

Clinical Pharmacology

In this issue of the Faculty Newsletter, we have three articles about Clinical Pharmacology (CP). Each of the authors, two based in academia and one in industry, raises topics of importance: some long term sequelae of the TeGenero catastrophe, the increasing appreciation of the role of biomarkers, the interface between academia and industry, the British Pharmacological Society and training of pharmaceutical physicians in CP. Perhaps of greater significance than any individual topic is the fact that these articles raise awareness of CP, for it is ironic that the specialty has been going through a tough time in the last few years when its importance has never been greater. Both academic institutions and pharmaceutical companies have failed to invest in their CP departments, whose contribution in the past was far greater than the sum of the studies they performed. All doctors need to understand the pharmacological principles underlying therapeutics and all pharmaceutical physicians need to be able to interpret CP data relating to new drugs in development. Use of biomarkers and pharmacokinetics to establish dose-concentration-response relationships for desired and undesired effects and the application of this information to make early go / no-go decisions underscores the critical role of CP in drug development. Perhaps, with new initiatives, such as the proposal to establish a Diploma in Human Pharmacology under the auspices of the Faculty, we, and more importantly, patients can look forward to a renaissance of clinical pharmacology.

Dr John Posner

*Chairman,
FPM Clinical Pharmacology
Working Group*



The Faculty of Pharmaceutical Medicine

Newsletter
Issue 21 06/07



The interface between academic clinical pharmacology and industry

Academia and the pharmaceutical industry have had a long and mutually beneficial relationship. Academic researchers have often spent time working in industry, and in that way often had access to facilities and resources which – in the present difficult climate of research funding – they would not otherwise have done, and this has enabled some very important scientific questions to be addressed. On the other side, industry has frequently profited from the depth and breadth of scientific expertise present in our universities. Such relationships have both advanced scientific knowledge and allowed the development of novel therapeutic agents; obvious recent examples include the cannabinoids and the biological therapies.

On the other hand, the opportunities for academia and the industry to interact are limited by the very different nature both of what they do and of the drivers underlying their work. Academic clinical pharmacologists are a small but close-knit community, who meet at scientific meetings, in particular at the British Pharmacological Society (BPS); whereas pharmaceutical physicians attend other meetings, including those of the Faculty of Pharmaceutical Medicine. Thus, despite the commonality of their interests, often each side has very little idea of what the other is up to. We appreciate that Pharmaceutical Medicine covers a broad spectrum of jobs and that discrete departments of Clinical Pharmacology even within “Big Pharma” can be hard to identify. However, the principles of Clinical Pharmacology underpin virtually all the work for which a pharmaceutical physician could be responsible, not least at the stages of drug discovery and of safety monitoring. What we would like to see is an increased opportunity for dialogue between academic clinical pharmacology and industry, as this would benefit both sides. Although a number of pharmaceutical physicians do belong to the BPS, the majority do not. The BPS would appear to provide an ideal forum for such interaction to occur.

The BPS, including its Clinical Pharmacology Section, is the professional association for pharmacologists in the UK and is one of the leading pharmacological societies in the world. It is the primary UK learned society concerned with research into drugs and the way they work, and its members work in academia, industry and the health services. The Society covers the whole spectrum of pharmacology, including the laboratory, clinical and toxicological aspects. Its object is to promote and advance pharmacology, including clinical pharmacology. It holds several scientific meetings per year across the UK, and the Clinical Pharmacology section meets at the main annual meeting of the BPS, which occurs in December. At these meetings, symposia are held, usually relating to current and topical issues in pharmacology, clinical pharmacology and toxicology, and original papers are presented in all of these areas both orally and as posters. In addition, the meetings provide an excellent forum for meeting with colleagues and networking. Finally, the annual membership fee is currently only £63, which allows free registration for BPS meetings.

We would encourage Faculty members to consider joining the BPS and attending their meetings. Anyone who is interested and would like to find out more can contact Albert Ferro at albert.ferro@kcl.ac.uk. The BPS website can be found at: www.bps.ac.uk.

Dr Albert Ferro

*Senior Lecturer in Clinical Pharmacology, King's College London
Clinical Vice President, British Pharmacological Society*

Professor Nigel Baber

Visiting Fellow and Director of the Clinical Trials Co-ordination Centre, University of Hertfordshire

Understanding the requirements of the Clinical Pharmacology module of Pharmaceutical Medicine Specialty Training (PMST)

Specialty training in Pharmaceutical Medicine aims to “produce accredited Pharmaceutical Physicians who are equipped with specialist knowledge and comprehensive skills and competences to practise to the highest ethical and professional standards for the benefit and safety of patients and the public in the development and maintenance of medicines” (ref. PMST Curriculum, 2006).

This overarching objective encompasses professional standards of competency, care and conduct including the principles of Good Medical Practice and Good Pharmaceutical Medical Practice across a range of specialist areas relevant to pharmaceutical medicine.

Clinical Pharmacology is one of seven modular areas identified in the Pharmaceutical Medicine Specialty Training curriculum (PMST, formerly Higher Medical Training, HMT) for which professional standards of competency, care and conduct must be demonstrated in order to obtain a Certificate of Completion of Training (CCT) in Pharmaceutical Medicine.

In keeping with other medical specialties, the PMST curriculum differentiates between knowledge, applied knowledge and attitude/behaviours required for every item within each module. Specialty knowledge is assessed through the Diploma in Pharmaceutical Medicine examination. The practical competency-based modules of PMST build on this knowledge during the indicative four or more years of PMST in a personalised education and training programme across the breadth of pharmaceutical medicine. The key elements of the recently revised Clinical Pharmacology curriculum covering pharmacokinetics, preclinical and exploratory healthy volunteer/early clinical studies are outlined in Table 1.

There are several routes by which the experience and evidence required to demonstrate satisfactory completion of the Clinical Pharmacology module of PMST can be obtained, depending on the individual's role within their organisation. This can be achieved through “on the job” experiential training and learning, taught courses or a combination. While these routes could be regarded as very different in the experience they offer they must be considered in the context of the individual's overall exposure to the specialty of pharmaceutical medicine. The intention of PMST is not to create specialists but rather to facilitate understanding across the drug development spectrum of relevance to the individual's chosen area of expertise. A specialist in Medical Affairs may have little “hands on” experience of Clinical Pharmacology but needs to understand the fundamental principles and apply the information gained from pharmacokinetics, preclinical and early clinical studies of relevance to their Medical Affairs role. This learning could be reasonably gained from a taught course in Clinical Pharmacology. Essential elements irrespective of the route chosen include accurate recording of training and collation of the appropriate evidence to demonstrate satisfactory assessment of competencies for presentation at the annual RITA reviews. Some examples of the various routes available and steps required for successful module completion are outlined in Table 2.

Dr Ruth Hargreaves

Programme Director and Senior Lecturer in Pharmaceutical Medicine, University of Surrey



Table 1: Clinical Pharmacology PMST curriculum *

Knowledge	Applied Knowledge	Attitudes / Behaviour
1. Non-clinical pharmacology & toxicology		
1.1 Preclinical tests of pharmacology & toxicology 1.2 Preclinical data required for early human and long-term toxicology 1.3 In-vitro and in-vivo animal pharmacology 1.4 Animal toxicology study design and kinetics 1.5 Differences in drug behaviour between animals and human	<ul style="list-style-type: none"> • Understand value gained from pre-clinical studies • Relate animal toxicology to therapeutic indications/doses 	<ul style="list-style-type: none"> • Contributes to decision-making based on pre-clinical pharmacology and toxicology from patient therapeutic need and safety perspectives • Recognises benefits and pitfalls in extrapolation of preclinical data to humans • Communicates relevance of preclinical data to others working on drug's development
2. Relevant literature & publications		
2.1 Read literature in field 2.2 Conversant with relevant publications 2.3 Statistical methods/analyses 2.4 Pharmacokinetic models & analyses	<ul style="list-style-type: none"> • Provide a comprehensive review in a therapeutic field • Prepare a clinical development plan • Critically review relevant publications • Prepare a manuscript for publication/regulatory review 	<ul style="list-style-type: none"> • Maintains knowledge of current literature in therapeutic area • Encourages colleagues to write impartial critiques of recent publications
3. Regulatory requirements		
3.1 Relevant and current regulations 3.2 Design, review and approval of pharmacology & toxicology data needed for Phase 1 studies 3.3 Components of clinical development plan (Europe) 3.4 Components of regulatory submission (Europe) 3.5 US and Japanese regulatory needs	<ul style="list-style-type: none"> • Define planned clinical pharmacology of drug • Anticipate disease-related differences in patients • React promptly to unexpected findings • Awareness of past problems/issues • Write expert reports, clinical overviews, product information 	<ul style="list-style-type: none"> • Accepts pivotal role in preparation of development plan • Recognise value of expert input to study design and interpretation • Compliance with regulations and guidelines • Understands need to keep senior management informed
4. Design, execution & analysis of early phase human studies		
4.1 Purpose and methods for investigation of drug in humans 4.2 Maximise information obtained and minimise risks to study subjects 4.3 Human pharmacokinetics, pharmacodynamics & pharmacogenetics 4.4 Selecting appropriate dose ranges 4.5 Regulatory and legal requirements in human studies 4.6 Biological variation in normal population 4.7 Reasons and need for healthy volunteer screening	<ul style="list-style-type: none"> • Contribute to design of human studies • Define aims and safeguards in healthy volunteer and early patient studies • Select safety measures based on preclinical data • Check and interpret physiological changes observed • Propose dosing changes for Phase II/III studies 	<ul style="list-style-type: none"> • Recognise responsibilities for study volunteers' safety • Ensure appropriate safeguards are being applied • Recommend actions needed as studies progress • Consult with internal and external experts

Table 1: Clinical Pharmacology PMST curriculum* continued

Knowledge	Applied Knowledge	Attitudes / Behaviour
5. Ethical principles and practices in volunteer studies		
5.1 Basic principles of protection of research subjects 5.2 Practical procedures in provision of information to participants and their doctors and informed consent 5.3 Ethical review of studies from first-in-human to large clinical trials	<ul style="list-style-type: none"> • Maintain ethical principles and practice in investigator sites • Involvement in study information and consent forms • Experience of Ethics Committee meetings • Skill in use of lay language for study subjects • Oversee site inspections and audits 	<ul style="list-style-type: none"> • Regard human research with new drugs as imposing similar responsibility to routine medical practice • Instil these principles within the research organisation and with local teams
6. Good Clinical Practice in Clinical Pharmacology		
6.1 Apply ICH GCP principles throughout development programme 6.2 Up to date procedures known and fulfilled 6.3 Safeguards for volunteers and patients followed	<ul style="list-style-type: none"> • Plan clinical pharmacology investigations in sequence within GCP framework for critical judgement of therapeutic potential and safety • Ensure quality assurance checks made and acted on 	<ul style="list-style-type: none"> • Recognise welfare of subjects in studies is paramount • Recognise need for stringent adherence to procedures and maintenance of full and accurate records
7. Clinical pharmacology within the clinical development plan		
7.1 Clinical pharmacology requirements in regulatory submission and Summary of Product Characteristics 7.2 Apply clinical pharmacology knowledge and methodology across development programme	<ul style="list-style-type: none"> • Establish main pharmacological actions of new medicine in healthy people and those with target disease • Identify dose range and measure proof of concept • Identify further studies to determine comparative efficacy and ADME profiles • Judge real and potential benefits and likely safety concerns • Anticipate adverse drug/disease interactions 	<ul style="list-style-type: none"> • Recognise need to characterise drug behaviour in body in ADME studies • Realise ADME impairment may be due to disease and/or other drugs • Communicate importance of clinical pharmacology to other members of development team
8. Apply therapeutic area knowledge in identification of unmet needs		
8.1 Causative factors, pathophysiology and therapeutic options in one major organ-based disease 8.2 Understand benefits and shortcomings of current therapy and identify new therapeutic needs 8.3 Understand role of advancing knowledge in pharmacogenomics & pharmacogenetics	<ul style="list-style-type: none"> • Bring together scientists working on underlying disease process to fulfil unmet needs • Contribute to profiling of new agents by application of key principles of efficacy, safety and economic value 	<ul style="list-style-type: none"> • Consult with academic and clinical experts in therapeutic area to learn therapeutic aims, achievements and needs • Create idealised drug profile within constraints of clinical practice and health service provisions

* for details see PMST curriculum

Table 2: Routes and steps for successful completion of Clinical Pharmacology PMST module

Knowledge	Pass the Diploma in Pharmaceutical Medicine Exam
Applied Knowledge, Attitudes/Behaviour	<p>1. “On the job” workplace-based experiential training</p> <ul style="list-style-type: none"> • Clinical Pharmacology role eg. screening, undertaking medical examinations, investigations, obtaining informed consent and liaising with GP for volunteer studies, study preparation, design, applying tests, collecting results, analysing data, writing reports and publication etc. • Structured Clinical Pharmacology secondment to cover PMST curriculum • Specific supervised project to cover PMST curriculum
	<p>2. Taught courses</p> <ul style="list-style-type: none"> • Approved PMST CLP Module course eg. University of Surrey Clinical Pharmacology module • In-house courses • Other relevant commercially available courses
	<p>3. Combination of “on the job” experience supplemented by taught course(s) as agreed with Senior Specialty Adviser (SSA) & Educational Supervisor (ES)</p>
Collect and collate evidence	<p>Complete and organise all PMST documentation</p> <ul style="list-style-type: none"> • Training records • Evidence (consider including a reflective journal or commentary if appropriate) • Educational and Annual appraisals • RITAs and PYA
Assessment	<p>Knowledge assessment: evidence of success in Dip Pharm Med examination</p> <p>Applied Knowledge, attitudes/behaviour assessment: appropriate individualised evidence of competency in each item of the modules. Selected generalised assessments of competency</p>
Appraisals	<p>Record of Educational appraisals (with ES or other)</p> <p>Record of Annual Performance Appraisal (with ES or other)</p>
Review	<p>Annual RITA review (Record of In-Training Assessment)</p> <p>PYA (Penultimate Year Assessment)</p>
Exemption options	<p>Either a Degree or Accredited Diploma in Clinical Pharmacology</p> <p>Or a detailed Portfolio of acquired prior experience <i>covering all PMST curriculum items</i></p>

Would you like to contribute to the Faculty Newsletter?

The aim of the Faculty Newsletter is to provide updates on some of the current issues that may be of interest to our wide readership. Some Newsletters have been themed editions when it was felt that certain topics were sufficiently relevant.

The Faculty is always interested in hearing ideas of future topics to ensure that the Newsletter remains topical and of relevance. Should you have any ideas for future editions or wish to contribute as an author we would be very pleased to hear from you.

Please feel free to discuss your ideas with Dr Jit Solanki, a member of the Communications Committee via the Faculty Office (c/o b.muzzeroll@fpm.org.uk or 020 7224 0343).

**Are you involved
in the conduct of
clinical
trials?**

**Are you
certified
in Good
Clinical
Practice?**



**FACULTY OF
PHARMACEUTICAL MEDICINE
OF THE ROYAL COLLEGES
OF PHYSICIANS
OF THE UNITED KINGDOM**

What is GCP?

Good Clinical Practice (GCP) is a set of internationally-recognised ethical and scientific quality requirements that must be observed throughout the various stages of a clinical trial.

Why is it important?

The EU Clinical Trial Directive stipulates that all clinical trials on human subjects involving medicinal products in the EU, irrespective of their purpose, must be conducted in compliance with GCP. It is therefore vital for all personnel involved in the conduct of clinical trials to have a good working knowledge of GCP. Certification in GCP is a mechanism for demonstrating this.

GCP examination

The Faculty has established an examination in GCP, which is open to all personnel involved in the conduct of clinical trials, to help promote the highest standards in clinical research.

The examination comprises one written paper in multiple choice question format; lasting 1 hour 30 minutes.

Successful candidates will be awarded the Certificate of Good Clinical Practice, which will remain valid for 5 years.

Exam Fee	£165
Certificate Fee (if successful)	£25

Further information and an examination pack can be obtained from the Faculty Office at the address below. Details are also available on our website: www.fpm.org.uk

1 St. Andrew's Place, Regent's Park
London NW1 4LB
Tel: +44 (0)20 7224 0343
Fax: +44 (0)20 7224 5381
E-mail: fpm@fpm.org.uk
Website: www.fpm.org.uk
Registered Charity No 1011631

Hot topics in clinical pharmacology – a view from the industry

Clinical pharmacologists within the pharmaceutical industry are currently having a busy and high profile time. I would like to take this opportunity to highlight just two of the hot topics responsible for this attention –

The serious adverse effects suffered by healthy volunteers taking part in TeGenero entry-into-man study at the Parexel Unit in Northwick Park, and the continuing media coverage of this event, have brought the potential risks associated with Phase I studies to the attention of Main Boards of Pharma companies and CROs. Every company will have reviewed their activities to reassure senior management that these risks have been minimised, and as the risks can never be totally removed, that the prearranged responses, processes and procedures to manage any such event, from immediate medical care through to media management, is best practice standard.

We now face the challenges of dealing with the less immediate impact of the incident, in that we are beginning to find that those responsible for governing individual hospitals are now less welcoming of the establishment of a new Phase I Unit within their premises, due to concerns that their hospital name could become associated with adverse international media attention.

The final Duff report into the event has now been published, in which 22 recommendations were made to the Minister of Health. These recommendations are generally welcomed and supported by industry. However, it is within the detail of the implementation that gives some anxiety. After major incidents, it is possible to react in a way that has implications beyond those which were

intended, for instance the MHRA are currently consulting on the recommendation to have Units conducting Phase I studies accredited. Accreditation could benefit Ethics Committees in their site assessment; however, it would be disastrous for the future strength of medical research in the UK if the accreditation criteria were so stringent that this area of research ended up moving overseas.

On a more positive note, we are seeing a significantly increased appreciation of the value of biomarkers in drug development, as evidenced by the number of commercial and academic meetings and symposia on the topic! The challenges include the need to ensure that the right numbers of samples are taken from the right subjects, at the right times, for the analysis of the right markers, and that the results of the analyses are interpreted correctly in time for the next decision or regulatory submission. On top of this, we must ensure that the samples are collected appropriately and transported in compliance with the various guidelines and legislation. In the UK, new for 2006, we had the arrival of the Human Tissue Authority, which becomes another regulatory body with impact upon how we can carry out our business. The good news is that there is now increasing attention (ie availability of resources and finance) to research the potential of biomarkers, not just as predictors of efficacy, but also of human safety, and as a means of increasing the applicability of data from animals to man (ie translational medicine).

*Professor Graham McClelland
Global Head, Roche Center for Applied Clinical Development*

How to contact us

Address:

Faculty of Pharmaceutical Medicine
1 St Andrews Place, Regents Park
London NW1 4LB, United Kingdom

Telephone: +44 (0)20 7224 0343

Fax: +44 (0)20 7224 5381

E-mail: fpm@fpm.org.uk

Web-site: www.fpm.org.uk

Chief Executive

Mrs Kathryn Swanston Tel Ext.22
K.Swanston@fpm.org.uk

Membership and Finance Administrator

Mr Barry Muzzeroll Tel Ext.21
B.Muzzeroll@fpm.org.uk

Education Administrator

Ms Laura Thornton Tel Ext.23
L.Thornton@fpm.org.uk

Deputy Education Administrator

Mr Konrad Obiora Tel Ext. 20
K.Obiora@fpm.org.uk

Registered charity 1011631
(England and Wales)

If you have recently moved or are planning to move, please notify the Faculty by telephone, post or e-mail (fpm@fpm.org.uk) of all changes of address.

To explore advertising opportunities please contact Barry Muzzeroll at the Faculty Office

This Newsletter is published by the Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the United Kingdom. Opinions expressed in articles do not necessarily represent those of the Faculty or its parent Colleges or their policies.