The clinical pharmacologist in drug regulation: a European perspective

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- 1 The clinical pharmacologist in drug regulation has many roles to play. These include responsibilities for the premarketing assessment of a new product's efficacy and safety, for scrutiny of the summary of Product Characteristics, and for monitoring its performance after marketing. Furthermore, the clinical pharmacologist has a subsidiary responsibility in examining the results of preclinical pharmacological and toxicological studies.
- 2 Clinical pharmacologists in regulatory authorities have one further, and crucial, responsibility—humility. From their training and experience they will (or should) know of their own scientific limitations and of the necessity for seeking help and advice from other disciplines.

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Introduction

Clinical pharmacologists play a central role in European drug regulation. In the United Kingdom the Chief Executive of the Medicines Control Agency (MCA), the Chairman of the Medicines Commission (MC), and the Chairman on the Committee on Safety of Medicines (CSM), are all clinical pharmacologists. The Chairman of, and many of the delegates to, the Committee on Proprietary Medicinal Products are also clinical pharmacologists. Furthermore, the principles underlying the theory and practice of clinical pharmacology are indispensable to other clinicians and scientists working in drug regulation.

There are, however, aspects of drug regulation in which clinical pharmacologists play a more limited role. It behoves us, therefore, to acknowledge the discipline's strengths and weaknesses as it impinges on the drug regulatory process.

Strengths

Clinical pharmacologists, whether as members of the staff of a regulatory authority (e.g. MCA), or as members of independent expert advisory committees (e.g. MC, CSM) have special contributions to make in the preclinical and clinical assessments of applications for marketing authorization, and in the monitoring of the safety of marketed medicines.

Preclinical assessment

The assessment and evaluation of the preclinical aspects of a drug development programme necessarily fall within the provenance of basic pharmacologists and toxicologists. Nevertheless clinical pharmacologists play an important subsidiary role.

First, the clinical pharmacologist should be able to provide confirmation that a compound's primary pharmacological activity gives a biologically plausible basis for its putative therapeutic efficacy. Although biological plausibility is not a prerequisite for demonstrating a new drug's clinical efficacy, a clear understanding of its primary pharmacological properties (qualitative and quantitative) is of considerable importance in its evaluation.

Second, scrutiny of the results of the secondary pharmacological and toxicological studies, with a new drug, should give the clinical pharmacologist some insight into its likely human tolerance. Moreover these studies should indicate (at least in part) the range and scope of any special clinical investigations, in volunteers or patients, that ought to be undertaken in order to delineate the product's adverse reaction profile.

Clinical development

Clinical pharmacologists, in industry and academia, play a central role in clinical drug development and have no less important a responsibility in drug regulation.

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The regulatory clinical pharmacologist will undertake a critical examination of the results of pharmacodynamic and pharmacokinetic studies with a new drug. Such investigations will have underpinned the subsequent development programme and are therefore pivotal. The data should confirm that the drug's primary pharmacological properties are, indeed, carried into man. They should identify those secondary pharmacological actions that may limit its tolerability. They ought to provide a basis for deciding the doses (and dose intervals) to be adopted in phase 2 dose-ranging studies. In some circumstances pharmacodynamic-pharmacokinetic (PD-PK) modelling may be possible although the wise clinical pharmacologist will, of course, appreciate its limitations. The biological events transposed between a drug's pharmacological effects, and its clinical benefits, may be sufficiently great to make extrapolation uncertain. Finally, the results should enable the effects of co-morbidity (e.g. renal disease, hepatic disease) and co-medication to be predicted with some confidence.

The regulatory clinical pharmacologist is expected to scrutinise, closely, the clinical trial data-base in order to evaluate the strength of the evidence for efficacy in the claimed indications. This will, inevitably, be normally based on the results of appropriate randomised controlled trials. The assessment needs to ensure that such studies are of a robust design, execution and analysis; that any surrogate end-points, or rating scales, are valid markers of true clinical benefit; and that, in trials involving active comparators (rather than placebo), these have been appropriately selected. Few European regulatory authorities employ biostatisticians as assessors (the MCA is one of the exceptions). Unless there is a biostatistician as a member of a regulatory authority's advisory committee clinical pharmacologists will need to offer an assessment of the statistical analysis. Potential issues will include the power of individual studies, the use of techniques to take account of baseline imbalances, and the rigour of any meta-analysis. Finally, in reviewing the efficacy data as a whole, the regulatory clinical pharmacologist must offer a judgement as to its generalisability. Do, for example, the data support the precise terms of the proposed indication(s)? If not, is extrapolation supportable and reasonable?

The clinical pharmacologist in a regulatory authority has the further task of reviewing the safety data, in volunteers and patients, supporting an application for marketing authorisation. This is likely to be primarily based on an analysis of withdrawals, and of adverse events, in randomised clinical trials. It may also include safety data from trials examining efficacy in indications for which no license is (currently) sought, and from 'named patient' ('compassionate use') experience. This evaluation demands considerable expertise. It requires the clinical pharmacologist to be alert to those adverse events that may represent type A adverse reactions (ADRs) and to seek evidence for a dose-response relationship. Because individual clinical trials may, themselves, be too small to identify significant ADRs it needs a close examination of the so-called 'global analysis'. The latter is fraught with interpretative problems since the technique, which is analogous to

meta-analysis, has yet to be supported by a well-developed statistical methodology. Safety analyses amongst specially vulnerable groups (e.g. children, elderly) are also essential where they fall within the terms of the proposed licensed indications.

The final role of the regulatory clinical pharmacologist, in assessing new drug applications, is an examination of the draft Summary of Product Characteristics (SmPC). This is the document that informs prescribers on how to use the product optimally. It is also the framework document that authors of formularies, prescribing guidelines and protocols use as a basis for their own recommendations. It therefore needs to be accurate and coherent. As I have often said to new UK clinical pharmacological assessors 'it needs to be readily intelligible to a tired Senior House Officer, in a District General Hospital, at 3 o'clock in the morning'.

Pharmacovigilance

At the time that a new active substance is first marketed, its pharmaceutical quality and therapeutic efficacy (in the claimed indications) will have been established. Any assessment of its safety at this stage, however, is inevitably provisional. The homogeneity, and limited numbers, of patients exposed during premarketing clinical trials, and the relatively short duration of treatment, places limitations on any predictions of its performance during widespread use. Clinical pharmacologists involved in drug regulation have an important contribution to make for monitoring the safety of marketed medicines.

First, they play an important role in the collection, assessment and analysis of spontaneous ADR reports. All member states of the European Community (EC) have national ADR reporting schemes which, though differing in their details, have a common basis. This involves the encouragement of health professionals to report suspected ADRs either directly to their national regulatory authority, or indirectly via the pharmaceutical manufacturer. These schemes are of proven value [1, 2] in 'signalling' potential novel ADRs, in identifying risk factors such as dose or age, and in providing comparisons of ADR profiles between members of the same therapeutic class. The regulatory clinical pharmacologist is expected to play an important role in signal recognition, and in establishing a biologically plausible basis for the identification of risk factors.

Second, clinical pharmacologists may also play a major role in the design, execution and analysis of formal epidemiological studies intended to confirm or refute ADR 'signals'. Traditionally, clinical pharmacologists have largely been experimentalists but increasing numbers have developed expertise in epidemiology. Even those without special training in pharmacoepidemiology, however, must now be expected to possess some knowledge of its fundamental tenets, and have more than a passing knowledge of the strengths and weaknesses of epidemiological approaches to the assessment of drug safety problems.

Third, clinical pharmacologists are expected to take

a major part in determining the regulatory response to suspected, or proven, ADR issues arising during the post-marketing period. These responses can range from 'do nothing' to 'suspension' of the product's marketing authorisation. The factors influencing such decisions include the degree of confidence of a causal association between drug exposure and the particular adverse event; its public health impact; the extent to which vulnerable patients can be identified prior to exposure; and the ADR profile of alternative forms of treatment. The resolution of such issues is seldom simple and can offer clinical pharmacologists some of their greatest challenges.

Weaknesses

No individual clinical pharmacologists can fulfil all the roles discussed above. Whilst they must be expected to have some knowledge of a wide range of scientific disciplines, there is an obvious danger that they may have too superficial an approach. Regulatory pharmacologists must therefore take heed of Clint Eastwood's words (*Dirty Harry*) 'A man's gotta know his limitations'. They are neither basic pharmacologists, toxicologists, experimental pathologists or biostatisticians.

Similarly, whilst clinical pharmacologists may have a broad knowledge of contemporary therapeutics, and have a special area of clinical interest, there will inevitably be large areas of clinical medicine where they must depend on the advice and judgement of other specialists. In the field of pharmacovigilance, only a

minority of clinical pharmacologists are well-versed in epidemiology or public health. Even fewer possess more than a vague understanding of epidemiological biostatistics. I have yet to meet one who could, unaided, perform conditional logistic regression on a matched case-control data-set.

If regulatory clinical pharmacologists are tempted to become too arrogant it is only necessary to remind them of some of the lessons of history. Thus, whilst only one new active substance granted a full product licence under the provision of the Medicine Act has been withdrawn for lack of efficacy, 22 have been withdrawn for reasons of safety. And, of course, clinical pharmacologists (many of whom claim a special interest in the management of hypertension) were unable to identify the optimal starting doses of prazosin, captopril or enalapril at the time of their first marketing in the UK.

Conclusions

Clinical pharmacologists have a special role to play in drug regulation. But in proclaiming the discipline's strengths it is crucially important to admit its weaknesses—for that is the surest sign of its maturity.

References

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