



Continuing Professional Development / Masters of Advanced Safety Sciences degree

Full Course Brochure: upcoming courses 2012–2014

The course modules in the SafeSciMET programme are clustered within five separate domains. Each domain deals with one or more specialised topics and contains from two to six individual courses. The course objectives and key subjects of these courses are introduced in detail in this brochure on pages 7–20.

Domain	Course	Course leader Academic/EFPIA	Locations	Course Date
Drug Discovery and Development	1.1: Drug Discovery and Development	Crommelin /Newall	Amsterdam	5.11.2012 – 9.11.2012
	1.2: Drug Safety of Stem Cells and other novel Therapeutics	Park/Goldring/Williams/Piner	Liverpool	26.11.2012 – 30.11.2012
Pharmaceutical Aspects of Drug Safety	2.1: Pharmaceutics and Safety	Mahlin/von Keutz	Uppsala	25.2.2013 – 1.3.2013
	2.2: Regulatory Requirements and Guidelines	Silva Lima/von Keutz	Lisbon	18.3.2013 – 22.3.2013
	2.3: Pharmacokinetics and Pharmacodynamics	Hammarlund-Udenaes/Dietrich	Uppsala	8.4.2013 – 12.4.2013
Adverse Drug Reactions / Predictive Toxicology / 3 Rs	3.1: Biochemical and Molecular Toxicology: Biotransformation, Bioactivation and Adverse Drug Reactions	Commandeur/Harrel	Amsterdam	27.5.2013 – 31.5.2013
	3.2: Cellular Toxicology/Predictive Toxicology	van de Water/von Keutz	Leiden	24.6.2013 – 28.6.2013
	3.3: Organ/Systems Toxicology	Dietrich/Karlsson	Constance	30.9.2013 – 4.10.2013
	3.4: Reproductive Toxicology	Stahlmann/Bouisset-Leonard	Berlin	21.10.2013 – 25.10.2013
	3.5: Mutagenesis and Carcinogenesis	Grasl-Kraupp/Martus	Vienna	18.11.2013 – 22.11.2013
	3.6: Safety Pharmacology	Park/Goldring/Williams	Liverpool	25.11.2013 – 29.11.2013
Non-Clinical Assessment	4.1: Non-Clinical Safety assessment: Strategies, Ethics and Protocols	Schmerold/Foth	Vienna	9.12.2013 – 13.12.2013
	4.2: Biomolecular Analysis: From Method Development to Clinic	Niessen/Herling	Amsterdam	13.1.2014 – 17.1.2014
	4.3: Predictive Cell Culture Systems	Foth/Mueller	Halle	3.2.2014 – 7.2.2014
	4.4: Toxicogenomics and Systems Toxicology	Meerman/Hewitt	Leiden	10.3.2014 – 14.3.2014
	4.5: Pathology Interpretation in Drug Development	Price	Surrey	5.5.2014 – 9.5.2014
	4.6: In silico ADME and Predictive Toxicology	Steen Jørgensen/(Amberg)	Copenhagen	19.5.2014 – 23.5.2014
Clinical Safety	5.1: Clinical Safety: Pre-Approval	Dietrich/Doessegger	Basel	2.6.2014 – 6.6.2014
	5.2: Clinical Safety: Post-Approval	Pallardy/Caplain	Paris	23.6.2014 – 27.6.2014
	5.3 Stratification: Pharmacogenetics and Drug Safety	Ingelman-Sundberg/McHale	Stockholm	25.8.2014 – 29.8.2014

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For further information: <http://www.safescimet.eu>



Please note:

More and the most up-to-date information can always be obtained from our website: www.safescimet.eu
Please check this site before registration.

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SafeSciMET is a new and unique pan-European network of academia and pharmaceutical industry, who have come together to establish a comprehensive modular education and training in **Safety Sciences** for medicines. The programme will cover all aspects of safety in drug development, in order to fulfil 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.

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's working experience in a related discipline.

Principle learning outcomes

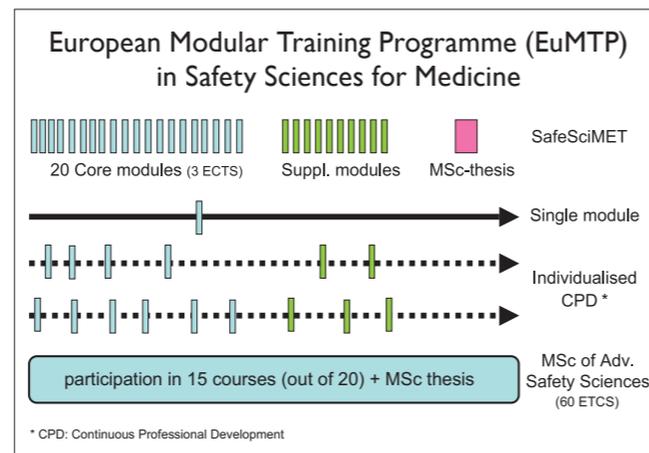
SafeSciMET will ensure that Europe's biomedical education landscape is enhanced to provide maximum support in revolutionizing the conventional drug discovery and development paradigm.

SafeSciMET will provide novel competences in translational safety sciences, an aspect which was found largely lacking in today's educational programmes.

It will lead to a new generation of safety scientists who are able to perform holistic and critical evaluations of the safety of drug candidates and new medicines. Linking animal and human data more effectively, both *in vitro* and *in vivo*, will contribute to a better understanding of drug safety and how to bridge and make best use of animal and human data collected in drug development and safety assessment.

Programme structure

A set of 20 core and a number of supplementary courses will be made available, of which all are introduced in detail in this brochure. The teachers are experts from academia, regula-



tory agencies and industry at an academic centre or industry location. Each course will include translationally oriented case studies provided by the experts. In this context, 'translational' typically refers to the translation of basic research into therapies for real patients where translational safety sciences concern all 'safety related aspects'.

All courses have a common format (set at 3 European Credit Transfer System ECTS). The courses will consist of one week of on-site face-to-face training concluded by an exam. Immediately subsequent to the week of on-site training, students will receive an individual home assignment and a case study, which have to be completed within six weeks after the course. The modular set up has major advantages:

- part-time study, spread over 2 – 5 years, is possible
- participants can follow single courses, follow sub-sets of the programme aiming at CPD credits, or join the full Master of Advanced Safety Sciences programme
- dedicated quality assurance for courses
- the course setup is already consistent with the requirements of the Bologna process. At the moment, the full master program is undergoing evaluation for being accredited and certified as a regular MSc degree from the University of Constance/Germany.
- the programme can be adapted to cope with new scientific insights in safety sciences and legislation or the emergence of new top-institutes for safety sciences. Apart from the core courses, a set of supplementary courses will be made available in the future.

How to register

Entry requirements

Participants on this programme are normally science, medical or veterinary graduates either currently working in a safety science environment or seeking to gain knowledge on safety science at a specific time-point of their career. Competence in both written and spoken English to an IELTS level or equivalent of 7.0 is an absolute requirement.

Participants can also attend courses as 'stand alone' for Continuing Professional Development (CPD) purposes.

Continuing Professional Development (CPD)

Applicants who wish to follow individual courses as part of a CPD will normally possess a minimum of a higher academic qualification (e.g. a MSc degree or equivalent) and a minimum of one year experience in the Safety Sciences field.

Master of Advanced Safety Sciences (MASS)

Applicants who wish to register for the Advanced Master will normally possess a minimum of a higher academic qualification (e.g. a MSc degree or equivalent) and a minimum of one year experience in the Safety Sciences field. Participation in 15 courses and a written Master thesis (60 ECTS) are required to receive the MASS degree.

Application

Please visit our website www.safescimet.eu and sign up for an Master of Advanced Safety Sciences, for Continuing Professional Development (CPD), or for single courses.

By uploading your CV and the associated certificates (MSc/diploma or PhD documents) you demonstrate your eligibility for participation in the SafeSciMET programme. For non-native English speaking participants, documentation of English competence (TOEFL, IELTS) is advised.

What happens next?

When you have applied as indicated above, your qualifications will be reviewed by the Student Office at Uppsala University and the SafeSciMET Admission Board.

Within one week after the application deadline you will be informed upon your acceptance to the course.

Just prior to the starting date of the face-to-face course week you will be given a password that will allow you to enter BlackBoard (BB), an E-Learning platform which will contain all necessary information pertinent to the course.

Congrex® (Sweden) will instruct you how to pay the course fee.

Student voices

"Good balance between theory and practical exercises."

"The quality and the content of the lectures were excellent and met what I expected when I applied for the programme."

"The teachers are experts in their field."

"Very good quality, rich content of presentations, very good contact with the teachers."

SafeSciMET course fees and discounts

Employment	€ per course
Industrial	2500
Governmental	1500
Academic	750
New Member State	400

- Multiple participants from the same organization:**
2nd participant: 20% reduction; 3rd and following participants: 30% reduction.
- Multiple courses for the same participant:**
3 – 5 courses: 20% off each; 6 – 9 courses 30% off each, 10 or more courses 40% off each.
- Entire SafeSciMET MASS:**
For the entire MSc curriculum covering 15 out of 20 courses, 50% reduction is offered, if signed up before completion of the first 3 courses.

d) **Participants from EFPIA SafeSciMET partner:**

SafeSciMET is supported financially by EU and members of European Federation of Pharmaceutical Industries and Associations (EFPIA) under the umbrella of Innovative Medicines Initiative (IMI).

Participants from EFPIA SafeSciMET partners are not eligible for discounts, until their respective in kind contribution quota are reached.

Course fees for the SafeSciMET courses of participants employed by those EFPIA companies should be paid as instructed on this page.

The EFPIA companies will be continuously informed on their financial contribution by the fees paid.

e) **Cancellations policy:**

Cancellation of a pre-registered student is possible, upon written notice until 2 weeks in advance. Before that date the course fee will be refunded except for an administrative fee of EUR 75.- After that date, no refunds can be made for cancellations. Substitutions may be made at any time provided that the entrance level requirements are fulfilled. Use info@safescimet.eu for cancellation.

Programme overview

The course modules in the SafeSciMET programme are clustered within 5 separate domains. Each domain deals with one or more specialised topics and contains from two to six individual courses. They are:

- DOMAIN 1** Drug Discovery and Development
- DOMAIN 2** Pharmaceutical Aspects of Drug Safety
- DOMAIN 3** Adverse Drug Reactions / Predictive Toxicology / 3R's
- DOMAIN 4** Non-Clinical Safety
- DOMAIN 5** Clinical Safety

The individual courses are introduced in detail on the following pages. Dates, locations and topics for all courses can also always be obtained from our website.

Please visit www.safescimet.eu for details of the full course programme and confirmation of course dates.

Fact file

Course dates and locations

More and the most up-to-date information can always be obtained from our website: www.safescimet.eu
Please check this site before registration.

Typical entry requirements

The applicants will normally possess an MSc degree in a Life Science discipline or equivalent. In addition, applicants are expected to have at least one year work experience in a related discipline.

Course duration and assessment

Each course will consist of one week of on-site face-to-face training concluded by an exam and followed by an individual home assignment. The teachers are experts from academia, regulatory agencies and industry at an academic centre or industry location. The courses will include translationally oriented case studies provided by the experts.

Maximum number of participants per course

In order to maximize interaction of participants with the experts the maximum number of participants is restricted to 20.

DOMAIN I – Drug Discovery and Development

Course I.1 Drug Discovery and Development | 5 – 9 November 2012, Amsterdam, The Netherlands

Course objectives

Drug development processes from discovery to approval and marketing require the interaction of numerous disciplines and specialists with the ability to understand the connections between all stages. This introductory course will provide the participants with a comprehensive overview of the steps involved in drug development with special emphasis on drug safety. The lectures cover the basic steps of discovering and developing new medicines, the clinical development phase, regulatory matters, safety pharmacology and marketing management processes. The students will learn to identify critical factors and bottlenecks during the overall development process and how the various disciplines are integrated. By the end of the course, the students have the appropriate knowledge to outline the key concepts in drug development processes and to communicate them in professional terms. Thus, this module provides an ideal background for the more detailed and specific courses that make up the rest of the programme.

Key subjects covered by this course

- Roadmap to drug discovery and development
- Target evaluation and validation
- Lead optimization and synthesis
- Pharmacology and animal biology
- Pharmacokinetics, safety pharmacology and toxicology
- Development of biologics
- Pharmaceutics
- Translational medicine
- Clinical development and safety
- Regulatory process
- Health economics, IP and marketing

Course I.2 Drug Safety of Stem Cells and other Novel Therapeutics November 2012, Liverpool, UK

Course objectives

This course will introduce the emerging area of the safety science of the therapeutic application of stem cells, and will address all the key issues that need to be considered by developers of these therapies, including academics and the pharmaceutical/biotech industry, as well as the important area of regulation. Other new areas of therapy will also be considered, such as genetically-engineered cells. The use of stem cells in the screening of conventional drugs for efficacy and particularly safety will also be investigated. UK and European leaders in these fields, from Industry, Academia and the Regulatory Agencies, will contribute teaching sessions in a small, informal and interactive learning environment.

Key subjects covered by this course

- Therapeutic treatment of diseases via :
 - Adult and embryonal stem cells
 - Induced pluripotent stem cells (iPS)
 - Genetically engineered cells
 - siRNA / RNAi
 - Exon-skipping oligonucleotides
- Basic biology of stem cells and molecular therapies
- Drug safety aspects of novel therapeutic approaches – the key issues
- Regulatory requirements for adult and embryonal stem cells and novel therapies
- Use of stem cells in safety assessment

DOMAIN 2 – Pharmaceutical Aspects of Drug Safety

Course 2.1 Pharmaceuticals and Safety | 25 February – 1 March 2013, Uppsala, Sweden

Course objectives

Pharmaceutics is the discipline that deals with the design and manufacturing of the drug product. Drugs are rarely used only as a pure substance but instead are used in the form of a medicine, i.e. a formulated preparation or a dosage form. This course aims to introduce the various aspects of the administration routes (e.g. oral, nasal, transdermal), the formulation (e.g. liquid, solid, powder) and the manufacturing of medicines. Besides a broad overview about basic concepts of pharmaceutics in general students will acquire specific knowledge of excipients, dosage forms and their physical constraints as well as understand the functions of the several pharmaceutical packagings and devices used for medication. The participants will receive knowledge about methods and procedures used in the quality control of medicines, both in development and manufacturing. Lastly, standards of Good Manufacturing Practice and regulatory aspects will be part of the course.

Key subjects covered by this course

- Administration routes and drug formulation
- General pharmaceutics
- Excipients and dosage forms
- Packaging and devices
- Unit operations and manufacturing
- Microbiological aspects, clean room and sterilization
- Quality systems and GMP Regulatory aspects, harmonization between major market regions

Course 2.2 Regulatory Requirements and Guidelines | 18 – 22 March 2013, Lisbon, Portugal

Course objectives

Drug development and production underlies laws and regulations to secure protection of human, test animals and the environment. Guidelines provide advice to applicants on specific scientific issues reflecting a harmonized EU approach to fulfil the pharmaceutical legislation. This course will provide participants with a comprehensive overview of the required *in vitro* and *in vivo* nonclinical studies, strategies for the development and risk assessment of new pharmaceuticals. Special emphasis is put on the translational science methodologies for the transfer into humans of nonclinical data generated from integrated *in vitro* and animal models. The study needs for specific patient populations (pregnant women, paediatric, geriatric) are also part of this course's curriculum. At course completion students will have knowledge of the type and rationale of the tests required and will be able to determine which data need to be generated in each situation and for which stage of the development.

Key subjects covered by this course

- Drug development process and regulatory requirements
- EU & ICH guidelines and the Common Technical Document
- ICH guideline on nonclinical safety
- Extrapolation of animal data, human translation and risk assessment
- Species selection for nonclinical studies and 3Rs principles
- Reproductive toxicity testing, pregnancy labeling
- Testing genotoxic and carcinogenic potential
- First in Human studies and regulatory guidelines for safe dose estimation
- Nonclinical safety testing of biologics
- Environmental risk of pharmaceuticals

Course 2.3 Pharmacokinetics and Pharmacodynamics

8 – 12 April 2013, Uppsala, Sweden

Course objectives

Investigating and understanding the physiological pathways of absorption, distribution, metabolism and excretion (ADME) of a drug candidate is crucial in drug discovery and development. The course will give scientists who work in drug discovery and development, but also scientists and decision makers not directly involved in these fields, a working knowledge of PK/TK and PD/TD principles. Students will receive knowledge of the mechanisms of drug transport and metabolism in plasma and tissues, learn about half-life determination, concentration effects and clearance rates. A part of the lectures deals with *in vitro* testing and the scaling from animal models to human. Special emphasis is put on safety margins, inter-individual variance, counteracting processes and drug-drug interactions. Case studies from current research provided by EFPIA partners aim to improve the practical understanding of PK/TK and PD/TD and their applications. Upon completion of the course, the participants will be able to understand, explain and apply the principles of PK/TK and PD/TD in pre-clinical and clinical drug development.

Key subjects covered by this course

- Basic pharmacokinetic and pharmacodynamic concepts
- Drug transport and metabolism
- *In vitro* and *in vivo* correlations and interspecific scaling
- Preclinical applications of ADME
- Concentration effect and concentration-toxicity relationships
- Causes of inter-individual variance in pharmacokinetics
- Principles and applications of PK/PD and TK/TD modeling and strategies in preclinical and clinical drug development



DOMAIN 3 – Adverse Drug Reactions/Predictive Toxicology/3R's

Course 3.1 Biochemical and Molecular Toxicology: Biotransformation, Bioactivation and Adverse Drug Reactions | 27 May – 31 May, Amsterdam, The Netherlands

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 this 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



Course 3.2 Cellular Toxicology/Predictive Toxicology | 24 – 28 June 2013, Leiden, The Netherlands

Course objectives

In drug development the non-specific interactions of drugs substances or their metabolites pose problems on the cellular level. Therefore there is a need of experts in pre-clinical safety who interpret and understand pre-clinical and clinical data, especially in terms of evaluating the toxicological profile of a candidate drug. It is important for safety scientist to have a broad overview and the ability to understand the connections between molecular events at the cellular level upon chemical exposure and the consequences for organ functioning. The course will provide participants with a comprehensive overview how cells deal with chemical stress at the molecular and cellular level and make them familiar with the fundamentals necessary to understand cellular mechanisms of adverse drug reactions. Special emphasis is put on the recognition that during drug development the involvement of specialist scientist is often required to achieve a multidisciplinary solution. Participant will receive knowledge about the major processes in cytotoxicity, become aware of technologies (use of stem cells, bioimaging, in silico modelling) to evaluate cellular stress responses and cytotoxic reactions and will be able to extrapolate the knowledge from the cellular level to the organ and human level.

Key subjects covered by this course

- Consequences of cell injury and biochemical mechanisms
- Cellular defence mechanisms against cell stress
- Molecular mechanisms of cellular senescence, autophagy or cell death
- Intra- and intercellular signalling and mechanisms of cell injury
- Translation of cell injury to in vivo models and the clinic
- Molecular mechanisms of idiosyncratic drug toxicities and ADR
- Stem cell technology and applications in understanding mechanisms of toxicity
- Functional genomic technologies



Course 3.3 Organ/Systems Toxicology | 30 September – 4 October 2013, Constance, Germany

Course objectives

During drug development the evaluation of the toxicity potential of a new compound to the different organ systems plays a crucial role in drug safety concepts. This course will provide participants with a comprehensive overview of organ specific toxicity and familiarize them with fundamental toxicity mechanisms. Emphasis will be given to organ function, anatomical structures, physiological aspects and the site-specific toxicities of heart, immune system, renal system, liver and lung. Lectures will cover experimental design and statistics as well as include real case studies, regarding apical, pre-clinical and clinical endpoints in drug safety research. Participants will be able to identify critical points in drug development and recognize when and how specialists of the several fields involved (especially liver, kidney, cardiovascular) need to be involved in order to receive a multidisciplinary solution.

Key subjects covered by this course

- Physiology and function of main organ systems
- Acute, subchronic and chronic effects
- Apical, pre-clinical and clinical endpoints
- Mechanistic understanding of toxicity (molecular, biochemical and pathological level)
- Distinction between primary organ with subsequent systemic effects from *prima facie* systemic effects
- Extrapolation from animals to human
- Experimental design
- Principal requirements for the detection, robust analysis and evaluation of endpoints
- Statistical evaluation of endpoints and measure for extrapolation

Course 3.4 Reproductive Toxicology | 21 – 25 October 2013, Berlin, Germany

Course objectives

During embryo-fetal development xenobiotic substances can interfere with the “normal” development of the organism, while the effects and severity are dependent on the timing and developmental stage during which the exposure takes place. In contrast to other types of toxicity, interpretation of reproductive toxicity studies is more complicated and, due to the inclusion of a broad range of endpoints, requires a profound knowledge in order to detect any effects a new compound can have on mammalian reproduction. Additionally, it is essential to investigate and interpret these results in relation to all other pharmacological and toxicological data available. The reproductive toxicity of drugs is usually assessed with animal experiments, using the classical three “segment testing protocols”. The course will also present newer alternative methods in reproductive toxicity testing such as the “whole-embryo-culture” or the embryonic stem cell test. An additional part of the lectures will discuss the authority guidelines.

Key subjects covered by this course

- Morphology and physiology of the male and female reproductive tract
- Prenatal and postnatal development of mammalian organisms
- Standard testing for fertility impairment and developmental toxicity
- Developmental neurotoxicity / immunotoxicity
- Reproductive toxicity of selected drugs and workplace chemicals
- Relevance of maternal toxicity
- Pharmacokinetic issues in reproductive toxicology
- Endocrine disrupting chemicals
- Toxicogenomics in developmental toxicology
- Guidelines (ICH, OECD etc)

Course 3.5 Mutagenesis and Carcinogenesis | 18 – 22 November 2013, Vienna, Austria

Course objectives

The development of new chemical compounds holds the potential risk of harmful mutagenic and/or carcinogenic effects to humans. Minimising these risks during drug development requires appropriate experimentation and expert knowledge whose basic principles will be delivered with this course. Special emphasis will be given to the biology of cancer formation, the identification of mutagens and carcinogens and their modes of action on the cellular, biochemical and molecular level. *In silico* methods prediction as well as animal test systems and tissue culture assays for carcinogenicity testing will be presented. Furthermore, the importance of responsibly estimating dose-dependent probabilities of mutagenic/carcinogenic effects (risk assessment) and the risk-benefit evaluation will be discussed. In case studies, participants will review and assess safety data for mutagenic and carcinogenic compounds.

Key subjects covered by this course

- Overview on the biology of carcinogenesis
- principles of mutagenesis and carcinogenesis
- examples of the mutagenic/carcinogenic actions at the cellular, biochemical and molecular level
- experimental design for specific identification of mutagenic/carcinogenic compounds
- interpretation of dose-response curves
- extrapolation of animal findings and experimental data to human
- safety data reports, authority guidelines
- risk-benefit evaluation

Course 3.6 Safety Pharmacology | 25 – 29 November 2013, Liverpool, UK

Course objectives

Translational Safety Pharmacology is a dynamic science that embraces basic pharmacology, clinical pharmacology and toxicology. Translational safety pharmacologists support the discovery and development of novel therapeutics from low molecular weight chemicals to biologics, assisting in target identification to post-marketing pharmacovigilance. In order to assess the safety of a drug candidate state of the art approaches are necessary to analyse how compounds interact with the physiological systems. An integrated experimental design with core, supplemental and investigative studies forms the centre of safety management, considering the clinical route of administration and the relevant organ systems (i.e. cardiovascular, central nervous, respiratory, renal and gastrointestinal systems).

Key subjects covered by this course

- Organ-specific safety pharmacology: CNS, cardiovascular, respiratory, and other
- Use of integrated animal models in safety pharmacology
- Telemetric methods
- Role of the biological clock
- The preclinical regulatory dossier
- Safety pharmacology of biologics
- Emerging trends in safety pharmacology, including stem cells and biotherapeutics

DOMAIN 4 – Non-clinical safety assessment

Course 4.1 Non-Clinical Safety Assessment: Strategies, Ethics and Protocols

9 – 13 December 2013, Vienna, Austria

Course objectives

The development of new medicines underlies multiple regulatory and scientific aspects dealing with the safety assessment of a drug candidate during nonclinical testing. This course presents key lectures referring to the knowledge and understanding of the legal requirements and how safety science and toxicology fit into strategies, timelines and project plans of pre-clinical safety pharmacology. Emphasis is given to experimental designs, the relevance and predictability of animal models including the 3 Rs and ethical aspects. The course also covers the safety assessment requirements of special compounds classes (e.g. biologics, MABEL, stem cells) and special product classes (e.g. high risk products or veterinary medical products). Participants will acquire a comprehensive overview of nonclinical safety assessment focussing on strategies, protocols, experimental design and the role of ethic committees.

Key subjects covered by this course

- The role of nonclinical safety assessment in drug development
- *In vitro* and *in vivo* nonclinical study types
- Nonclinical safety strategies and principles of protocol design
- Safety implication of target choice
- Regulatory requirements behind nonclinical safety testing
- Investigative toxicology and pathology
- Experimental design and application of the 3Rs
- Translation from nonclinical to first in human studies
- Special approaches and special products
- The role of ethics committees

Course 4.2 Biomolecular Analysis: From Method Development to Clinic

13 – 17 January 2014, Amsterdam, The Netherlands

Course objectives

Integrated bioanalytics represent a variety of important methods to acquire reliable information about the state of a biological system, e.g. by analysing tissues, body fluids. Common used methods include gas chromatography, HPLC, capillary electrophoresis etc. and are important tools to follow the physiological course of a new compound during drug development and define the PK/PD profile of the drug candidate. This course deals with the application of bioanalytical methodology, with emphasis given to sample preparation, small molecule strategies and biopharmaceuticals. As compounds differ in their physico-chemical properties, appropriate analysis strategies are required for sample separation, pre-treatment, detection methodology and validation. Students will acquire the necessary knowledge to understand the most common methods applied and will be able to define the basic needs to develop, prepare and perform integrated biomolecular analyses, as well as to review and evaluate studies in the bioanalytic field.

Key subjects covered by this course

- Physico-chemical parameters at the basis of method development
- Bioanalytical strategies for small molecules: sampling, sample pretreatment, separation, detection, validation, and data handling
- General considerations in bioanalytical strategies for biopharmaceuticals
- PK/PD and biomarker assay formats
- Development of immunogenic assay strategies: background, assay strategies, predictive immunogenicity
- Integrated bioanalytical assay strategies
- Novel developments: therapeutic oligonucleotids, reactive drug metabolites, profiling of body fluids and metabolomics

Course 4.3 Predictive Cell Culture Systems | 3 – 7 February 2014, Halle, Germany

Course objectives

Cell culture systems are integral parts of standard *in vitro* test methods in research and development of new drugs covering the major toxicology pathways for preclinical safety evaluation to generate robust data in screening assays on a sound cost effect relationship. This course introduces the principles of cell culture systems as a tool to monitor homeostasis and early onset of functional imbalance leading to toxicity as well as their use and impact for drug development. Upon completing the course students will be able to evaluate the strengths and the limits of specific cell culture systems and to discriminate between biochemical and cellular assays, *in vitro* and *in vivo* tests for safety purposes. Recent developments and new biomarker and their ability to improve predictability regarding species differences and extrapolation to human will be discussed.

Key subjects covered by this course

- Limits and strengths of permanent versus primary cells
- Robust parameters to monitor cell functions
- Early cellular responses to stressors
- Test batteries for cytotoxicity and cellular dysfunction
- Competence to cope with oxidative/cellular stress
- Pathways of toxicity involving impairment of glutathione
- Search for drug targets versus drug safety using *in vitro* tests
- Use of '-omics' technologies to identify critical pathways of toxicity
- Requirements on cell culture systems for screening and high throughput techniques
- Alternative methods and regulatory requirements

Course 4.4 Toxicogenomics and Systems Toxicology | 10 – 14 March 2014, Leiden, The Netherlands

Course objectives

Toxicogenomics is the study of how drugs influence the actions of the genome. Systems toxicology integrates data generated from high throughput genomics, proteomics and metabolomics methodologies with bioinformatics in order to assess and predict adverse effects across multiple levels of biological complexity. Typical datasets usually have a high content data integration, therefore data integrity, storage, visualisation and presentation play a major role. This course deals with established as well as novel methods in toxicogenomics and systems toxicology research and their application in drug safety by introducing and comparing the principles of the various genomics and bioinformatics tools used. Students will gain understanding of the design of such studies, their statistical evaluation and the biological interpretation of the data, including cross-platform consistency and extrapolations from *in vitro* to *in vivo* and from animal to man. Emphasis is given to development, validation and use of relevant biomarkers in toxicology and early phase clinical development. Regulatory aspects relevant for toxicogenomics data and drug registration within the context of risk assessment are also covered.

Key subjects covered by this course

- Design of DNA-microarrays and microarray experiments, (phosphor-) proteomics
- Quality control, data pre-processing, normalisation and statistics
- High-throughput data visualisation and presentation
- Building biological networks and systems toxicology
- Functional genomics screening to identify biological networks
- Genetic susceptibility and inter-individual variation
- Predictive toxicology and biomarkers of adverse effects
- *In vitro* to *in vivo* translations and extrapolation from animal data to human
- Regulatory aspects, toxicogenomics data and drug registration
- Perspectives for future developments in toxicogenomics, systems toxicology and their applications in drug research

Course 4.5 Pathology Interpretation in Drug Development | 5 – 9 May 2014, Surrey, UK

Course objectives

The aim of this course is to introduce the principles of pathology, including the preparation, examination and interpretation of tissues from toxicity studies. In addition, the relevance of pathology findings in animal studies to clinical risk assessment will be addressed by consideration of pathological processes and common target organs, including the liver and cardiovascular system. Pathology forms an important part of the data used to characterize the hazard of new drugs in research and development. All those individuals involved in designing pre-clinical safety studies or in interpreting or using data from these studies, will benefit from a deeper understanding of pathology. The course is carefully designed to be of value to those with little pathology knowledge and also to those already working in this area. The course aims to provide attendees with the knowledge they need to integrate pathology data into risk assessments. In addition, many of the current hot topics in toxicological pathology will be included in the course.

Key subjects covered by this course

- Pathological processes and causes of cell injury. General pathology including acute and chronic inflammation
- Pathology of organ systems including the immune, cardiovascular, CNS, kidney, liver and respiratory system
- Disorders of tissue growth including neoplasia
- Introduction to toxicological pathology
- Integration of anatomic and clinical pathology
- Distinguishing spontaneous from test article-related lesions in toxicity studies
- Determining adverse versus non-adverse findings
- Interpretation and reporting of pathology, including data from carcinogenicity studies
- Extrapolation of animal data to human risk assessment
- Specialised techniques used in histology and electron microscopy including image analysis.



Course 4.6 *In silico* ADME and Predictive Toxicology | 19 – 23 May 2014, Copenhagen, Denmark

Course objectives

In silico methods, defined as experiments and compound testing performed via computer simulation, have become an important tool in drug discovery and in the development of medicines. Predictive *in silico* methods are getting considerably more reliable, they cover a broader spectrum of predictive endpoints and are getting easier to use also for non-specialists. Reliable predictive models may replace costly experiments and thereby contribute to a cost-reduction of the drug discovery and development process. This course will provide the participants with a comprehensive overview of *in silico* methods in drug discovery and development as well as where they can be used and what their strengths and limitations are. Additionally, students will get hands-on experience with several predictive *in silico* methods, e.g. web-based tools to predict simple ADME/Tox endpoints and purpose-developed software to predict more complex ADME/Tox endpoints.

Key subjects covered by this course

- Computational tools used in drug discovery and development, with focus on ADME/Tox
- Absorption and distribution from a PK point of view
- Critical analysis of experimental data
- Prediction of absorption and distribution
- Phase I and II metabolism – the Cytochrome P450 enzymes
- Prediction of metabolism,
- Prediction of site of metabolism
- Prediction of toxicity (e.g. genotoxicity, phospholipidosis, hERG etc)
- Genomic effects on metabolism and toxicity
- Different QSAR systems available



DOMAIN 5 – Clinical safety assessment

Course 5.1 Clinical Safety: Pre-Approval | 2 – 6 June, Basel, Switzerland

Course objectives

The clinical phase during drug development requires translation of safety information from previous pre-clinical trials of the new compound. Signal detection depends on the understanding of mechanisms of action, preclinical safety findings including histopathology and the monitoring of applicable baseline biomarkers. The translation of animal findings regarding toxicity levels and target organs to human has to ensure a safe *First Dose in Man* where appropriate risk mitigation strategies play major roles. Therefore the aim of this course is to introduce the principles of translational safety as a tool to bridge preclinical and clinical safety assessments as well as safety management throughout the clinical phase of drug development. Lecturers and students will discuss the strengths and limits of these approaches and will have insight into the overall strategy of clinical safety evaluation prior to drug approval. Case studies from the development of successful new drugs as well as from discontinued compounds are used to illustrate the process of developing safe medicines. Also regulatory requirements from the major target markets are presented and discussed. Upon completion of the course the students will have an overall understanding of integrated drug safety activities, how to approach safety margins during translation from animal to man and the benefit / risk assessment methodology used during drug development.

Key subjects covered by this course

- Integrated and translational drug safety
- Signal detection and biomarkers
- Clinical safety with organ focus on main target toxicities: liver, kidney, cardiovascular system, immune system, neurotoxicity
- Clinical trials methodology and safety issues
- Integrated safety management planning
- Population selection, epidemiological and statistical aspects
- Risk benefit assessment, stratification and management
- Risk evaluation, mitigation strategies



Course 5.2 Clinical Safety: Post-Approval | 23 – 27 June 2014, Paris, France

Course objectives

This course will provide participants with an overview of the current knowledge on the clinical assessment and follow-up of drug safety post-approval and human safety.

Drug safety in human patients is the ultimate goal of drug safety scientists. Because limitations of patient populations studied during drug development and uncertainties related to potential drug-drug interactions or rare or idiosyncratic adverse reactions, it is important to pay careful attention to human safety to achieve a better understanding of the safety of drugs on the market used in a wider patient population, for long treatment duration and on various co-medication compared to the population included in the approval package. Human safety plays an important role for assessing drug safety profile in daily conditions of use, which includes adherence to recommended modalities of therapeutic use (pharmacovigilance) as well as exposures deriving from accidental or intentional acute poisonings (clinical toxicology and toxicovigilance), misuse or abuse of therapeutic agents (pharmacodependence) or unintended indications. Aspects of occupational exposure to active ingredients used in the manufacture of therapeutic agents (occupational toxicology) are also covered.

Key subjects covered by this course

- Modalities of detection, analysis and validation of drug-induced adverse events (pharmacovigilance)
- Pharmacoepidemiology as a tool for the identification and study of drug-induced adverse events
- Diagnosis and management of acute drug poisonings
- Risk minimization activities in the post-marketing phase
- Medication errors, assessment of drug abuse and misuse
- Occupational safety in workers exposed to active drug ingredients
- Post-approval safety commitments
- Legal, societal and economic aspects of adverse drug reactions
- Statistical evaluation of endpoints and measure for extrapolation



Course 5.3 Stratification: Pharmacogenetics and Drug Safety
25 – 29 August 2014, Stockholm, Sweden

Course objectives

Pharmacogenetics is rapidly growing partly as a result of the very rapid development in techniques for studies of the human genome and genome function. The aim is e.g. to find pharmacogenetic biomarkers which can predict drug response and drug toxicity. In addition, drugs aimed for genetically defined populations have become a reality.

Knowledge about drug action requires information about the involvement of polymorphic genes encoding e.g. drug metabolising enzymes, drug transporters, drug targets and human leukocyte antigens. Pharmacogenetics is now an integrated part in drug development. Already today we know about specific genomic biomarkers that effectively predict ADRs and this development is expected to continue in the future. The regulatory agencies now require pharmacogenomic aspects to be integrated into all different phases of drug development. Pharmacogenetic knowledge can also help to identify novel drug targets as well as to understand the bases for interindividual variation in drug response. In addition, there are examples where drugs have been rescued based on novel pharmacogenetic information.

Key subjects covered by this course

- Human genome and web accessible databases
- Methods to identify mutations and to study their functionality
- Clinically important genetic polymorphism of drug metabolizing enzymes
- Clinically important genetic polymorphism of drug transporters
- Pharmacogenetics of importance for therapy of different types of diseases
- Association between certain HLA alleles and adverse drug reactions
- Useful pharmacogenomic biomarkers for prediction of adverse reactions
- Regulatory guidelines for pharmacogenetics in drug development
- Ethical issues in pharmacogenetics and the use of material from biobanks
- Personalized medicine in the future



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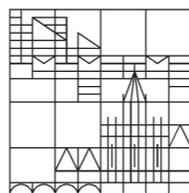
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