

PharmaTrain Syllabus 2018

Pharmaceutical Medicine / Medicines Development Science

Jointly developed by



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1. Discovery of Medicines

- 1.1 Strategy and organisation of research including collaborative approaches with academia and small- and medium-sized enterprises; in- and out-licensing, medical due diligence; intellectual property
- 1.2 Unmet medical need; target identification and validation
- 1.3 Receptor-based approaches (agonists and antagonists), enzyme inhibitors; genomics, proteomics, metabolomics

- 1.4 Other therapeutic approaches: natural products, drug-coupled devices, advanced therapies e.g. gene therapy, cell therapies, tissue engineering
- 1.5 Hit-to-lead, lead optimisation and candidate compound selection for further development
- 1.6 *In silico*, *in vitro* and *in vivo* testing of new compounds
- 1.7 Principles of translational medicine
- 1.8 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 planning
- 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 and life-cycle management
- 2.4 Programme-planning in special populations e.g. elderly, children, people with rare diseases, incapacitated people
- 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
- 2.8 Corporate finance relevant to medicines development: financial control, return on investment, fixed assets, budgeting, accounting, profitability

3. Non-Clinical Testing

- 3.1 Use of *in silico*, animal- and cell-based models of disease mechanisms to study the pharmacology of a new drug
- 3.2 Differences in non-clinical safety and toxicity packages between small molecules, biological medicines, advanced therapies

- 3.3 The differences and similarities between the pharmacology and toxicology of compounds and their metabolites in animals, humans and cell preparations that provide qualitative and quantitative assessment through: genotoxicity, general toxicity, toxicokinetics, pharmacokinetics, drug metabolism, safety pharmacology, immunotoxicity, reproductive toxicity, carcinogenicity; duration of studies to support clinical trials and marketing approval
- 3.4 The purpose of descriptive and quantitative *in silico*, *in vitro* and *in vivo* toxicity testing; the choice of appropriate tests for acute and chronic drug administration
- 3.5 The common mechanisms of drug-induced organ damage and dysfunction; detection and elucidation; pathological assessment e.g. structural staining and immunohistochemistry; functional assessment e.g. QTc interval testing, liver and lung function tests
- 3.6 The scheduling of toxicity tests linked to product development plans, regulatory needs, human and animal pharmacology, intended clinical use and route(s) of administration
- 3.7 The size, cost and administration of the toxicology programme, its data management, quality assurance and reporting
- 3.8 The regular review of toxicity, 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
- 3.9 Safety pharmacology including drug hypersensitivity of both small and large molecules
- 3.10 Toxicokinetics; *in vitro* and *in vivo* study of metabolism; administration, distribution, metabolism, elimination (ADME)
- 3.11 The non-clinical study of biological medicines, vaccines, advanced therapies e.g. gene therapy, cell therapies, tissue engineering
- 3.12 The non-clinical study of biopharmaceutical formulations

4. Pharmaceutical Development

- 4.1 Pharmaceutical development of drug substance and drug product, including biological medicines and advanced therapies: formulations; manufacture and supply of materials; labelling and presentation; stability and storage; purity; compatibility; disposal
- 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 *in vitro* and *in vivo* testing of formulations for bioequivalence, stability, impurity and incompatibility leading to a final specification, including formulations of follow-on drugs - generics, biosimilars
- 4.5 Planning clinical trial supply requirements; packaging and labelling of clinical trial supplies; stability and storage requirements; supply distribution; disposal of remaining stocks
- 4.6 Clinical trial supplies: preparing matching placebo and competitor products
- 4.7 Pharmacopoeias: role, use and hierarchy

5. Exploratory Development (Molecule to Proof of Concept)

- 5.1 Intended therapeutic indications, biomarkers for target engagement, efficacy and safety requirements, efficacy and safety end-points and criteria for 'go' / 'no-go' decisions for entry into humans and progression to Proof of Concept trials
- 5.2 Assessment of non-clinical data and the risk of hazards as prerequisites before administration to humans
- 5.3 Phase 0 studies: exploratory microdose and sub-therapeutic dose studies; the importance, limitations and uses of microdoses (ICH M3)
- 5.4 The early clinical development plan: exploratory development studies:
 - from First in Human to Proof of Concept
 - modelling and simulation
 - tolerability, metabolism, pharmacokinetics, pharmacodynamics, safety in humans
 - safety assessment in patient and healthy volunteer populations
 - dose escalating safety committees (membership and role)
 - special considerations for advanced therapies and drug-coupled devices
- 5.5 Pharmacokinetics, ADME, pharmacokinetic / pharmacodynamic models, including concepts of half-life, volume of distribution, clearance; intrinsic and extrinsic factors which affect the pharmacokinetics of an innovative medicinal product; dosage and accumulation, bioavailability, bioequivalence and population pharmacokinetics
- 5.6 Pharmacogenetics / pharmacogenomics
- 5.7 Starting dose and dose escalation plan for First in Human and early clinical studies, including applicability of pharmacokinetics to dosage regimen and study design in First in Human studies and subsequent Phase II and Phase III clinical trials
- 5.8 First in Human studies: patients and healthy volunteers; principles of Proof of Concept and dose-finding studies; biomarker qualification / validation for Proof of Concept studies

- 5.9 Impact of results on planned therapeutic indications, predicted dosage schedules and drug delivery concepts / formulations; additional animal toxicology requirements; reformulation studies; new pharmacology studies; risk prediction algorithms to assess safety risks and enable development of risk management approaches to be applied during continued development

6. Confirmatory Development

- 6.1 Options for the clinical development plan (CDP); asset risk assessment and mitigation; schedules and decision points for the confirmatory clinical development programme
- 6.2 Translation of the defined target product profile (TPP) into the confirmatory clinical development programme design; pivotal and other Phase III studies; selection of primary and secondary endpoints and comparators for Phase III clinical trials; final definition of therapeutic indications; risk minimisation measures for research participants
- 6.3 Choice of countries / regions to participate in confirmatory clinical trials; patient numbers and selection criteria; delivery systems; dosage forms; dosage regimens; clinical trial supplies - ensuring all these are appropriate for this stage of development
- 6.4 Planning and global coordination including alignment of pre-licensing and post-licensing clinical trial programmes; permitted use of competitor class data, non-clinical data and existing clinical trial data
- 6.5 Life-cycle management planning: label extension of therapeutic claims and new formulations
- 6.6 Obtaining and implementing feedback from regulatory agencies and / or health technology assessment bodies on emerging research results and development plans through scientific advice procedures; consulting with other external bodies on proposed development plans

7. Clinical Trials

- 7.1 Choice of trial design, considering: non-inferiority / superiority / other design; placebo / other comparators; patient populations; sample size; locations; randomisation; endpoints; statistical analysis
- 7.2 New trial designs and required technologies
- 7.3 Post-authorisation clinical development: Phase IV clinical trials; non-interventional / observational studies; Real World Evidence (RWE) generation; post-authorisation studies; patient group registries
- 7.4 Investigator Brochure: content, review and maintenance
- 7.5 Protocol development and amendments

- 7.6 Clinical trial feasibility and investigator recruitment; pre-study visits; investigator meetings and investigator training
- 7.7 Trial management including investigational site management and site qualification assessment
- 7.8 Contractual arrangements with investigators, academic institutions / hospitals, contract research organisations, site management organisations; publication rights
- 7.9 Clinical trial registries
- 7.10 Within-trial decisions e.g. code-breaking, interim analysis, data and safety monitoring committee (DSMC), premature termination
- 7.11 Study medication handling and drug accountability
- 7.12 Adverse event assessment and reporting; emergency cover
- 7.13 Monitoring and source document verification; evolution of clinical trial monitoring
- 7.14 Trial master file (TMF)
- 7.15 Quality management system; quality manual; standard operating procedures; quality assurance and quality control; independent audits; inspections
- 7.16 Reporting of clinical trial data: data sharing and open data, transparency, aggregate clinical trial report reviews, annual clinical trial reports
- 7.17 Consideration for special populations in clinical trials e.g. elderly, children, extreme ages e.g. preterm neonates, incapacitated people; clinical trials in rare diseases
- 7.18 Medical device and drug-coupled device trials

8. Ethics and Legal Issues

- 8.1 Ethics: principles, history including Declaration of Helsinki, Directive 2001/20/EC, ethical review, informed consent, safety and human dignity of research participants, role of ICH GCP and other Good Practices (GxPs)
- 8.2 Ethical issues in biomedical research and pharmaceutical medicine
- 8.3 Protection of research participants; sponsor and investigator responsibilities, in particular, to avoid conflicts of interest
- 8.4 Ethical aspects in research questions and study designs for First in Human to post-marketing and epidemiological studies, including scientific rationale, statistical

robustness, appropriate patient populations, comparators and choice of endpoints; ensuring equipoise in comparator clinical studies; consideration of conflicts of interest

- 8.5 Ethical aspects of methods of recruitment including database searches and advertising; participant contact; participant reimbursement
- 8.6 Informed consent process, including defining benefit-risk balance, requirements for study participation including for special populations e.g. elderly, children, emergency research, incapacitated people
- 8.7 Privacy, confidentiality, international standards for data protection and consensual dissemination of clinical trial data
- 8.8 Indemnity and insurance for participants, investigators and institutions; complaint procedures
- 8.9 Ethical aspects of clinical trial follow-on: continuation of study medication to study participants, pre-marketing authorisation, availability pre-reimbursement
- 8.10 Ethical aspects of trial samples for genomic and related analyses: scientific rationale, ethics and consequences of anonymisation; biobanks
- 8.11 Ethical aspects of clinical trials in special populations e.g. elderly, children, emergency research, incapacitated people
- 8.12 Ethical aspects of all stakeholders involved in research of advanced therapies e.g. gene therapy, cell therapies, tissue engineering
- 8.13 Ethical aspects of clinical trials in developing countries
- 8.14 Fraud and misconduct in biomedical research and clinical development

9. Data Management and Statistics

Statistical Aspects of Study Design

- 9.1 Fundamentals: randomisation, choice of endpoints, avoidance of bias, avoidance of missing data, sample size calculation
- 9.2 Interim analyses: efficacy, futility, harm
- 9.3 The design of dose-finding studies
- 9.4 Equivalence and non-inferiority trials: rationale, choice of margin
- 9.5 Adaptive designs: basic ideas including advantages, concerns, avoidance of statistical and operational bias

Data Management

- 9.6 Data collection: options, to include manual and electronic, including diaries
- 9.7 Case report form (CRF) design and completion; source data verification, query generation and resolution
- 9.8 Data processing: data entry, coding of adverse events, medical history and concomitant medications; identification of protocol violations and deviations
- 9.9 Databases: maintenance, security, standardisation, streamlining the processes; Clinical Data Interchange Standards Consortium (CDISC)

Statistical Methods for Analysis

- 9.10 Fundamentals: Null and alternative hypotheses, type I and type II errors, p-values, confidence intervals, power, analysis sets
- 9.11 Endpoints: endpoint types (continuous, binary / categorical, time-to-event, rating scales), data transformation, primary and secondary endpoints, dealing with multiplicity, evaluating equivalence and non-inferiority
- 9.12 Specific methodologies: simple statistical tests (parametric and non-parametric), Odds Ratios, Risk Ratios, Hazard Ratios, Kaplan-Meier curves, modelling to correct for baseline imbalances and to reduce variation
- 9.13 Evaluating homogeneity: Forest plots and subgroup evaluation, testing for interaction
- 9.14 Dealing with missing data through imputation
- 9.15 Bayesian statistics; basic ideas
- 9.16 Safety data: tables and graphs for the evaluation of adverse events, laboratory data and other data relating to safety
- 9.17 Diagnosis: sensitivity, specificity and introduction to Receiver Operating Characteristic (ROC) curves
- 9.18 Meta-analysis: distinction versus pooling, fixed and random effects models
- 9.19 Observational studies: matching to minimise bias

The Statistics Process

- 9.20 Content for the protocol statistical methods section and the Statistical Analysis Plan
- 9.21 Writing the Statistical Study Report and contributing to the Clinical Study Report and clinical publications; to include the clinical interpretation of statistical analyses
- 9.22 Critical review of publications

10. Regulatory Affairs

- 10.1 Background to and general principles of medicines regulation; evolution of control mechanisms; differences between agencies
- 10.2 Philosophy of regulatory oversight; practical input of international bodies e.g. World Health Organisation (WHO), World Medical Association (WMA), Council for International Organisations of Medical Sciences (CIOMS), and national agencies
- 10.3 Activities and contribution of International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
- 10.4 Good Practices relevant to medicines development e.g. Good Manufacturing Practice, Good Laboratory Practice, Good Clinical Practice, Good Clinical Laboratory Practice, Good Pharmacovigilance Practice
- 10.5 Integration of regulatory affairs into pre- and post-marketing; planning and review of product strategy
- 10.6 Regulatory processes in Europe for the evaluation and approval of new medicinal products; scientific advice; appeal and arbitration procedures; procedures for maintaining, varying and cancelling European Marketing Authorisations; referrals processes; confidentiality and transparency
- 10.7 Regulatory processes: rare diseases, children, advanced therapies
- 10.8 Regulatory processes: generics and biosimilars
- 10.9 Comparison of international regulatory systems: Europe, US, Japan, and the Rest of the World; local special regulatory requirements
- 10.10 European regulations and guidance for Clinical Trial Application (CTA), maintenance and completion; EU single submission portal; substantial protocol modifications; transparency; clinical trial regulations in Europe, US, Japan and the Rest of the World
- 10.11 Common Technical Document (CTD and eCTD); Clinical Overviews; Clinical Summaries
- 10.12 The preparation and submission of marketing applications in major countries e.g. Marketing Authorisation Application (MAA), New Drug Application (NDA), Japanese NDA, Canadian NDA
- 10.13 Product Information regulation: Summary of Product Characteristics; Package Insert; Patient Information Leaflets
- 10.14 Prescription-only and over-the-counter medicines; switches

- 10.15 Regulatory provisions for the use of unlicensed medicines
- 10.16 Product restriction, suspension and withdrawal procedures; product defects and recall
- 10.17 Medical device regulations
- 10.18 Regulation of natural products e.g. herbals, synbiotics, traditional remedies, Chinese medicines
- 10.19 Risk management: Risk Management Plan (EU); Risk Evaluation and Mitigation Strategies (USA); additional monitoring of authorised medicines e.g. inverted black triangle (EU), black box warning (USA)
- 10.20 Periodic Benefit Risk Evaluation Report (PBRER); Periodic Safety Update Report (PSUR); Development Safety Update Report (DSUR)
- 10.21 Regulation and procedures for early access to medicines
- 10.22 Falsified and counterfeit medicines
- 10.23 Post-authorisation safety studies; post-authorisation efficacy studies; investigator-initiated studies

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, Adverse Drug Reactions, Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions (SUSARs); evidence for association and causality
- 11.3 The concept of benefit-risk balance assessment
- 11.4 Collection of adverse events in clinical trials
- 11.5 The role of investigators, clinicians, study monitors, sponsors and manufacturers in the pre- and post-marketing phases to detect, assess and report adverse events and suspected adverse drug reactions; regulatory reporting requirements in the pre- and post-marketing phases; medical literature reports
- 11.6 Predisposing factors and the impact of pre-existing disease on the susceptibility for and severity of adverse events and how to minimise risk
- 11.7 Post-marketing spontaneous reporting

- 11.8 Reportable events: overdose, medication errors, off-label use, misuse and abuse, experience during pregnancy
- 11.9 Drug interactions
- 11.10 Pharmacoepidemiology
- 11.11 Main sources of epidemiological pharmacovigilance information
- 11.12 Signal detection, interpretation and management
- 11.13 Post-authorisation risk management including issue and crisis management
- 11.14 Risk communication

12. Information, Promotion and Education

- 12.1 Information and disclosure to patients and patient organizations; compliance in patient engagement activities
- 12.2 Non-promotional product support, medical information, direct healthcare professional communication (DHPC) and other non-promotional activities; pre-licence activities
- 12.3 Codes of conduct: promotional policy and procedures; Good Promotional Practice; pre-approval and post-approval activities; disclosure of transfers of value
- 12.4 Advertising: claims, prescribing information, media and digital methods, audiences, compliance, ethics, control and approval
- 12.5 Publication strategy for clinical trials and clinical research studies
- 12.6 Support of the development of clinical guidelines
- 12.7 Post-marketing studies
- 12.8 Educational meetings; sponsored meetings and sponsored publications
- 12.9 Characterising patient preferences used in health technology assessment dossiers or research e.g. discrete choice experiments (DCE), focus groups
- 12.10 Principles and practice of marketing; market structure and competition; market analysis

13 Economics of Healthcare, Health Economics and Pharmacoeconomics

- 13.1 Principles and methods of the economics of healthcare, health economics and pharmacoeconomics
- 13.2 Evidence-based medicine (EBM)
- 13.3 Health-related quality of life / patient-reported outcomes: concepts and methods of measurement.
- 13.4 Pricing and reimbursement strategies e.g. value-based pricing, reference pricing, risk-sharing schemes, advance budgetary notifications
- 13.5 Market access, national and local formularies
- 13.6 Measurement of healthcare efficiency: principles of international governmental policy and third-party reimbursement
- 13.7 Economics of industry: competition, licensing, co-marketing and life-cycle management to include generics, biosimilars, parallel imports and switching strategies
- 13.8 The appraisal of health-economic evidence, systematic reviews and meta-analyses, health technology assessment
- 13.9 Patient access to medicines: alternative funding routes for non-reimbursed products; preparing a simple economic impact model