

safescimet course 3.1 - Biochemical and Molecular Toxicology: Biotransformation, Bioactivation and Adverse Drug Reactions

Key Questions Addressed

- Role of drug metabolism in pharmacokinetics, toxicology, and clinical adverse drug reactions
- Biotransformation of drugs to active, reactive and disproportionate metabolites
- Drug interactions and adverse events resulting from induction or inhibition of human enzymes or transporters
- Cellular targets and toxicological effects of reactive metabolites – constitutive and inducible defense systems
- ADME studies and how they integrate into drug development plans
- Current regulatory guidance on metabolites and drug interactions

Feedback from the Previous Course

“The teachers availability was really good.”

“It was a two way communication during the lectures.”

About safescimet

safescimet is a unique pan-European network of academia and pharmaceutical industry, which have joined forces to establish a comprehensive modular education and training in Safety Sciences for medicines. The programme covers all aspects of safety in drug development, in order to fulfill the needs of drug safety scientists in the pharmaceutical industry, regulatory authorities and academia. The aim of the programme is to bridge crucial gaps in the education and training of scientists evaluating the safety of drug candidates and new medicines and to ensure that European drug safety scientists are at the forefront of their field.

The course Biochemical and Molecular Toxicology: Biotransformation, Bioactivation and Adverse Drug Reactions and the other single courses of the safescimet programme provide new opportunities for Continuous Professional Development (CPD) and are part of European Master for Advanced Safety Sciences for Medicines degree at the University of Konstanz. The individual courses are clustered within five separate domains. Each domain deals with one or more specialised topics and contains from two to six single courses. Please visit www.safescimet.eu for details of the full course programme and confirmation of course dates.

Course Objectives

Adverse drug reactions (ADRs), which usually occur in small subgroups of patients, are still difficult to predict in preclinical studies. Therefore knowledge of the underlying mechanisms of drug toxicity is considered crucial to improve extrapolation of animal model data to human. ADRs originate from molecular interactions of drugs or drug metabolites to critical targets in sensitive tissues. The course looks closely at biochemical and molecular aspects of toxicology especially concentrating on bioactivation processes, drug interactions and resulting ADRs. Polymorphism in genetic factors and idiosyncratic drug toxicity are also given some attention. Special emphasis is given to the biological effects of metabolites (cellular targets and defence systems) and potential safety concerns. Participants will receive an understanding how pharmacokinetic effects (bioactivation, biotransformation) impact drug safety, interrogate experimental approaches and review case studies.

Key Subjects Covered by the Course

- ADME studies and how they are integrated into drug development
- Role of drug metabolism in pharmacokinetics, toxicology and clinical adverse drug reactions
- Current regulatory guidance on metabolites and drug interactions
- Biotransformation of drugs in general but with an emphasis on active, reactive and disproportionate metabolites
- Enzymology of drug metabolising enzymes and role of genetic factors
- Drug interactions and adverse events resulting from induction or inhibition of human enzymes/transporters
- Cellular targets of reactive metabolites and resulting toxicological consequences
- Constitutive and inducible defensive systems against reactive metabolites
- Hypotheses concerning molecular mechanisms underlying idiosyncratic drug reactions

Target Audience

safescimet courses are open to all scientists and students from industry, academia and regulatory authorities, who need a broad comprehensive understanding of the drug development process with particular emphasis on safety. The applicant will normally possess an MSc degree in a Life Science discipline or equivalent. In addition, applicants are expected to have an at least one year working experience in a related discipline.

Why Join the Course

The on-site training of the course in Amsterdam during the first week consists of five days with lectures, practical exercises, group work and discussions. This setup offers an intense and broad training with leading experts in their field and ample opportunities for lecturer-student interactions. The balance of academic, industry and regulatory teachers provides knowledge directly available to drug safety assessment, including dataset discussions from real case studies.

Learning Outcomes

On successful completion of the course, participants should have an integrated view on the biochemical and molecular aspects of adverse drug reactions, and understand how bioactivation of drug compounds or their metabolites can influence the drug safety profile. More specifically, participants will be able to

- identify individual drug metabolising enzymes involved in bioactivation and inactivation reactions
- recognise circumstances when the body's handling of a drug might be altered resulting in changes to either its safety or efficacy profile
- identify safety concerns resulting from active, reactive, and disproportionate metabolites
- apply strategies to mitigate risks which consider closely the latest regulatory guidance on metabolites and drug interactions

- propose biochemical / molecular mechanisms for specific types of toxicity
- interrogate experimental approaches and integrate ADME studies into development plans

Course Programme

The first week of the course in Amsterdam consists of five days lectures, practical exercises, group work and discussions, provided by specialists from academia, pharmaceutical industry and regulatory authorities with diverse backgrounds on drug safety aspects.

On-site Training

Day 1	Introduction; DMPK Studies
Day 2	Enzymology of drug metabolizing enzymes; Drug-drug interactions
Day 3	Current safety and toxicology testing; Understanding animal toxicities during development
Day 4	In silico tools; Risk assessments
Day 5	Case studies

Individual Home Assignments

After the week of on-site training, students will receive an individual 38 hours home assignment consisting of written questions and a case study. These individual assignments are to be completed through a frequent exchange with the SafeSciMET teachers using distance learning approach. Written individual assignments are to be completed and submitted via Moodle within 6 weeks after the on-site training and will then be approved by the course leader.

Course Credits

Participants attending the on-site training week only, without completing the exam and/or the home assignment, will be given a certificate of attendance confirming completion of a Continuing Professional Development (CPD) course.

In order to receive the full 3 ECTS credits for a successfully completed course, participants need to pass the written exam of the on-site training week as well as to have successfully completed the home assignment.

Syllabus

The syllabus contains lecture hand outs, list of abbreviations and list of reading materials and will be provided by the course leaders 14 days prior to the course. The information and the material for the individual home assignment will be provided during the first week of the course.

Assessment

The assessment is based on a 2-hour written examination on the last day of the first course week and on the evaluation of the home assignment.

Type	<ul style="list-style-type: none"> - The purpose of the examination is to test that the examinee has acquired a broad knowledge and comprehension of the course subjects during the lectures. - The percentage of items on the test devoted to a particular topic will roughly correspond to the emphasis given on the topic during the course. - Experimental Design: 5% - Pre-clinical: 55% - Clinical: 25% - Translational: 15%
Assessors	Course leaders
Exam aids	All written exam aids are allowed, especially the provided material: lecture hand outs, list of abbreviations and case studies.

Contact Person

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Course Leaders

Dr Jan N M Commandeur - Section of Molecular Toxicology, VU University, Amsterdam NL

Andrew Harrell - GSK, Park Road, Ware, Herts. UK

Practical Information

Course credits	3 ECTS credits
Level	Master's level (second cycle higher education)
Location	Human and Environmental Toxicology, University of Konstanz.
Teaching methods	Lectures, case reports, demonstrations and home assignments.
Student workload	<ul style="list-style-type: none"> - Preparation: 12 hours - Course: 38 hours - Assignment: 38 hours - Examination: 2 hours - Total: 90 hours
Course fee	Please visit on www.safescimet.eu Fees and How to apply for more information.
Course capacity	20 participants
Language	<ul style="list-style-type: none"> - The official language of the course is English. - No simultaneous translations will be provided.
Course notes	Complete course notes, except for the textbook, will be available for all the participants.
Course accreditation	<ul style="list-style-type: none"> - safescimet courses meet the criteria for Continuous Professional Development (CPD) diplomas, and are part of Master programme Advanced Safety for Medicines. - When registering for one or several "Stand Alone" courses of our programme, this course provides CPD credits for your individual CPD portfolio. Each course is credited with 38 contact hours. - The course setup is already consistent with the requirements of the Bologna process. The full Master programme is undergoing evaluation for being accredited and certified as a regular postgraduate MSc degree at the University of Konstanz/Germany.

Accommodation

VU University has arranged special prices with some of the hotels in Amsterdam for visitors of the university. All these hotels are situated near tram stops, from where you can travel to the university. Please visit www.vu.nl/en/about-vu-amsterdam/hotels-in-amsterdam/index.asp.

Otherwise, there are more hotels in Amsterdam which are close to VU University and reservations can be arranged individually via www.hotels.nl/amsterdam.

Transport

VU University is easily reached by train from Schiphol airport. Trains leave Schiphol (about six per hour) to Amsterdam Zuid (8 minutes). VU University can be reached from Amsterdam Zuid via a short walk (10 minutes), by tram 51 (direction Amstelveen Westwijk) or tram 5 (direction Amstelveen Binnenhof) both taking about 1 minute. Please visit www.vu.nl/en/about-vu-amsterdam/contact-info-and-route/route-description/index.asp for more information.

Registration

To apply please visit www.safescimet.eu. Your application needs your registration on www.safescimet.eu.

Cancellation

For our cancellation policy please visit **How to Apply/Terms and Conditions** on www.safescimet.eu.