



## Speakers



Dr Karl Abele  
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Dr Ulrich Rose  
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Astra Zeneca, UK

# The Impurities Workshop

Practical approaches for assessing the risks of Impurities



Live Online Training from 18 - 20 October 2022



Save up to  
1.000 €  
by registering for  
all 3 parts

## Part I - General Strategies for Identification and Control of Impurities

Live Online Training on 18 October 2022

## Part II - Nitrosamine Impurities

Practical Approaches for Assessing the Risk of Nitrosamines and other Mutagenic Impurities in Drug Substances and Drug Products

Live Online Training on 19 October 2022

## Part III - Elemental Impurities

Practical Approaches for Identification and Control

Live Online Training on 20 October 2022

## Objectives

Part I of the Impurities Workshop will provide an opportunity to reinforce and expand your knowledge of the general area of impurities in chemical entities from initial development to the market with emphasis on

- Detection, profiling and control of impurities in drug substances, intermediates and drug products
- Practical aspects of method validation for impurities determination
- Analytical techniques used for detecting and qualifying impurities
- Extractables and Leachables as a source of impurities
- Approaches for investigation and determination of unexpected impurities

This Live Online Training is designed to provide a comprehensive review of impurities analysis and characterisation in drug substances and drug products and their recording and reporting.

## Background

Setting specifications for impurities are one of the most critical topics in the development of new drug products. Impurities analysis in drug substances and drug products and their recording and reporting is quite often a challenge for the scientific experts in routine production and quality control. This challenge is even bigger when profiles of unknown impurities in complex matrices have to be established. The Sartan case made clear the importance of a thorough process understanding.

## Target Audience

This Live Online Training is addressed to all personnel involved in development of drug substances and drug products from scientific staff to laboratory heads involved in R&D. The needs of Laboratory Managers, Supervisors and Analysts in pharmaceutical quality assurance and quality control departments will also be covered. This Live Online Training will also address regulatory requirements and hence is applicable to people working in the regulatory affairs area.

## Programme

### Analysis and Qualification of Impurities in Drug Substances and Drug Products – General Overview

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- Impurity profiling in synthetic drug substances
- Qualification of impurities
- Degradation studies
- Identification of chiral impurities, polymorphic phases and new impurities
- Residual solvents
- Impurities in starting materials and intermediates
- Pharmacopoeial tests and acceptance criteria
- Drug product specifications and parametric release

### Analytical Method Validation for Impurities Determination at Various Development Stages

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- Quantification of impurities
- How to define an impurity profile (stress tests)
- Reference substances
- Validation of methods at various development stages
- Statistical approaches to method validation (LOD & LOQ)



### Presentation and Workshop: Selecting Analytical Procedures and setting Acceptance Criteria of Impurities during Drug Substances Synthesis

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- Purity analysis by HPLC, impurity profile
- Residual solvents by GC
- Inorganic impurities (heavy metals, sulphated ash)
- For chiral compounds in addition: enantiometric purity and proof of the absolute configuration

In the Workshop the participants will learn which activities are necessary to characterize drug substances taking into account the following aspects:

- Analytical procedures are necessary for the characterization
- Experiments necessary to check the downstream impurities in order to justify acceptance criteria for the respective impurities
- Other impurities have to be taken into account
- Experiments to be performed in order to get a stability-indicating analytical procedure

### Leachables and Extractables

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- Why should Extractables & Leachables be assessed?
- Regulatory requirements in the EU and US
- Compendial requirements and industry standards
- Safety qualification of Leachables and Extractables

### Unexpected Impurities: Approaches for Investigation and Determination

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- Is there such a thing as ‘unexpected impurities’ or is there a lack of process understanding?
- Valsartan – overview of events
- Source of contamination
- Mechanistic understanding
- Examination of risk within other Sartans – overview of how to conduct a risk assessment and to identify key factors
- Are there other Mutagenic Impurities related risks?

## Objectives

In Part II of the Impurities Workshop the relevant aspects of root cause analysis and risk assessment 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,
- which practical approaches can be applied to assess the risks related to potential Nitrosamine contamination,
- which safety aspects need to be considered regarding Nitrosamine Impurities in drug products,
- which regulatory actions are to be taken in case of Nitrosamine Impurities and what authorities expect in these cases.

You will get advice from industry experts on how to cope with the challenge of performing risk assessments. Furthermore a representative of the EDQM will inform you about the European Pharmacopoeia activities (policy) on mutagenic impurities with focus on Nitrosamines.

## Background

In June 2018 EU authorities were notified that a Chinese API manufacturer has 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. As a consequence in case of contamination with Nitrosamines Marketing Authorisation Holders are requested to file a variation application.

## Target Audience

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## Programme

### European Pharmacopoeia Activities (Policy) on Mutagenic Impurities with Focus on Nitrosamines

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- Ph. Eur. General policy on DNA reactive impurities
- Control of Nitrosamines in Ph. Eur.
- Changes in individual and general monographs following the Sartan case
- New general chapter on control of nitrosamines

### Root Causes for Nitrosamine Impurities and other Mutagenic Impurities – Practical Approaches to Assess the Risks

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- Development of a systematic risk based approach
- Key factors and the development of a decision tree
  - API
  - Drug Product
  - Packaging

### Analytical Solutions for Monitoring Presence/Formation of N-Nitrosamines within APIs and Drug Products

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- Detection limits requested by in Article 5(3) of Regulation EC (No) 726/2004
- Techniques used for analysis of non-API related N-Nitrosamines
- Formation of N-nitrosylated APIs in drug products
- Analytical methods used for quantification of N-nitrosylated APIs in drug products



### Workshop: Conducting a Risk Assessment

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In this Workshop the participants will work on several case studies and perform a risk assessment for different scenarios taking into account e.g. manufacturing equipment, dosage form of the drug product etc.

### Nitrosamines and Other Genotoxic Impurities – Authorities' Expectations and Dossier Requirements

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- The assessor's approach: principles of toxicological assessment
- Structural alerts
- Limits and Permitted Daily Exposure
- The ALARP principle
- Examples of low daily dose drug substances
- Impurities derived from alkylating agents (mesilate, besilate, tosilate, diisothionate); examples
- Nitrosamines – the Valsartan case
- Potential mutagenic residual solvents
- Impurities derived from metal catalysts

## Objectives

In Part III of the Impurities Workshop the key principles of the ICH Q3D Guideline on elemental impurities will be highlighted. You will get to know the essential aspects and approaches of how to assess the risks and control elemental impurities in drug substances, drug products and excipients.

You will learn

- what has to be considered with respect to the drug substance monographs of the European Pharmacopoeia,
- how to perform a risk assessment in order to establish a control strategy for elemental impurities,
- how the route of administration and the duration of exposure affect the limits of elemental impurities and
- which potential sources of Elemental Impurities within the supply chain you have to be aware of.

## Background

In November 2014 the ICH Q3D Guideline for Elemental Impurities was published as Step 4 document. This document outlines

- the evaluation of the toxicity data for potential elemental impurities
- the PDEs for each element of toxicological concern
- the basis for an EI risk assessment and the key factors for evaluation.
- the development of controls designed to limit the inclusion of elemental impurities in drug products to levels at or below the PDE

Meanwhile ICH Q3D was revised twice, regarding Cadmium Inhalation PDE (ICH Q3D(R1); Step 2 document) and cutaneous and transdermal products (ICH Q3D(R2); Concept Paper).

## Target Audience

This Live Online Training is addressed to all personnel involved in development of drug substances and drug products from scientific staff to laboratory heads involved in R&D. The needs of Laboratory Managers, Supervisors and Analysts in pharmaceutical quality assurance and quality control departments will also be covered.

## Programme

### European Pharmacopoeia Activities (Policy) on Elemental Impurities – an Update

- Implementation of Q3D in Ph. Eur.
- Changes in individual and general monographs
- Harmonisation of general chapter 2.4.20
- Second phase for revision of excipient monographs

### Risk-Based Approach for Elemental Impurities in the Supply Chain

- APIs, excipients, packaging materials impacting the purity profile
- Evaluation of supply chain processes
- Risk analysis as evaluation tool
- Audits and monitoring programs as important sources
- Testing strategies



### Control Strategies for Elemental Impurities in Final Dosage Forms – Case Studies

- Utilisation of Data as part of an Integrated EI Risk Assessment Process
- Potential Sources of Elemental Impurities in the Finished Product
  - API
  - Equipment
  - Container-closure system
  - Excipients
- Conclusions



### Workshop: Conducting a Risk Assessment

In this Workshop the participants will work on several case studies and perform a risk assessment for different scenarios taking into account e.g. manufacturing equipment, dosage form of the drug product etc.

#### Your Benefit



#### Internationally Acknowledged Certificate from ECA Academy

The EU GMP Guide requires: „... All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training...“.

This is why you receive an acknowledged participant certificate, which lists the contents of the seminar in detail and with which you document your training.

## Organisation and Contact

ECA has entrusted Concept Heidelberg with the organisation of this event.

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Mr Ronny Strohwalde (Organisation Manager) at

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## Ordering Recordings

Independent from the Live Online Training Courses, you can also order recordings of selected Live Online Training Courses at the same conditions – at [www.gmp-compliance.org/recordings](http://www.gmp-compliance.org/recordings). These recordings will be provided on our media server. All you need to watch it is an Internet browser – no additional software

## Speakers



**Dr Karl Abele**  
Solvias AG, Switzerland

Dr Karl Abele holds a Ph.D. in organic chemistry and is user of LC/MS and GC/MS systems since 1985. He worked as application specialist for several large MS manufacturers in Switzerland and since 2010 he is head of the team organic trace analysis II (OSII) at Solvias. Impurity qualification, profiling and identification are his daily business.



**Dr Ward D'Autry**  
Nelson Labs, Belgium

Dr Ward D'Autry is Study Director Extractables & Leachables at Nelson Labs. His key technical expertise is chromatography coupled to (high resolution) mass spectrometry, for the identification of small molecules. As study director I'm on the interface between the sponsor's requests and the analytical laboratory.



**Dr Gerd Jilge**  
formerly Boehringer Ingelheim, Germany

In 1991, Dr Gerd Jilge came to Boehringer Ingelheim working in drug product development, where he was responsible for method development and validation for the application of analytical procedures. In 2000, he took a position in Drug Regulatory Affairs of Boehringer Ingelheim GmbH with the focus on CMC documentation for the submission of new and registered drug products.



**Jürgen Martin**  
Martin-Consulting, Germany

Mr Jürgen Martin has more than 25 years of experience in pharmaceutical industry and quality control.

After his education at the university of Konstanz he has held different leading positions focusing on quality control topics at Byk Gulden, Altana Pharma and Nycomed. Between 2011 and 2019 he was building up and heading the quality control of the BIPSO GmbH. Since 2019 he is operating his own consultancy and software development office.



**Dr Cornelia Nopitsch-Mai**  
Quality Assessor, Germany

Dr Cornelia Nopitsch-Mai is scientist at the Federal Institute for Drugs and Medical Devices 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 Ulrich Rose**  
Former Deputy Head of the European Pharmacopoeia Department, EDQM, France

Dr Rose was Deputy Head of the European Pharmacopoeia Department at the EDQM in Strasbourg and in this context responsible for the preparation of monographs on chemical defined APIs, finished products, herbal drugs & preparations, and general chapters. He was also involved in the harmonization of international pharmacopoeias. Previously, he was responsible for the establishment and control of Ph. Eur. Reference Standards, and later served as coordinator and auditor for EDQM's Mutual Joint Audit Program, which audits Official Medicines Control Laboratories in Europe (OMCLs).



**Dr Xaver Schrott**  
GBA Pharma GmbH, Germany

Dr Xaver Schrott is head of department R&D 2 and an expert for chromatography and mass spectrometry. In charge of national and international pharmaceutical companies he manages all analytical aspects of projects from preclinical stage up to phase III and post market approval with focus on method development, validation and qualification of reference standards.



**Dr Andrew Teasdale**  
Astra Zeneca, United Kingdom

Dr Andrew Teasdale PhD has over 20 years' experience in the pharmaceutical industry as an analytical chemist and 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.

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## The Impurities Workshop, Live Online Training from 18 - 20 October 2022

- Part I: 18 October 2022  
 Part II: 19 October 2022  
 Part III: 20 October 2022
- Part I and II: 18 - 19 October 2022  
 Part II and III: 19 - 20 October 2022  
 Part I - III: 18 - 20 October 2022

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## Date of the Live Online Training

The Impurities Workshop Part I: General Strategies for Identification and Control of Impurities  
18 October 2022, 08.30 – 17.15 h CEST

The Impurities Workshop Part II: Nitrosamine Impurities  
19 October 2022, 09.00 – 16.30 h CEST

The Impurities Workshop Part III: Elemental Impurities  
20 October 2022, 09.00 – 15.30 h CEST

## Technical Requirements

For our Live Online Training Courses and Webinars, we use Cisco WebEx, one of the leading suppliers of online meetings. At <http://www.webex.com/test-meeting.html> you can check if your system meets the necessary requirements for the participation at a WebEx meeting and at the same time install the necessary plug-in. Please just enter your name and email address for the test. If the installation is not possible because of your rights for the computer system, please contact your IT department. WebEx is a standard nowadays and the necessary installation is fast and easy.

## Fees (per delegate, plus VAT)

The Impurities Workshop Part I  
ECA Members € 890 | APIC Members € 990  
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The Impurities Workshop Part II  
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The Impurities Workshop Part I and II:  
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## Registration

Via the attached reservation form, by e-mail or by fax message. Or you register online at [www.gmp-compliance.org](http://www.gmp-compliance.org).

## Conference language

The official conference language will be English.

## Presentations/Certificate

The presentations will be made available to you prior to the Live Online Training as PDF files. After the event, you will automatically receive your certificate of participation.