



## The Impact of Phase IV Trials and Post-Marketing Surveillance on Real-Life Clinical Practice

R. K. RONDEL

Woking, Surrey, U.K.

**Abstract** – *The need to monitor the effects of new drugs, following their introduction into the market, is a subject of major and growing concern to government health authorities worldwide.*

*Whilst Phase IV studies may be useful in generating information on type A effects (those due to unwanted, concomitant, pharmacological actions) their scale is limited and their principal value up to now has largely been linked to market promotion through what are commonly referred to as promotional or 'seeding' trials. These promotional studies do not, commonly, provide much in the way of reliable data on efficacy and/or safety and governmental regulatory bodies in most countries are now acting to restrict or even eliminate such practices.*

*Because they usually occur relatively rarely, type B (idiosyncratic) adverse drug effects are more difficult to pick up and many thousands (or even hundreds of thousands) of patients may need to be monitored in order to detect them. The various techniques of Post-Marketing Surveillance (PMS) now available have their strengths and weaknesses but PMS is agreed to be an essential activity, as reflected by the growing importance, and acceptance, of the discipline of pharmaco-epidemiology.*

*However, PMS should not be seen solely as an exercise in detecting rare and unpleasant adverse drug effects. It can also be of value in generating data leading to the safer and more effective use of drugs in the community and to a more accurate appraisal of their true place in therapeutics.*

Once a drug is marketed, experience tells us that the pattern of usage will almost certainly be widely different from that covered by the programme of clinical trials conducted before registration, in Phases I, II and III. The company's recommendations for its prescription will be contained in a data sheet based on the outcome of the pre-registration trials. This will cover indications for usage, any specific

precautions to be taken during administration and especially the types of side effects that can be expected or that may occur during treatment, based on those actually seen during clinical trials, or those that could be predicted on the basis of the drug's chemistry or therapeutic family.

However, it has to be realised that the average drug, at the time of marketing, will have been tested

\* Director, Oxford Workshops, Woking, Surrey, GU 24PW, U.K.

on only a relatively small number of patients; certainly less than ten, and in the majority of cases probably less than five, thousand.

Such small numbers will certainly allow demonstration of the normal Type I adverse reactions – that is, those pharmacological effects of the drug which are unwanted for the therapy in question. A simple example would be the troublesome dry mouth experienced by many patients taking anticholinergic drugs for suppressing gastrointestinal motility. On the other hand, the same dry mouth becomes part of the wanted effects of the drug when it is given for surgical pre-medication.

Such Type I reactions are normally predictable and, to a variable extent, controllable.

More troublesome are the Type II or so called idiosyncratic reactions. These cannot be predicted, will usually occur rarely, or infrequently, and are often much more troublesome than Type I reactions. Again, a simple example would be the bone marrow depression seen with certain classes of drugs. The thalidomide and practolol disasters of recent years provide further vivid examples.

In all these cases, the likelihood of such events will occur at low incidence ranging from 1 in 10,000 cases to 1 in 50 or 1 in 100,000 or more. Clearly, this means that the chances of them being detected in the pre-marketing clinical trial programme are low, or nil. Even if an isolated event should occur at this time it would be difficult to evaluate it and to distinguish it from the rare events which occur as part of the natural background of unwanted, random biological happenings.

The clinical use of drugs in Phase IV is thus complicated by these two uncontrolled aspects: sudden widespread use of the drug in conditions not necessarily encountered before marketing; and the possibility of unexpected, or rare, adverse events of low incidence.

These considerations have a progressively more marked impact on real-life clinical practice, as the medical profession and the government health authorities become more aware of the need for surveillance of drugs once they become available for widespread use in the country. Doctors now realize the need for vigilance especially in the early stages after marketing, but also on a longer time-scale. (The practolol problem emerged only after the drug had been on the market for several years and had been taken by hundreds of thousands of patients).

The immediate response to this situation up to now has been to instigate large-scale Phase IV trial programmes. These are usually sponsored by the companies and are normally conducted in the general practice setting. Doctors will be asked to record on

a special form, the outcome of treatment with the new drug in a certain number of patients. A typical example, in Britain, would be to ask, say 1000 GPs each to record the results of treating 5 to 10 patients. Even with numbers of this kind, there can be considerable logistic and financial barriers to surmount. Indeed many companies would be unable to mount such an operation, because of manpower and/or cost considerations.

If such trials are successfully mounted, the best of them might produce data on no more than 10,000 patients and this over a period that could span two or more years before results were finally analysed and reported. It is then clear that even the largest of such trials are unlikely to produce helpful and prompt data regarding Type II reactions. What they can do, is to produce valuable confirmatory evidence on the efficacy, tolerability and safety profile of the drug. They may also throw up information on previously unexpected merits (or demerits) of the drug. They will certainly help to quantify more accurately dose-response relationships and sharpen the patients' profiles in respect of responders and non-responders to the particular therapy.

In this way, the orthodox Phase IV trial, as currently conducted, can have a major impact on the use of the drug in real life clinical practice. It will also be of help to government health authorities by providing additional, quantified data, in particular on safety aspects.

Such studies still leave unanswered many questions on Type II reactions and, to address this aspect, exercises of much wider scope must be mounted. These are described under the generic title of Post Marketing Surveillance, or PMS studies. Where the orthodox Phase IV trials, described above, deal usually in numbers of not more than 5000 patients, PMS will attempt to monitor the outcome of drug usage in complete populations at either national or international level.

There are a number of techniques that can be used (Table 1) and these are now briefly described.

TABLE 1. Post Marketing Surveillance Techniques

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- Spontaneous Reporting Systems
  - Vital Statistics
  - Case Control Studies
  - Cohort Studies, either Experimental, or Observational.
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● **Spontaneous Reporting Systems:** The best known example of this is the 'Yellow Card' pioneered in Britain by Professor Inman in the 1960s during his time with the Committee on Safety of Medicines.



This requires doctors to report to the Health Authority on a simple form (the yellow card) any untoward adverse reaction they see with a particular drug – especially but not exclusively, one recently marketed.

The benefits of such a system are that it is simple and cheap to operate, can start immediately the drug is launched and can operate indefinitely. The limitations are those of principally under-reporting (which is a perennial problem). Introduction of bias through media activity etc. and 'fatigue' of the system also operate. Another major disadvantage is that the system collects 'incidents'. It cannot relate these to the numbers of patients taking the drug. There is thus a numerator (the 'incident') but no denominator. It is therefore not possible to calculate 'incidence'.

What it can do is produce relative risk estimates between similar compounds. Examples of its use have been to detect undesirable effects with a member of the anti-diabetic biguanides (phenformin) and of the family of antidepressants (nomifensine).

It has also identified, for example, hepatotoxicity with amiodarone, and arthropathy associated with mianserin. Furthermore, yellow card data have facilitated the release of ibuprofen and loperamide from ethical prescribing limits to allow their sale over the counter (OTC).

● **Vital Statistics:** These are constantly being collected by governmental and other official agencies. Examples of their value are the detection of the increased mortality in earlier years associated with the use of isoprenaline inhalers; and the decrease in incidence of Reyes Syndrome associated with reduction in the use of aspirin-based medication in children.

● **Case Control Studies:** Here, drug use in patients with a specific disease ('the cases') is compared with that in a group of subjects without the disease ('the controls'). The technique is relatively cheap, and rapid. Patient exposure to drug can be limited; it can be used to identify rare adverse reactions as well as those with a long latency.

Examples of the use of this technique include the detection of vaginal carcinoma in the offspring of mothers taking stilbesterol and quantifying the influence of non-steroidal anti-inflammatory drugs (NSAIDs) in precipitating gastro-intestinal haemorrhage.

One drawback is that such studies can only confirm already suspected associations between a drug and a particular disease.

● **Cohort Studies:** In cohort studies, a group of patients receiving the drug in question is identified and the outcome ascertained. Such studies may be experimental or observational.

**Experimental Studies:** These look at groups of patients randomly assigned to either the drug or a

control treatment (placebo or active comparator). Such randomised, controlled studies have, for example, produced valuable data on clofibrate (WHO Clofibrate Study), and the treatment of mild to moderate hypertension (MRC Trial). Large numbers of patients are required, and the technique is usually reserved for special circumstances.

**Observational Studies:** These look at patients undergoing routine treatment and compare the outcome with that of a random sample of the general population; or with patients receiving an alternative treatment; or with nothing.

There are a variety of techniques for conducting such studies. Perhaps the most interesting of these is 'Prescription Event Monitoring' or PEM, which operates in the United Kingdom.

This technique is made possible by the fact that all prescriptions written by doctors working in the National Health Service are finally sent to a central office – the Prescription Pricing Authority (PPA) for processing and costing.

Each prescription identifies the patient, the drug(s) given and the prescribing doctor. In this way the use of any selected drug can be monitored. The PEM Centre (located near Southampton) will ask the PPA to send copies of all prescriptions, during a given period, for a certain drug. The Centre then writes to all the doctors who have signed the prescriptions enclosing a simple (green) form on which they are requested to record any 'event' experienced by the patient(s) who are taking the drug. These events are not limited to overt, identifiable adverse drug reactions but may be any kind of unusual happening, a fracture, admission to hospital, a fall, an acute illness of any kind, etc. No judgement of causality is required.

In this way, information can be rapidly collected on quite large numbers of patients (usually not less than 10,000) treated with the drug. The system has the advantage of producing both numerator and denominator so that accurate incidence data can be collected and precise comparisons made with similar data from other drugs. The method had been successfully employed in the investigation of new drugs such as cimetidine and ranitidine as well as established compounds like erythromycin.

## THE FUTURE

The above review gives a brief picture of some of the principal methods currently employed in Post Marketing Surveillance. It can be seen, incidentally, that these are almost always nationally based.

Undoubtedly, the major pre-occupation of those now involved in PMS is to collect data internationally, not only to provide a wider and more dependable

data base but to provide valuable information on transcultural and genetic variations. Such initiatives will have to cope with a number of new problems, of which nosology and terminology loom largest. National patterns of prescribing and medical care will also have their impact. Nevertheless, plans are now being developed to organise PMS on a community-wide basis within the European Economic Community. It has to be said that many of those involved in developing these plans are somewhat pessimistic about the rate at which such systems can be introduced and successfully operated.

**In conclusion**, it can be seen that the increasingly wide use of Post-Marketing Surveillance, in its various

forms, can only help in producing data to facilitate the rational and safer use of the large and ever-growing number of powerful drugs available to the prescribing physician. Such exercises require intense and sustained effort by all concerned and will – and should – increasingly involve all doctors involved in patient care.

#### RECOMMENDED READING

*Adverse Drug Reactions: The scale and nature of the problem and the way forward.* (1987) Edited by Ronald D Mann. Parthenon Publishing, Casterton Hall, Carnforth, Lancashire, LA6 2LA, United Kingdom.

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### **Treatment of Lung Cancer**

The developing countries are, in many ways, victims of the affluent world, which exploits their primary produce and dumps upon them its surplus tobacco. This has become even more of a menace in recent years because the use of tobacco in many of the affluent countries in the West is now reduced because of increased awareness of the irrefutable direct and indirect carcinogenic effects of cigarette smoking. The full spectrum of the increase in the risk of cancer in the developing countries is yet to be revealed although it is generally appreciated that cancer is rapidly climbing the ladder of comparative mortality in these countries.

In the light of the aforesaid facts, the treatment of lung cancer is a matter of undoubted importance. Unlike the significant improvements seen recently in the results of treatment of some less common cancers, the five-year survival rate is less than 10 per cent in patients who develop cancer of the lung. Surgery, although invariably not curative, is the treatment of choice for adenocarcinoma, large cell tumours and squamous cell carcinoma. However, the recommended treatment of small cell lung cancer continues to be chemotherapy because of the disseminated nature of this type of cancer. A small proportion of patients with small cell carcinoma if diagnosed early and with favourable prognostic factors may be cured. Radiotherapy is of no benefit to survival but is an effective palliative therapy for haemoptysis, pain and symptoms of local obstruction.

**Excerpted from** Spiro S G. Management of Lung Cancer. *British Medical Journal* 1990; **301**: 1287–88.

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“There is no doubt that many international pharmaceutical companies have in the past, and continue to, promote products for indications which would be quite unacceptable in the Western world. Further, the claims made for many of these products may be untrue in terms of both efficacy and toxicity and would not be accepted in say, the United Kingdom. In a developed country, the pharmaceutical industry is part of a balanced power structure in which the government, academia, the medical profession and consumer groups play a role in drug usage. Too often in developing countries these balancing influences do not exist and thus industry can do as it wishes in terms of pharmaceutical promotion”.

Breckenridge A. The Pharmaceutical Industry and Developing Countries. *British Journal of Clinical Pharmacology* 1986; **22**: 275–95.