Candidate Guide and Syllabus

Certificate in Human Pharmacology

Faculty of
Pharmaceutical
Medicine

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1 Summary

The Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the UK (FPM) established the 'Certificate in Human Pharmacology' (CHP) in 2008. The CHP is a part-time programme of courses and an examination intended for physicians and scientists in the pharmaceutical industry, academia and regulatory authorities who have an interest in early clinical drug development. The two residential courses cover exploratory development of investigational medicinal products (IMPs) including 'First-in-Man' studies and principles of pharmacology at an advanced level. The courses involve pre-course preparatory reading and post-course assignments which are assessed. At the end of the period of study, there is an examination. It is expected that trainees will take approximately 12 months to complete the CHP. This document outlines the objectives, curriculum, syllabus and courses comprising the CHP.

2 Objectives

The purpose of the CHP programme is to enable trainees:

- to attain a comprehensive knowledge of Phase I studies, with particular emphasis on the design, conduct and analysis of 'First-in-Human' and other early exploratory studies of IMPs conducted in healthy and patient volunteers. The primary end-points in such studies generally include tolerability, pharmacokinetics and evidence of drug effects on biomarkers of efficacy and safety;
- to gain up-to-date knowledge of the scientific basis of drug action.

3 Curriculum

The Certificate curriculum comprises:

- two five-day CHP training courses with associated assignments and assessments;
- an examination comprising one written paper.

Each of these elements is briefly described in the following paragraphs.

3.1 Courses and private study

There are two CHP courses:

1. Exploratory Drug Development – 40 contact hours (five days);
2. Drug Development Pharmacology – 40 contact hours (five days).

These courses, which are run at King's College London, involve:

- preparatory reading using recommended texts, guidelines, directives and other documents from regulatory and scientific sources;
- active participation in case studies and workshops as well as tutorial-style lectures;
- completion of assignments as private study and submission for assessment within a specified time.

Trainees are expected to supplement their learning on the formal courses with private study, conducting their own searches of appropriate literature. Assignments are assessed and must

be of a satisfactory standard. Assessments by course tutors are moderated by the FPM. The content, material and delivery of the courses are quality assured by the FPM. It should be noted that the courses are at an advanced level and are not appropriate for persons without a basic knowledge of Phase I or pharmacology.

3.2 Examination

The Certificate examination, which is run once per year, is prepared and conducted by a subcommittee of the FPM Board of Examiners. It comprises one written paper which is intended to test factual knowledge and ability to interpret data and apply knowledge to practical problems relating to any part of the syllabus. Topics of a strictly clinical nature are excluded.

The paper is as follows:

- Multiple Choice Question paper in True/False format. Each stem question has five completions. Candidates are required to indicate which are true and which false; any number may be true or false.

Please refer to FPM Examination Regulations and Appeal Procedures for further details.

4 Eligibility

Candidates eligible to enter the CHP programme are required to have a degree e.g. BSc in a relevant biological science, a BPharm or a medical degree. Applicants who do not have a basic knowledge of Phase I studies may be recommended to attend a basic course in Clinical Pharmacology prior to registering for the CHP.

5 Equal Opportunities

FPM is committed to promoting equal opportunity and eliminating discrimination in all areas of its activity. Equal opportunities monitoring will be undertaken and information obtained may be analysed to assess compliance with the policy. Information will be held confidentially and used for monitoring purposes only. Any reports will be anonymised to ensure that individuals cannot be identified.

6 Fees

The fee for trainees enrolling on the CHP programme is currently £1000, which covers administration of the programme and the examination. The fees for the two compulsory courses are paid directly to King's College London and are currently £1650 per course. Trainees must enrol with King's College to register for the courses. The fee does not include travel or accommodation expenses or the Certificate document if successful. Refer to *CHP Terms and Conditions* for more information on fees and the rules for non-attendance and refunds.

7 Syllabus

Science

1. Clinical Pharmacology and Therapeutics. Major therapeutic small molecule drug classes and their mechanisms of action. Monoclonal antibodies and other biologicals. Vaccines. Gene therapies. Factors affecting therapeutic outcome.

2. The molecular basis of drug action. Receptor pharmacology, signal transduction, second messengers, enzymes, regulatory proteins, transcription factors, cellular sites of drug action, ion channels. Agonists, partial agonists, antagonists, dose-concentration-response.

3. Integration of information. Sources and critical review of scientific literature; evaluation of benefit / risk based on preclinical / early clinical data.

Guidelines

4. Guidelines for human pharmacology studies. Content of guidelines concerning the conduct of non-patient and patient volunteer studies including the elderly and women (e.g ABPI Guidelines for Phase 1 clinical trials, Guideline on strategies to identify and mitigate risks for First in Human clinical trials with Investigational Medicinal Products, EMEA/CHMP/SWP/294648/2007)

Study Design

5. Principles of Study Design. Advantages and disadvantages of different types of study design; specific study designs for first administrations of single and multiple doses (including methods for selection of starting dose, dose increments, maximum doses, stopping rules, details of study conduct including interim reviews); drug interactions; bioequivalence and bioavailability; demographic factors; organ failure.

Study Facilities and Conduct

6. Facilities, Equipment and Personnel. Standards for clinical facilities; guidelines, resuscitation equipment; qualifications and experience of physicians, nursing staff and non clinical scientific staff; key issues in the organisation and administration of research units for the conduct of studies in healthy non-patient volunteers.

7. Selection of Non-Patient Volunteers.[#] Identification of the healthy volunteer; screening for significant conditions; laboratory testing; cardiorespiratory assessment; allergy risks; psychiatric assessment; screening for metabolic phenotype; detection of asymptomatic conditions; avoidance of multiple study participation; recruitment of volunteers; hazards of drugs of abuse; the issues surrounding studies in women of child bearing potential.

8. Studies in Patient Volunteers.[#] Facilities; types of study, issues specific to patient studies; selection of patient volunteers; avoidance of multiple study participation.

9. Clinical Conduct of Studies.[#] Responsibilities of the PI, other investigators, nursing staff and non clinical scientific staff; potential `hazards' of participation for volunteers; follow-up of volunteers; non-drug influences on study outcome, monitoring of safety including cardiorespiratory, laboratory, drug specific measurements.

10. Routes of Administration. The safety, scientific and technical issues relevant to different routes of administration including oral, parenteral, topical, inhaled and modified release.

PK, PD, Data Analysis, Presentation and Interpretation

11. Pharmacokinetics. Principles of PK and ADME, importance of pharmacogenetics, objectives of and issues to be considered in the design of PK studies, presentation and interpretation of data, principles and performance of different bioanalytical techniques.

12. Pharmacodynamics. Principles underlying use of biomarkers, PD measurements, surrogates for clinical endpoints, objectives of and issues to be considered in the design of PD studies, commonly used biomarkers and surrogates for desired and undesired effects in different therapeutic areas, application of imaging techniques in the assessment of drug action.

13. Proof of Concept. Definitions of Proof of Concept (PoC), Benefit / Risk Balance, Use of PK/PD.

14. Principles of Medical Statistics. Hypothesis testing and hypothesis generation; within- and between-subject variation; power calculations; data summarising and display.

Pharmaceuticals with Particular Requirements

15. Biopharmaceuticals. The specific issues relating to early development of biopharmaceuticals, biopharmaceutical manufacture and formulations, particular issues relating to agonists, extrapolation of animal data to man, cross reactivity, toxicological evaluation, early clinical evaluation, determination of starting dose and duration of effect.

16. Radioactive molecules. Radiation protection in biological research. The specific legal requirements, facilities and radiation protection measures relating to administration of radiopharmaceuticals for mass balance, imaging and other studies including requirements of the Administration of Radioactive Chemicals Advisory Committee.

17. Gene therapies. The specific issues relating to the introduction of genetic material into human somatic cells for therapeutic, prophylactic or diagnostic purposes e.g. genetically modified viral vectors, naked DNA injection and anti-sense techniques. Familiarity with Gene Therapy Advisory Committee guidelines.

Safety

18. Animal Safety Assessments for Initial Studies in Man. Design, conduct and interpretation of general and reproductive toxicology studies, genotoxicity and safety pharmacology, the use of preclinical pharmacological and pharmacokinetic assessments; principles of human risk assessment from animal toxicology studies; importance of toxicokinetics; inter-species scaling; differences between man and animals.

19. Adverse Events.[#] Methodology for collection, mechanisms, types of adverse events, drug allergy, the extent of variation in normality; principles of event attribution; actions required and influence of adverse events on drug development.

20. Management of Medical Emergencies.[#] Pre-trial interviews and screening procedures; up-to-date resuscitation procedures and guidelines; diagnosis and management of anaphylaxis and other severe allergic phenomena, cardiac arrhythmias, respiratory emergencies, syncope, convulsions and other neurotoxicity, dermatological adverse events; clinical pharmacology of drugs used in emergencies.

Quality

21. Quality of raw material and drug product. Identity of material, nature and quantity of impurities, stability, storage, certificates of analysis, role of the Qualified Person.

Regulatory, Ethical and Legal

22. Regulatory Requirements and Procedures for Phase I/II studies

23. Ethics Review. Principles of ethics review; ethical issues in non-therapeutic clinical research; guidelines for ethics committee composition and practice; principles of informed consent.

24. Indemnity and Negligence. Principles; types of indemnity; legal responsibilities; negligence, definition and avoidance.

25. Good Clinical Practice. Principles to ensure the validity of the data collected and the conclusions drawn; record keeping in clinical research; essential documents, responsibilities of the investigator, sponsor, monitor, regulatory authority, auditor; regulatory audit; fraud in clinical research.

26. Documentation. Summary of Data and Guidance for the Investigator section of Investigator's Brochure, protocols, clinical study reports, Clinical Trials Authorisation applications, Investigational Medicinal Product Dossiers.

[#] The above syllabus is common to the Diploma and Certificate in Human Pharmacology but trainees in the Certificate programme are not expected to have comprehensive knowledge of items marked #.

APPENDIX 1: Outline of Exploratory Drug development Course

Duration: 5 days

Pre-reading

Day 1

- Assessment of Preclinical Data before FIH – small molecules, biologicals
- Selecting the starting dose for FIH with case study

Day 2

- Preclinical assessment of biologics
- Study designs for FIH – small molecules, biologicals,
- Ethics of Healthy Volunteer studies – consent, compensation, ethical dilemmas
- Pharmacokinetics I – Principles, PK parameters, FIH studies

Day 3

- Pharmacokinetics 2 – Formulations, bioavailability, bioequivalence, routes
- Pharmacokinetics 3 – Distribution, Blood Brain Barrier
- Pharmacokinetics 4 – Metabolism, renal elimination, pharmacogenetics
- Pharmacokinetics 5 – Demographics and Disease, Population PK, PK/PD
- Drug interactions

Day 4

- Study designs for early phase oncology
- PK of biologicals
- Biomarkers and surrogates
- Use of Imaging
- Case Study

Day 5

- Gene Therapies
- Vaccines for infectious diseases and cancer,
- Regulatory affairs and Accreditation
- When things go wrong
- Pharmacogenomics and other factors affecting PK and PD

NB: Self assessments will be performed each day

Assignments

There will be 2 written assignments to be submitted within 8 weeks of completing the 5-day course. The precise detail of the assignments may vary from year to year but essentially, they are about design of specific clinical pharmacology studies.

APPENDIX 2: Outline of Drug Development Pharmacology Course

Pre-reading

Day 1

Fundamentals

- Pharmacological terms: affinity, potency, efficacy, selectivity, specificity
- Dose - Response
- The therapeutic window
- Agonists, antagonists, partial agonists, inverse agents, paradoxical pharmacology
- Chirality – relevance to drug action
- Targets for drug action: receptors, ion channels, enzymes, nucleus, other targets

Day 2

Targets for drug action

- Cell signalling- relevance to drug action e.g. cyclic nucleotides, phosphorylation of G-proteins, transcription factors
- Techniques for assessing drug action: radioligand binding, high throughput screening, cell culture, isolated tissues, whole animal studies,
- structure activity relationships

Evaluation of preclinical data before 'First-in-Human'

- Informed decision making
- The investigator's brochure

Day 3

Pharmaceutics

- Bioavailability,
- Routes of administration,
- Dosage forms and formulations

Drugs and the nervous system

- Autonomic pharmacology – parasympathetic and sympathetic agonists, nicotinic antagonists, anticholinesterases
- Pharmacology of drugs used for degenerative CNS disorders, in particular Parkinson's disease, Epilepsy, psychiatric disorders in particular depression, schizophrenia
- Use of animal models for discovery of CNS drugs and identification of side effects

Day 4

Drugs and the cardiovascular system

- Physiology of the vasculature
- Ischaemic heart disease
- Heart failure: ACE inhibitors and related drugs, diuretics, pre-load reduction, afterload reduction; inotropes
- Hypertension
- Hyperlipidaemia

Workshop on assessment of preclinical data and the Investigator's Brochure

Day 5

Immunopharmacology and biologics

- Inflammation - pathophysiology
- Rheumatoid arthritis
- Psoriasis
- Approaches to modifying the immune system: immunosuppressants, immunomodulators, immune stimulants with examples of mAbs for antiangiogenesis, EGFR, MHC molecules, vaccines, fusion proteins,

Drugs and the Respiratory System

- Asthma
- COPD
- Rhinitis
- Cough

Drugs and cancer

- Targets for new classes of cancer therapies

Assignments

There is one written assignment for this module comprising an essay on a particular aspect of clinical pharmacology requiring some in-depth scientific writing supported by references. A wide choice of subjects is available. The assignment must be submitted within 8 weeks of completing the 5-day course.