



## Speakers



Dr Gerd Jilge  
Boehringer Ingelheim, Germany



Jürgen Martin  
Martin-Consulting



Dr Lutz Müller  
F. Hoffmann-La Roche, Switzerland



Dr Corina Nachtsheim  
Quality Assessor, Germany



Dr Ulrich Rose  
EDQM, France



Dr Xaver Schrott  
GBA Pharma GmbH, Germany



Dr Andrew Teasdale  
Astra Zeneca, UK



Dr Lise Vanderkelen  
Nelson Labs, Belgium

# The Impurities Workshop

Practical approaches for assessing  
the risks of Impurities

2020



Live Online from 01 - 03 December 2020



**Part I - General Strategies for Investigation and Control of Impurities**  
Live Online on 01 December 2020

**Part II - Nitrosamine Impurities**  
Practical Approaches for Assessing the Risk of Nitrosamines and other  
Mutagenic Impurities in Drug Substances and Drug Products  
Live Online on 02 December 2020

**Part III - Elemental Impurities**  
Practical Approaches for Identification and Control  
Live Online on 03 December 2020

## 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 event 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 Valsartan case made clear the importance of a thorough process understanding.

## Target Audience

This Live Online Training addresses 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 event will also address regulatory requirements and hence is applicable to people working in the regulatory affairs area.

## Programme

### Impurities 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: Analytical Techniques for Determination and Qualification of Impurities in Starting Materials and Intermediates

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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. All regulatory activities with regard to such cases have to be completed within a 3 years period (end of march 2022).

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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

#### ICH M7 Safety Risk Assessment and the Cohort of Concern – How to Deal with e.g. Nitrosamines

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- Principles of cancer risk estimation in ICH M7
- Why was the cohort of concern excluded from ICH M7?
- Applicability to use ICH M7 based cancer risk assessment to the cohort of concern
- Nitrosamines, why are they in the cohort of concern?
- Major risk factors for sources of nitrosamines in drugs
- Way forward to handle cohort of concern within ICH M7



#### 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,
- 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

The Live Online Training addresses 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.



**Dr Gerd Jilge**  
Boehringer Ingelheim, Germany

Dr Gerd Jilge was responsible for method development and validation for the application of analytical procedures. After having taken a position in Drug Regulatory Affairs with the focus on CMC documentation for the submission of new and registered drug products he joined the Quality Management department where he is working on method development for new drug substances.



**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 Lutz Müller**  
F. Hoffmann-La Roche, Switzerland

Dr Lutz Müller is Toxicology Project Leader in R&D and has dedicated expertise in Genotoxicity, Carcinogenicity, Immunotoxicity, Impurities management, In vitro systems, safety risk assessment and regulatory toxicology. He is member of various Roche Drug Development and Portfolio Committees and EFPIA representative to the ICH Guideline Expert Working Groups, currently Mutagenic Impurities – M7. Moreover he is author of over 100 original publications in peer reviewed journals and various book chapters and lecturer on many international meetings and workshops.



**Dr Corina Nachtsheim**  
Quality Assessor, Germany

Dr Corina Nachtsheim is working as a quality assessor at the German Federal Institute for Drugs and Medical Devices (BfArM) since Jan. 2001. Since Nov. 2007, she is an external expert in the framework of the certification procedure of the EDQM in Strasbourg. She became a member of the chemical Technical Advisory Board (EDQM) in Nov. 2011 and is currently chairperson.



**Dr Ulrich Rose**  
EDQM, France

Dr Ulrich Rose works since 1991 at the EDQM in Strasbourg. Until 2011 he was responsible for establishment and monitoring of the Ph. Eur. reference standards and was involved in the elaboration and revision of monographs of the European Pharmacopoeia. After that he became coordinator and auditor for EDQM's Mutual Joint Audit Program where he had to audit the Official Medicines Control Laboratories (OMCLs) in Europe. Since 2014 he is head of division A and deputy head of the Ph. Eur. Department where he is overlooking the monograph work on chemicals, excipients, herbals and general chapters of Ph. Eur. and is involved in the international harmonisation of pharmacopoeias.



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

Dr Xaver Schratt 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.



**Dr Lise Vanderkelen**  
Nelson Labs, Belgium

Dr Lise Vanderkelen was study director at the Extractables & Leachables Department and is now Department Head Pharma Services at Nelson Labs Europe. The main focus of this department is identifying organic impurities in drug products as well as in use stability of drug-device combination including all microbiological testing offered at Nelson Labs Europe.

## Organisation and Contact

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

CONCEPT HEIDELBERG

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Dr Gerhard Becker (Director Operations) at  
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For questions regarding organisation please contact:

Mr Ronny Strohwald (Organisation Manager) at  
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strohwald@concept-heidelberg.de

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Reservation Form (Please complete in full)



## The Impurities Workshop 2020, Live Online Training from 01 - 03 December 2020

- Part I: 01 December 2020  
 Part II: 02 December 2020  
 Part III: 03 December 2020
- Part I and II: 01 - 02 December 2020  
 Part II and III: 02 - 03 December 2020  
 Part I - III: 01 - 03 December 2020

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### General terms and conditions

If you cannot attend the conference you have two options:

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 %
    - Cancellation until 1 week prior to the conference 50 %
    - Cancellation within 1 week prior to the conference 100 %
- CONCEPT HEIDELBERG reserves the right to change the materials, instructors,

or speakers without notice or to cancel an event. If the event must be cancelled, registrants will be notified as soon as possible and will receive a full refund of fees paid. CONCEPT HEIDELBERG will not be responsible for discount airfare penalties or other costs incurred due to a cancellation.

Terms of payment: Payable without deductions within 10 days after receipt of invoice.

Important: This is a binding registration and above fees are due in case of cancellation.

cancellation or non-appearance. If you cannot take part, you have to inform us in writing. The cancellation fee will then be calculated according to the point of time at which we receive your message.

In case you do not appear at the event without having informed us, you will have to pay the full registration fee, even if you have not made the payment yet. Only after we have received your payment, you are entitled to participate in the conference (receipt of payment will not be confirmed!) (As of January 2012). German law shall apply. Court of jurisdiction is Heidelberg.

Privacy Policy: By registering for this event, I accept the processing of my Personal Data. Concept Heidelberg will use my data for the processing of this order, for which I hereby declare to agree that my personal data is stored and processed. Concept Heidelberg will only send me information in relation with this order or similar ones. My personal data will not be disclosed to third parties (see also the privacy policy at <https://www.gmp-compliance.org/privacy-policy>). I note that I can ask for the modification, correction or deletion of my data at any time via the contact form on this website.



## Date of the Live Online Training

The Impurities Workshop Part I  
Tuesday, 1 December 2020, 09.00 – 17.45 h CET

The Impurities Workshop Part II  
Wednesday, 2 December 2020, 09.00 – 16.30 h CET

The Impurities Workshop Part III  
Thursday, 3 December 2020, 09.00 – 15.30 h CET

## Technical Requirements

For our 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  
Non-ECA Members € 1,090 | EU GMP Inspectorates € 545

The Impurities Workshop Part II  
ECA Members € 890 | APIC Members € 990  
Non-ECA Members € 1,090 | EU GMP Inspectorates € 545

The Impurities Workshop Part III  
ECA Members € 890 | APIC Members € 990  
Non-ECA Members € 1,090 | EU GMP Inspectorates € 545

The Impurities Workshop Part I and II  
ECA Members € 1,590 | APIC Members € 1,690  
Non-ECA Members € 1,790 | EU GMP Inspectorates € 895

The Impurities Workshop Part II and III  
ECA Members € 1,590 | APIC Members € 1,690  
Non-ECA Members € 1,790 | EU GMP Inspectorates € 895

The Impurities Workshop Part I - III  
ECA Members € 2,070 | APIC Members € 2,170  
Non-ECA Members € 2,270 | EU GMP Inspectorates € 1,135

## 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.

## 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.