Syllabus 2010

The European Training Syllabus for Pharmaceutical Medicine /

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1. Discovery of Medicines

1.1 Strategy and organisation of research including collaborative approaches e.g. with academia

1.2 Disease models; target identification, validation and selection

1.3 Receptor-based approaches: agonists, antagonists, enzyme inhibitors, genomics, proteomics

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1.4 The principle steps in discovering, modifying, assessing and patenting new chemical and biological compounds

1.5 Other therapeutic approaches e.g. herbal and other natural products, drug-coupled devices and advanced therapies

1.6 Lead optimisation and candidate compound selection for further development

1.7 *In vitro* and *in vivo* testing of new compounds

1.8 Principles of translational medicine

1.9 Relationship between animal and human pharmacology, molecular biology and physiology e.g. biomarkers, functional imaging, modeling and simulation

2. Development of Medicines: Planning

2.1 The elements and functions necessary in the integrated development of a new medicine at a corporate and international level

2.2 Quality management

2.3 Project management techniques: drug development plan, project teams, tools and decision-making from target product profile (TPP) and target product claims (TPC) to registration dossier submission

2.4 Programme planning in special cases e.g. women, elderly, paediatrics, orphan drugs

2.5 Programmes in developing countries

2.6 R&D portfolio planning including in- and out-licensing of medicines (business development)

2.7 Resource planning: budgeting and cost control

3. Non-Clinical Testing

3.1 Pathophysiology- and molecular biology-based pharmacology

3.2 Differences in non-clinical safety and toxicity packages between small molecules and biological

3.3 The fundamental differences and similarities between the pharmacology and toxicology of compounds and their metabolites in animals and man, and their qualitative and quantitative assessment

3.4 The purpose of descriptive and quantitative *in vitro* and *in vivo* testing

3.5 The choice of and the predictive value of these tests for acute, chronic, reproductive, genetic and immune toxicology, and carcinogenicity

3.6 Common mechanisms of damage to organs and their detection or elucidation

3.7 The scheduling of toxicology tests linked to development plans, to regulatory needs, to human and animal pharmacology, and to intended clinical use and route(s) of administration

3.8 The size, cost and administration of the toxicology programme, its data management, quality assurance and report writing

3.9 The regular review of toxicology, its inclusion into clinical trial protocols and investigator brochures, and the appropriate planning and correlation with the clinical evaluation of potential and observed toxicity in patients

3.10 Safety pharmacology; hypersensitivity

3.11 Toxicokinetics; *in vitro* and *in vivo* study of metabolism; ADME

4. Pharmaceutical Development

4.1 Pharmaceutical development of drug substance and drug product: formulations; manufacture and supply of materials; labelling and presentation; stability and storage; purity; compatibility; disposal, including biotechnology products

4.2 The economic primary production of new compounds and secondary production of research and market formulations

4.3 The choice of formulations depending upon the characteristics of the compound and the intended uses of the product

4.4 The principles of testing formulations for bioequivalence, stability, impurity and incompatibility leading to a final specification, including the development of biosimilar formulations

4.5 The concept of blinding: preparing matching placebo and competitor products

4.6 Planning clinical trials supply requirements; packaging and labelling of clinical trial supplies (including stability and storage requirements); distributing supplies and disposing of remaining stocks

5. Exploratory Development (Molecule to Proof-of-Concept)

5.1 Intended therapeutic indications, biomarkers, efficacy end-points and criteria for ‘go’, ‘no-go’ decisions

5.2 Assessment of non-clinical data and risk as prerequisites before administration to man

5.3 Exploratory phase 0 trials

5.4 The early clinical development plan: the objectives, design, conduct and analysis of early exploratory development studies; modelling and simulation; tolerability, metabolism, pharmacokinetics, pharmacodynamics and safety in man; problems of participant’s safety in the concept of blinding

5.5 Pharmacokinetics, ADME and pharmacokinetic / pharmacodynamic models

5.6 Concepts of half-life, volume of distribution, clearance

5.7 Bioavailability and bioequivalence

5.8 Extrinsic and intrinsic factors

5.9 Population pharmacokinetics

5.10 Pharmacogenetics / pharmacogenomics

5.11 Applicability of pharmacokinetics to dosage regimen and study design

5.12 First administration to patients: principles of proof-of-concept and dose-finding studies

5.13 Impact of results on planned therapeutic indications, on predicted dosage schedule, on additionally required animal toxicology and on drug delivery concepts / forms

6. Confirmatory Development: Strategies

6.1 Final definition of therapeutic indications, categories of patients, delivery system(s), dosage forms and dosage regimens

6.2 Planning and global coordination / harmonisation of pre-licensing and post-licensing clinical trial programmes; use of non-clinical and existing clinical trial data

6.3 Estimated treatment population; clinical trial supplies and costs up to registration

6.4 Decision points, schedules and resources required for a confirmatory clinical development plan (CDP)

6.5 Life-cycle management planning: extension of therapeutic claims, new formulations, new dosage schedules by peri-marketing trials, post-marketing (surveillance) studies and quality of life measures

6.6 Regulatory review of existing and emerging research results

7. Clinical Trials

7.1 Choice of trial design, of placebo and of other comparators, of patient populations, of sample size, of locations, of randomisation, of end-points and of statistical analysis

7.2 New trial designs e.g. adaptive design

7.3 Non-interventional / observational study design

7.4 Principles of Good Clinical Practice and procedures applied in all stages of the clinical trial process to ensure subject protection, scientific validity and safety

7.5 Investigator Brochure: content, review and maintenance

7.6 Protocol preparation and review

7.7 Feasibility and investigator recruitment

7.8 Pre-study visits and investigator meetings; investigator training

7.9 Project management including resources; vendors and budget

7.10 Contractual arrangements with investigators and contract research organisations, including publication rights

7.11 Clinical trial registries

7.12 Investigative site management

7.13 Within-trial decisions e.g. code-breaking, interim analysis, premature termination

7.14 Study medication handling and drug accountability

7.15 Adverse event assessment and reporting; emergency coverage

7.16 Monitoring and source document verification

7.17 Trial master file (TMF)

7.18 Quality management system; SOPs; quality assurance and quality control; independent audits; inspections

7.19 Clinical trial report

8. Ethics and Legal Issues

8.1 Ethical issues in biomedical research and pharmaceutical medicine

8.2 Ethics: principles, history including Declaration of Helsinki, Directive 2001/20/EC, ethical review, informed consent, safety and human dignity of research subjects

8.3 Protection of research subjects, minimising risk including site qualification assessment

8.4 Ethical aspects in research questions and study designs for first-in-human to post marketing and epidemiological studies, including placebo and comparator choice

8.5 Conflict of interest and equipoise

8.6 Ethical aspects of subject contact and recruitment

8.7 Ethical issues of reimbursement, compensation and inducement

8.8 Risks, benefits and burden of study participation

8.9 The informed consent process

8.10 Privacy, confidentiality and data protection

8.11 Indemnity and insurance for participants, investigators, institutions; complaint procedures

8.12 Ethical aspects of study follow-on

8.13 Ethical aspects of taking trial samples for genomic and related analyses

8.14 Ethical aspects of clinical trials in vulnerable populations

8.15 Ethical aspects of advanced therapy medicinal products

8.16 Ethical aspects of clinical trials in third world and emerging countries

8.17 Fraud and misconduct in biomedical research and clinical development

9. Data Management and Statistics

9.1 Options for data collection (manual and electronic) and standardisation

9.2 Case report form (CRF) design and review

9.3 Creation, maintenance and security of databases, software validation and archiving

9.4 From source document to CRF completion, CRF review and corrections, data entry, query generation and resolution, coding of adverse events, database lock

9.5 The purpose and fundamentals of statistics

9.6 Role and responsibilities of the statistician

9.7 The statistical analysis plan

9.8 Trial design: pre-trial decisions and specifications; risk factors; confounding variables

9.9 Hypothesis testing: the null hypothesis, Type I and Type II error, significance, power

9.10 Sample size calculation

9.11 Minimising bias

9.12 Types of data and standardisation of measurement

9.13 Patient-reported outcomes e.g. diaries; quality of life measures

9.14 Statistical analysis of efficacy end-points and of safety

9.15 Interim analysis

9.16 Paired and non-paired tests, parametric and non-parametric tests, confidence limits

9.17 Handling of rating and visual analogue scales, patient diaries and laboratory values

9.18 Handling of missing data

9.19 Sensitivity and specificity of tests

9.20 True and apparent incidence and prevalence

9.21 Interpretation of analyses; assessment of violations, withdrawals, errors, bias

9.22 Statistical principles and issues in statistical report writing: data manipulation, transformation and merging; preparation of the statistical report

9.23 Clinical interpretation of trial results

9.24 Dealing with confounding factors and bias

9.25 Critical review of publications

10. Regulatory Affairs

10.1 Background to and general principles of medicines regulation

10.2 Philosophy of regulatory oversight; practical input of international bodies e.g. WHO, WMA, CIOMS and national agencies

10.3 The evolution of control mechanisms; differences between agencies

10.4 Activities and contribution of International Conference on Harmonisation (ICH)

10.5 Good Manufacturing Practices; Good Laboratory Practices; Good Clinical Practices

10.6 Integration of regulatory affairs into pre- and post-marketing; planning and review of product strategy

10.7 The approval, appeals and referrals processes in Europe; aspects of confidentiality, transparency and updating; maintaining Marketing Authorisations

10.8 Orphan drugs, paediatrics, advanced therapies, generics and biosimilars

10.9 Regulatory management systems in Europe, US, Japan, ROW and local special regulatory requirements

10.10 Clinical Trials regulations; EU Directives and Guidances and their diversity in national implementation, CTA including IMPD substantial amendments. Clinical trial regulations in other regions e.g. the US IND process

10.11 Common Technical Document (CTD and eCTD);Overviews

10.12 Aggregate clinical trial report reviews, including annual reports and Common Technical Document (CTD) summaries

10.13 The preparation and submission of marketing applications in major countries (MAA, NDA, JNDA, CNDA)

10.14 Product Information regulation: Summary of Product Characteristics; Package Insert; Patient Information Leaflets; Prescribing Information

10.15 Advertising and promotion regulation: promotional material

10.16 Prescription-only and over-the-counter medicines; switches

10.17 Provisions for and use of unlicensed medicines

10.18 Product defects and recall

10.19 Medical device regulations

10.20 Pharmacopoeias

10.21 Risk management: Risk Management Plans (RMPs) in the EU; Risk Evaluation and Mitigation Strategies (REMS) in the USA

10.22 Safety Specification

10.23 Direct Healthcare Professional Communication

10.24 Product withdrawal procedures

10.25 Drug abuse and dependence

10.26 Off-label use and misuse

11. Drug Safety, Pharmacovigilance and Pharmacoepidemiology

11.1 The role of the pharmaceutical professional in drug safety and pharmacovigilance

11.2 Assessment and classification of adverse events (AEs), adverse drug reactions (ADRs), Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs); evidence for association and causality

11.3 The concept of benefit / risk assessment, determination of causal relationship between the medicinal product and the adverse event

11.4 Collection of adverse events in clinical trials

11.5 Role of sponsors and investigators in reporting; regulatory requirements

11.6 Predisposing factors in health and disease

11.7 Spontaneous reporting post-marketing

11.8 Dosage, accumulation, medication errors and interactions

11.9 Drug adherence / compliance

11.10 Periodic Safety Update Reports

11.11 Pharmacoepidemiology

11.12 Main sources of epidemiological pharmacovigilance information

11.13 Signal detection, interpretation and management

11.14 Post-authorisation safety studies

11.15 Post-authorisation risk management including issue and crisis management

11.16 Risk communication

12. Information, Promotion and Education

12.1 Information to patients and patient organisations, prescribing and compliance

12.2 Product Information content and preparation: Summary of Product Characteristics; Package Insert; Patient Information Leaflets; Prescribing Information

12.3 Product support and promotion

12.4 Codes of conduct: promotional policy and procedures; Good Promotional Practice

12.5 Advertising: claims, ethics, control and approval

12.6 Publication strategy

12.7 Sales representative training: material and aids

12.8 Educational meetings; sponsored meetings and sponsored publications

13. Economics of Healthcare

13.1 Principles of healthcare economics; principles of justice and equity in healthcare economics

13.2 Principles of pharmacoeconomics

13.3 Evidence Based Medicine; outcomes research

13.4 Quality of Life, concept and measurement instruments

13.5 Principles and practice of marketing; market structure and competition; market analysis, pricing and reimbursement strategies; national and local formularies

13.6 Medical marketing and market access

13.7 Measurement of healthcare efficiency, governmental policy and third party reimbursement

13.8 Economics of industry: competition, licensing, co-marketing

13.9 Financial control, return on investment, fixed assets, budgeting, accounting, profitability

13.10 Generics and biosimilars, parallel imports, OTC; switching strategies

13.11 Health Technology Assessment (HTA) including meta-analysis and systematic review; health economics evaluation studies

14. Therapeutics

14.1 Major therapeutic areas and areas of unmet medical need, including rare diseases

14.2 Major drug classes, including small molecules, biologicals, advanced therapies: mode of action, use, safety, benefit-risk balance

14.3 Gene therapy, somatic cell therapy, tissue, medical devices, device-drug combinations, vaccines: mode of action, use, safety, benefit-risk balance

14.4 Therapy-related diagnostics

14.5 Prescribing for particular populations e.g. children, elderly, pregnant and breast-feeding women, patients with renal or hepatic impairment

14.6 Drug interactions

14.7 Controlled drugs, drug abuse and drug dependence

14.8 Overdose and treatment of poisoning

14.9 Therapeutic drug monitoring