

## **Chapter 7. Follow-Up of Drugs After Market Entry**

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## **I. INTRODUCTORY REMARKS**

There is a general agreement with the fact that our operational knowledge on drugs at the time they enter the market is grossly inadequate. It is also generally accepted that, in most cases, delaying entry into the market by requesting additional animal or clinical studies would not answer the remaining questions and would only delay the patients' access to useful and sometimes life-saving drugs (1). The solution is therefore to continue studying drugs in a formal way for an indeterminate period of time following their entry into the market (2). Those who consider indeterminate too long a period of time might wish to recall the cisapride experience.

Although few active participants and observers of the medication scene would disagree with the above statements, there is considerable confusion and indecision as to how to proceed in a practical and economical way in order to answer the numerous questions that still remain at the time of entry into the market.

It is important to realise at this point that the question is not necessarily global or universal, and that it has important connotations in regard to specific countries. This is due to the fact that some countries are traditionally allowing drugs into the market sooner than others (3). This analysis will therefore be done from a Canadian perspective, which takes into account the fact that most drugs have been marketed in the United States and/or the European Union from 6 to 12 months before being allowed access to the Canadian market (4-6). Of more than a theoretical interest is the question of whether Canadian patients benefit or suffer from this time lag.

## **II. WHAT DO WE KNOW OF THE DRUG ON THE DAY IT ENTERS THE CANADIAN MARKET?**

Essentially, we have two sources of information. The first being the results of the Phase III trials and the second, the "real life" experience in the countries where the drug was marketed for a significant period of time before Canada. The Phase III trials are designed to demonstrate efficacy and to reassure regulators that the drug doesn't produce clinically severe and relatively frequent adverse events after short periods of exposure. They are done in very artificial settings on very carefully selected patients by very experienced teams of nurses and doctors. As a result of these conditions, they have very high internal validity but very low generalisability; their main drawbacks being the relatively small number of patients (3,000 to 5,000) and their short duration of treatment with the drug in question (6 to 12 months). They are therefore incapable of providing us with critical information on potentially severe side-effects (that occur on less than 1 out of 1,000 patients) that manifest themselves after more than one year of exposure. From a pharmaco-economic point of view, Phase III clinical trials also fail to provide information that is instrumental to the decisions that drug plan managers have to make. Placebo is commonly used as a comparator, whereas what is needed is a comparison with the cheapest or the most frequently prescribed drug for the same indication. In addition, and almost by definition, they provide no information on the most critical question drug plan managers have to answer: How is it going to be used? That is, for which indications other than the officially approved ones, at what doses, in which populations, and most important of all: which drug(s) is it going to replace?

The other source of information usually available in Canada at the time the drug enters the market is the experience gathered from countries where the drug has already been marketed. In terms of safety, several European countries and the United States have reasonably good and spontaneous reporting systems (5,7), which in the recent past have resulted in drugs being withdrawn from these markets before getting Canadian approval. Although it is reasonable to assume that a drug that produces undesirable side-effects in Europeans and/or Americans would also harm Canadian patients, it is much more difficult to extrapolate the drug use data obtained in countries foreign to Canadian settings. The prescription patterns and the availability of competing drugs is usually so different from one country to another that it is extremely risky to predict the Canadian drug use based on data obtained in other countries.

The concept of conditional approval of new drugs, which was discussed by Rawson, West and Appel (2) in a recent paper in the Journal of Clinical Pharmacology, is central to the eventual implementation of the post-marketing study of new drugs. The concept of conditional approval would provide a framework and a structure under which drugs will be studied after their entry into the market. From a Health Canada point of view, these studies would permit a better understanding of the safety of the drug and its long-term efficacy. From the point of view of the drug plan managers these studies would be invaluable in providing information that would allow them to verify whether the drug is used appropriately.

### **III. TYPES OF PHASE IV STUDIES**

Phase IV studies can be divided in four classes: 1. the active pharmaco-vigilance cohort; 2. the prospective efficacy cohort; 3. the simplified clinical trial and; 4. the drug use study.

#### **III.1 The active pharmaco-vigilance cohort**

These are prospective patient cohorts who under their most simplified form can be considered as nothing else but patient registers. They allow a large number of patients to be followed for prolonged periods of time. Patients numbering up to 10,000 and treated for five years or more might be necessary to answer some questions, particularly those relating to safety. The object is to collect very specific information with a maximum degree of efficiency. From a practical point of view, this means a maximum of 20 questions with visits being no more frequent than every three months. These studies can be designed to provide additional information on specifically expected problems; for instance on drugs who in Phase III trial would have shown a low incidence of potentially serious problems, like the elevation of liver enzymes, allergic reactions or prolongation of the QT interval, which could be studied in such a cohort and thus provide information on whether these "red flags" will turn out to be predictors of rare but serious adverse events like hepatic necrosis, Stevens Johnson syndrome or sudden death. These prospective pharmaco-vigilance cohorts have to be flexible enough to be able to capture problems that were not suspected from the results of Phase III trials but could be fatal or life-threatening. Ideally, the collection and analysis of the data should be done in "real time" in order to allow a rapid response in cases where serious problems are encountered. These prospective pharmaco-vigilance cohorts have the great advantage of providing solid numerators and denominators, parameters that are notoriously fuzzy when provided by spontaneous case reports. A very practical problem relating to the implementation of an active pharmaco-vigilance cohort is to be able to distinguish them from "seeding" studies, which have contributed to give all Phase IV studies an undeserved bad reputation. The distinction is not that difficult. The implementation of a Phase IV study is legitimate if it answers an important public health question with an appropriate methodology.

#### **III.2. The prospective efficacy cohort**

The objective here is to demonstrate long-term efficacy. This is particularly important regarding drugs for which 6 to 12 months trials have demonstrated some degree of efficacy in an indication for which long-term effectiveness is notoriously difficult to obtain. Classical examples would be drugs used to treat obesity or to help in smoking cessation. The logistics can be extremely simple since the purpose would be to define whether the decreases in weight or if the rates of smoking cessation observed at the end of a six month trial are still present after two or three years.

#### **III.3. The simplified clinical trial**

This type of trial could be defined as a randomised controlled trial with a maximum degree of freedom as to how the patients are treated once randomisation has been implemented. These are extremely useful when the effectiveness (as opposed to the efficacy) of two drugs needs to be studied. Randomisation

becomes necessary when confounding by indication would create two groups whose clinical characteristics would be so different that the results could not be interpreted without complex, and sometimes not very credible, statistical manipulations. It is important that both patients and physicians are aware of which drug they have been assigned to. It is also critical that patients and their physicians have a maximum degree of leeway as to the frequency of the visits, the collection of laboratory tests and the treatment of adverse reactions from the drugs and /or complications of the disease. One of the main challenges of these studies is to convince the sponsors and the investigators, which have been brought up in the very structured classical Phase III trial, that useful information can be gathered without specific criteria about the frequency of the visits or the way blood pressure should be measured.

#### **III.4. The drug use study**

A critical question that drug plan managers would like to have answered at the time they decide on the inclusion of a new drug in their formulary is the following:

- a. What is it going to replace?
- b. A more specific form of this question would be: is the new drug going to be used as a first line or as a second line treatment?

These two questions are obviously not answered from the data available to the pharmaceutical company at the time the drug enters the market. Very hypothetical and speculative answers can derive from the knowledge of the medical practice, the companies marketing records and the way new drugs of the same class were previously used. The drug plan manager can only speculate on how the new drug will eventually be used. It is therefore perfectly reasonable to require drug use studies as a condition for listing new drugs, including the implicit acceptance by the pharmaceutical company that corrective measures will have to be taken in case the use of the drug happens to deviate excessively from what was predicted to be ideal in cost-efficient therapeutics. In addition, drug use studies can provide very useful information on the doses actually used in medical practice, which on some occasions can be much larger than those used in the clinical trials, and thus invalidate the initial pharmaco-economics studies based on the results of these trials. The appearance of the use of the drug for new, official or unofficial, indications can also dramatically invalidate the predictions of the pharmaco-economics studies based on Phase III data.

When the required information is contained in databases, these should be favoured since studies on databases have the advantage of being relatively cheap and fast. The other advantage of databases is that they permit one to obtain information on a population of doctors and patients who do not know they are being observed, and who therefore operate under their usual behavioural patterns. When the necessary information is not available in databases, it becomes necessary to implement field studies, which have the inconvenience of being much more expensive, but the enormous advantage of being designed specifically to capture all the necessary information. One of the problems with the prospective drug use studies done in the field is that the health professionals and the patients who agree to participate in the study might not be representative of the overall population. Another one is the fact that their knowing they are being observed might cause them to modify the way they practice. These two problems becoming extreme could render useless the interpretation of these studies because they would not represent the "real life" use of the drug under study.

#### **VI. CONCLUSION**

In conclusion, given their relative novelty, Phase IV studies constitute an absolute necessity for the protection of the patients and the proper use of the public funds used to reimburse drugs.

## **V. REFERENCES**

1. Inman WHW. Assessment of drug safety problems. In: Gent M, Shigematsu I, eds. *Epidemiological Issues in Reported Drug Induced Illnesses: SMON and Other Examples*. Hamilton: McMaster University Library Press, 1978:17-24.
2. Rawson NSB, West R, Appel WC. Could conditional release of new drugs provide the information required to study drug effectiveness? – A discussion paper. *Can J Clin Pharmacol* 2000;7:185-90.
3. George C. Atlantic crossing and drug lag. *Br Med J* 1980;281:507-8.
4. Inman WHW. Recorded release. In: Gross FH, Inman WHW, eds. *Drug Monitoring*. London: Academic Press, 1977:65-78.
5. *International Reporting of Adverse Drug Reactions. Final Report of the Council for International Organizations of Medical Sciences Working Group*. Geneva: Council for International Organizations of Medical Science Sciences, 1990.
6. Rawson NSB. Time required for approval of new drugs in Canada, Australia, Sweden, the UK and the USA in 1996-1998. *Can Med Ass J* 2000;162:501-4.
7. Coulter DM. Intensive Medicines Monitoring Programme: fluoxetine interactions. *NZ Fam Physician* 1993;20:110.