

## SPEAKERS



**DR GISELA FONTAINE**  
*Solvias AG, Switzerland*



**DR GERD JILGE**  
*Boehringer Ingelheim  
Pharma GmbH & Co. KG,  
Germany*



**GRACE KOCKS**  
*Lhasa Limited, United  
Kingdom*



**DR CORINA  
NACHTSHEIM**  
*Quality Assessor, Germany*



**DR XAVER SCHRATT**  
*GBA Pharma GmbH,  
Germany*



**DR ANDREW TEASDALE**  
*AstraZeneca, United  
Kingdom*



**DR LISE VANDERKELEN**  
*Nelson Labs, Belgium*



**PART I**  
26 June 2019

**GENERAL STRATEGIES FOR  
INVESTIGATION AND CONTROL**

**PART II**  
27 June 2019

**ELEMENTAL IMPURITIES AND  
GENOTOXIC IMPURITIES**

Free of charge\* Post-Conference Workshop on 28 June 2019:  
**"The Elemental Impurities Database"**

(\*only for those who participate in at least one part of the Impurities Forum)



## PART I: GENERAL STRATEGIES FOR INVESTIGATION AND CONTROL

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### Objectives

Part I of the Impurities Forum 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
- "Unexpected Impurities" – lessons learned from the Valsartan case

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 recent **Valsartan case** made clear the importance of a thorough process understanding.

### Target Audience

This workshop 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**

- 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 Impurity determination at various development stages**

- 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**

- Purity analysis by HPLC, impurity profile
- Residual solvents by GC
- Inorganic impurities (heavy metals, sulphated ash)
- For chiral compounds in addition: enantiomeric 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**

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



The subsequent plenary workshop will provide the opportunity to discuss case studies about Leachables and Extractables regarding detection and safety qualification. It will seek, through a practical exercise, to examine the steps involved in a comprehensive E&L evaluation.

#### **Unexpected Impurities: approaches for investigation and determination**

- 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?

## **PART II: ELEMENTAL IMPURITIES AND GENOTOXIC IMPURITIES**

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### **Objectives**

In Part II of the Impurities Forum the key principles of the ICH Q3D Guideline will be highlighted. You will get to know the essential aspects and approaches of determining and controlling elemental impurities in drug products. You will learn

- which are the principles of the elemental impurities risk assessment process,
- factors that affect the limits – route of administration and also duration of exposure.
- how to implement risk-based strategies to control elemental impurities,
- how to develop suitable analytical methods for genotoxic impurities determination,
- regulatory filing: what do regulatory authorities expect?

Moreover you will hear about recent developments regarding the control of Mutagenic Impurities according to ICH M7

### **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).

Equally the **ICH M7 Guideline for Assessment and Control of DNA reactive (mutagenic) impurities** has undergone a twofold revision: ICH M7(R1) (Step 4 document) being completed by an Addendum containing a summary of known mutagenic impurities commonly found or used in drug synthesis and ICH M7(R2) (Concept Paper) where PDEs for new DNA reactive (mutagenic) impurities have been incorporated.

### **Target Audience**

The conference 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**

#### **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

#### **Analytical methods to determine elemental impurities**

- Principles and characteristics of the most common spectrometric techniques AAS, ICP-OES, ICP-MS
- Compound methods (sample preparation plus spectrometric detection and quantification)
- Special considerations for trace-elemental analysis
- Application-based approach for choice of methodology
- Analytical process (method development, validation strategy, routine testing)

### **Mutagenic Impurities: how to develop suitable analytical methods for detection**

- Challenges associated with MI analytical method development
- Class based methods vs individually designed messages
- Technologies
- GC-vs LC
- Chromatography vs NMR
- Validation requirements



### **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.

### **Mutagenic Impurities – requirements, authorities expectations and case studies**

- General documents and Guidelines for the assessment of mutagenic impurities
- The assessor's approach: principles of toxicological assessment
- The TTC concept
- Structural alerts
- Limits and Permitted Daily Exposure
- The ALARP principle
- Applicability of the EU "Guideline on the Limits of Genotoxic Impurities"
- 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

### **Speakers**



#### **DR GISELA FONTAINE, SOLVIAS AG, SWITZERLAND**

Gisela Fontaine joined Solvias AG in 2013 as Senior Lab Manager for (Ultra) Trace Elemental Analysis. The analytical techniques covered by her team are ICP-MS, ICP-OES, ET-AAS as well as Polarography. Her work is focused on development and validation of analytical methods for determination of trace elements as well as their routine analysis.



#### **DR GERD JILGE, BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG, 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.



#### **GRACE KOCKS, LHASA LIMITED, UNITED KINGDOM**

Grace Kocks graduated from the University of Leeds with a BSc in Human Physiology. In 2013, she joined the science team of Lhasa Limited where she works on the Vitic database. Within the team she is responsible for curation and peer review of data.



#### **DR CORINA NACHTSHEIM, QUALITY ASSESSOR, GERMANY**

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 November 2011 and is currently chairperson.



#### **DR XAVER SCHRATT, GBA PHARMA GMBH, GERMANY**

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, ASTRAZENECA, UNITED KINGDOM**

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 EUROPE, BELGIUM**

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.



## POST CONFERENCE WORKSHOP ON 28 JUNE 2019 THE ELEMENTAL IMPURITIES DATABASE

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Free of Charge\*

The Elemental Impurities database is an initiative of a pharma consortium and aims to collect and share data from pharmaceutical excipients. In this workshop the following points will be discussed:

- I would like to contribute to/send data to the database:  
What is the procedure?
- I would like to get information out of the database:  
What is the procedure?
- What about confidentiality regarding the submission to or reception of information from the database?



As part of this workshop the importance of data in a step wise integrated risk based approach and potential sources of these data will also be examined.

\*For those who participate in at least one part of the Impurities Forum

## SOCIAL EVENT ON 26 JUNE

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You are cordially invited to a guided sightseeing tour on 26 June 2019. This is an excellent opportunity to share your experiences with colleagues from other companies in a relaxed atmosphere.



## LUFTHANSA IS MOBILITY PARTNER FOR ALL ECA EVENTS

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As an ECA course or conference attendee, you will receive up to 20% discounted travel fares (according to availability). And as Lufthansa German Airlines offers a comprehensive global route network linking major cities around the world you will most likely be able to benefit from these special prices and conditions.

And this is how it works: Once you registered for a course or conference you will receive a link together with your registration confirmation. Opening that link will take you to the Mobility Partner Program website where you can enter a code in the "Access to Event Booking" area you will also receive. This will take you into an online booking platform\* that will automatically calculate the discount offered or provide you with an even better offer if another promotional fare is available.

We look forward to welcoming at one of our next events – and we already wish you a pleasant flight!

\*Please note: You may have to enable pop-ups on the Mobility Partner Program website – otherwise the booking platform window will not open.

## Easy Registration



**Reservation Form:**  
**CONCEPT HEIDELBERG**  
P.O. Box 10 17 64  
69007 Heidelberg, Germany



**Reservation Form:**  
+ 49 6221 84 44 34



**e-mail:**  
info@concept-heidelberg.de



**Internet:**  
www.gmp-compliance.org

### Date

#### Impurities Forum Part I: General strategies for investigation and control

26 June 2019, 09.00 – 18.00 h  
(Registration and coffee 08.30 – 09.00 h)

#### Impurities Forum Part II: Elemental Impurities and Genotoxic Impurities

27 June 2019, 09.00 – 18.00 h  
(Registration and coffee 08.30 – 09.00 h)

#### Post Conference Workshop:

##### The Elemental Impurities Database

28 June 2019, 09.00 – 12.00 h  
(Registration and coffee 08.30 – 09.00 h)

### Venue

Corinthia Hotel Prague  
Kongresova 1  
14069 Prague, Czech Republic  
Phone +420 (261) 191 111  
Email prague@corinthia.com

### Fees (per delegate + VAT)

#### Impurities Forum Part I OR Part II

ECA Members € 890  
APIC Members € 990  
Non-ECA Members € 1.090  
EU GMP Inspectorates € 545

### Impurities Forum Part I and II

ECA Members € 1.590  
APIC Members € 1,690  
Non-ECA Members € 1,790  
EU GMP Inspectorates € 895

### Post Conference Workshop\*

ECA Members € 190  
APIC Members € 290  
Non-ECA Members € 390  
EU GMP Inspectorates € 195

\*The Post-Conference Workshop is free of charge only for those who participate in at least one part of the Impurities Forum!

### 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).

### Accommodation

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

### Organisation and Contact

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

CONCEPT HEIDELBERG  
P.O. Box 10 17 64  
D-69007 Heidelberg, Germany  
Phone +49 (0) 62 21/84 44-0  
Fax +49 (0) 62 21/84 44 34  
info@concept-heidelberg.de  
www.concept-heidelberg.de

### For questions regarding content please contact:

Dr Gerhard Becker (Operations Director) at +49(0)62 21 / 84 44 65,  
or per e-mail at [becker@concept-heidelberg.de](mailto:becker@concept-heidelberg.de).

### For questions regarding reservation, hotel, organisation etc. please contact:

Mr Ronny Strohwalde (Organisation Manager) at +49(0)62 21 / 84 44 51  
or per e-mail at [strohwalde@concept-heidelberg.de](mailto:strohwalde@concept-heidelberg.de).

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P.O. Box 10 17 64  
Fax +49 (0) 6221/84 44 34

69007 Heidelberg  
Germany

### Reservation Form (Please complete in full)

+49 6221 84 44 34

### IMPURITIES FORUM 2019, 26-27 June 2019, Prague, Czech Republic

- Part I: 26 June 2019  
 Part II: 27 June 2019  
 Part I and Part II: 26-27 June 2019  
 Post Conference Workshop: 28 June 2019

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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 %  
- until 1 weeks prior to the conference 50 %  
- 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.  
German law shall apply. Court of jurisdiction is Heidelberg.

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

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 [http://www.gmp-compliance.org/eca\\_privacy.html](http://www.gmp-compliance.org/eca_privacy.html)). 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.