsibility within QC / QA / Regulatory Affairs / Project Management / Medical Writing.

Dr Ulrich Kissel
European QP Association, KisselPharmaConsulting, Germany

Dr Ulrich Kissel is Qualified Person and Member of the Board of Directors of the European Qualified Person Association (EQPA). He works as a GMP consultant and contract QP to the Pharmaceutical Industry. Previous to his current role he held leadership positions in Quality and Supply Chain and served for many years as QP for Roche.

Dr Cornelia Nopitsch-Mai
Quality Assessor, Germany

Dr Nopitsch-Mai is scientist at the Federal Institute for Drugs and Medical Devices (BfArM) in the assessment of the quality part of the dossier since 1991. Since 2000 she is assessor for the Certification Procedure (EDQM) in Strasbourg. She was member of the Technical Advisory Board (EDQM) from 2001 until 2010; in that time she was chairperson from 2005 until 2010. From 2007 until 2011 she was a member of the EMA Quality Working Party.

Dr Lance Smallshaw
UCB, Belgium

Dr Lance Smallshaw is Global Analytical Expert (Global Pharmacopoeias Leader) within the Regulatory Intelligence Network (RIN) in the UCB Site Quality Operations Team. He is also Co-Chair of the Executive Board of ECA and Associate Director and European CMC Strategy Committee member for CaSSS Biopharm

Dr Andrew Teasdale
Astra Zeneca, United Kingdom

Dr Andrew Teasdale is an analytical chemist and held several positions within quality assurance and regulatory roles. He has led a number of industry expert groups within Pharmaceutical Research and Manufacturers of America (PhRMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Product Quality Research Institute (PQRI) and the Extractables and Leachables safety Information exchange (ELSIE). He is also currently the chairman of the Joint Pharmaceutical Analytical Group (JPAG) in the UK.

Dr Christian Trendelenburg
Novartis, Switzerland

Important Information
You will receive a USB memo stick when you register in Frankfurt.
Note: there will be no print-outs available during the conference.
### Reservation Form (Please complete in full)

#### Nitrosamine Impurities
19 March 2020, Frankfurt/Main, Germany

- **Mr**
- **Ms**

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**Date**
Thursday, 19 March 2020, 09.00 – 18.00 h  
(Registration and coffee 08.30 – 09.00 h)

**Venue**
Scandic Frankfurt Museumsufer  
Wilhelm-Leuschner-Straße 33  
60329 Frankfurt, Germany

Phone: +49(0)69 907 459 0  
Email: museumsufer@scandichotels.com

**Fees (per delegate plus VAT)**
- ECA Members € 990
- APIC Members € 1,090
- Non-ECA Members € 1,190
- EU GMP Inspectorates € 595

The conference fee is payable in advance after receipt of invoice and includes conference documentation (on USB memo stick), lunch and all refreshments. VAT is reclaimable.

**Accommodation**
CONCEPT HEIDELBERG has reserved a limited number of rooms in the conference hotel. You will receive a booking link when you have registered for the event. Reservation should be made directly with the hotel. Early reservation is recommended.

**Registration**
Via the attached reservation form, by e-mail or by fax message. Or you register online at www.gmp-compliance.org.

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**Conference Language**
The official conference language will be English.

**Certificate of Participation**
Shortly after the event, you will receive your certificate of participation by email.

**Organisation and Contact**
ECA has entrusted Concept Heidelberg with the organisation of this event.

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1. We are happy to welcome a substitute colleague at any time.
2. If you have to cancel entirely we must charge the following processing fees: Cancellation
   - until 2 weeks prior to the conference 10 %
   - until 1 weeks prior to the conference 50 %
   - within 1 week prior to the conference 100 %

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