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# THE DESIRE TO REGULATE: THE WISH TO DISCOVER*

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**Summary:** *In considering post-registration research, the paper deals with the motivation of the interested parties for such research, new uses for established drugs, ways of filling information gaps and concludes with a number of fundamental principles on which post-registration research should be based.*

## Introduction

Post-marketing surveillance is a term much in the spotlight these days. It is, unfortunately, an imprecise and ambiguous phrase. The semantic purist might prefer it to be called "post-approval" or "post-registration" since the phrase refers not to the period after marketing, but the period of or during marketing, that is, after regulatory approval. While this objection is perhaps easily dismissed as pedantic, it is more important that the term "surveillance" means different things to different people.

Some use "surveillance" to refer to formal schemes for monitoring adverse effects, while others use it to refer to a whole array of mechanisms, studies, and sources of data, covering the assessment of desired as well as undesired effects, in effect, to be equivalent to post-registration research.

In the present paper, it is intended to cover, rather superficially perhaps, the area of post-registration research, i.e., the broad spectrum of questions deserving attention once a drug is available to the physician to prescribe and the patient to take into his or her body, because one must consider the problem in its totality.

## Motivations for Interest

But first, one must consider the various motivations for interest in these matters. Regulators may need to reassure themselves, their superiors, and the public that the original decision to register a given drug was a defensible one, and one that does not require reversal.

Politicians may have a different agenda. They not only wish to avoid media accusations and public indictment for allowing drugs with a disproportionately high toxic effect for their benefits to remain on the market, but are of necessity interested in keeping the national drug budget down, especially by avoiding waste in the form of needless prescribing for the use of expensive drugs, when less expensive drugs can serve as well.

The pharmaceutical industry often wishes to explore new uses for registered drugs, or com-

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parisons of their new drugs with competitor drugs: industry will certainly wish to insure that adverse reaction reports are valid and not blown out of proportion, and that drugs are not unfairly accused of excessive toxicity.

Physicians and academics will place a different emphasis. They need to know how to use drugs with the greatest chance of benefit and the least harm, and therefore will be interested in delineating optimal dosage, optimal dosage intervals, and the optimal duration of treatment, in avoiding drug-drug interactions, and tailoring the use of drugs to the need of specific patients, who will differ in age, gender, severity of illness, presence of co-morbid conditions, and in their willingness to tolerate certain side-effects and to follow prescribing directions.

Unfortunately, the emphasis prior to registration is not on such detailed questions. Rather, the crucial studies on which regulatory approval is often based have to do with group responses, that is, it must be shown that when a group of patients is given the drug in question, that group will experience more benefit than a group that is untreated.

But the practice of medicine requires the physician to treat individuals, not groups. Only occasionally, as in public vaccination programmes, does the medical profession treat a population rather than individuals. When a sick patient consults a doctor, he is uninterested in the average performance of the drug. He wants a drug that will work well for him.

So, when a drug is first marketed, physicians are in a position analogous to that of the surgeon who is using a new operating procedure. With experience, the good surgeon not only improves his technique, but learns how to choose the right patients for a given procedure. New drugs are in principle no different from new surgical operations.

**Planning regulation**

In planning a national post-registration approach, therefore, it is logical to begin with a realistic assessment of what we know at the point of registration and what we do not know; of what we can and should demand in the way of data prior to regulatory approval, and what we must of necessity put off until there is significantly widespread use of a drug.

Approved drugs rarely lose their licenses. While drug tragedies like thalidomide, Dalkon shield and diethylstilboestrol (DES) attract a great deal of media attention, they are the exceptions rather than the rule.

Nevertheless, we are always, no matter how old the drug, in a state of imperfect knowledge and especially so at the time of registration. This is to be expected, when one recalls that before approval a drug may have been studied carefully in a hundred to a few thousand patients. (In the USA, the average is perhaps 1500.)

Such numbers are usually adequate to assess and predict common adverse effects, but they are not adequate to assess rare adverse effects. If a blood dyscrasia is not seen in 3000 patients (a large number for most drug data bases pre-registration) it only means that, with 95% confidence, the drug will not lead to one case of agranulocytosis in 1000 exposures.

When one remembers that aplastic anaemia after chloramphenicol is estimated to occur in one out of 20 000 to one out of 50 000 patients, one can see why rare events are seldom detected on the basis of anything other than the widest kind of post-approval clinical experience.

It is not feasible, on the basis of pre-registration data, to predict drug abuse, except possibly in regard to psychotropic drugs subjected to the standard animal and human addiction liability screens. How could one have predicted the abuse of anabolic steroids, amphetamines, and growth hormone by amateur and professional athletes? Or of amyl nitrite by male homosexuals?

While one can study, prior to marketing, the potential for drugs to interact with other drugs

likely to be frequently co-administered, the possible drug-drug interactions are almost numberless, so most will have to await the post-registration clues and then studies. And even for the possible interactions that are assessed pre-registration, these assessments are often limited to short-term pharmacokinetic studies in a handful of subjects, with data being generated that may or may not predict pharmacodynamic interactions in actual practice.

The long delayed adverse effect (such as vaginal adenocarcinoma in young women exposed to DES *in utero*) or the side-effects seen only after prolonged usage (such as tardive dyskinesia with phenothiazines or the host of adverse effects after corticosteroid therapy) or the risk to the fetus of transplacental passage will ordinarily be appreciated only after registration.

Nor will we know, except in the case of gross bad luck, the effects of massive overdosage, accidental or purposeful, prior to drug approval.

**New uses of established drugs**

Let us also not forget the imperative need to search post-registration, for "good news" as well as "bad news". Many important new uses for drugs have surfaced only after a drug has been registered, sometimes years after the drug's approval. Consider the following partial list of drugs showing this pattern:

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| oestrogens and progestogens | oral contraception |
| medoxyprogesterone acetate | long-term depot contraception |
| antibiotics | perioperative prophylaxis |
| acetyl cysteine | paracetamol poisoning |
| probenecid | gout |
| immunosuppressants | rheumatoid arthritis |
| methotrexate | psoriasis |
| nonsteroidal antiinflammatory drugs (NSAIDS) | dysmenorrhoea |
| beta-adrenergic stimulants | premature labour |
| dantrolene | malignant hyperthermia |
| beta-blockers | anxiety, hypertension, migraine, thyrotoxicosis |
| central nervous system stimulants | hyperkinesis in children |
| antihistamines and scopolamine | motion sickness |
| diuretics | hypertension |
| imipramine | nocturnal enuresis |
| lidocaine | cardiac arrhythmias |
| thalidomide | lepra reactions |

**Filling information gaps**

Let us now consider the ways by which some of these information gaps may be filled in the post-registration period.

First, there is a need for on-going, general, free standing programmes. The best example of this is the individual case report, be it the British yellow card system or any other country's means for individual experiences to be filed and acknowledged in some way. Voluntary reporting has been responsible for uncovering most of the adverse reactions that were unknown at the time of marketing, and there is no reason for ignoring this proven technique for post-registration surveillance. It is not without its faults. It is never quantitatively correct; it can overreport as well as underreport; and the pattern of reporting can change over time — physicians being excessively cautious

in reporting adverse reactions that have never been reported before and then negligent about reporting them when they are well known.

Griffin and Weber (1) have recently reviewed the world experience with voluntary reporting, and their conclusions are interesting. They remind us that adverse drug reaction reports supplied to different national adverse reaction registers are collected in different ways and from different sources, with some countries deriving such reports almost entirely from spontaneous reports from doctors and dentists, others relying also on pharmacists, and two countries utilizing reports from patients, with several countries relying primarily on reports from the pharmaceutical industry.

Griffin and Weber point out that the rate of reporting associated with individual drugs can be influenced by a number of factors not necessarily directly related to safety of the product, for example media and monitoring bias. To quote them directly: "National drug regulatory authorities should make their adverse drug reaction data available to each other, but should have regard to the heterogeneity of the data collected and realize that extrapolation of ADR (adverse drug reaction) data from one country to another may be unjustified. There is no justification for "lumping" data reported to, or collected by the various national regulatory authorities into a single pool and regarding it as homogeneous".

Whatever system is used in a country, the contributors of data must receive feedback from central headquarters, so as to provide incentive for continued cooperation. There is no more effective way to discourage voluntary reporting than to make the reporter feel that there is no point to his efforts, and no better way to positively reinforce him than to treat him as a valuable ally.

In addition, however, there is also needed some sort of record linkage of a large population. A notable example is the system in place in the Province of Sasketchewan in Canada. There, for a million people, one has computerized linkage of all prescriptions to hospital records. It allows for cohort and other studies and for reliable quantitative assessments of various sorts. An example of the utility of such a system is a study that is not yet published but which has evaluated the role of NSAIDs in fatal gastrointestinal haemorrhage or perforation. This study concluded that such fatal events are almost unheard of in people under 75 years of age, for example, and while there is an added risk from taking NSAIDs, there is a considerable background incidence of disease unrelated to drugs which must be taken into consideration. Such a study puts dimensions on the problem with or without drugs, and suggests a possibility for invalid conclusions if one or another of the drugs in this class is disproportionately prescribed for elderly patients.

A variety of registries is also desirable; most important are registries for birth defects and for cancer incidence.

Secondly, in addition to the general approaches, one also needs *ad hoc* approaches, limited in scope and time; a few examples of these are given below.

In the United Kingdom, Inman (2) has instituted a "green card" system, wherein events are reported by a large group of cooperating general practitioners, with benefit as well as harm being capable of report. The cooperating physicians are asked not to worry about cause and effect relationships. This is an example of the sort of prospective monitoring of practitioner experience that can provide useful data on incidence.

In addition, comparative efficacy needs to be assessed, usually in the form of randomized controlled clinical trials, with the intention of developing knowledge on the average performance of old and new medications.

Follow-ups will be needed on suspected drug-drug interactions arising out of clinical experience.

"Risk factors" that seem detected in clinical trials or naturalistic experience, whether they seem related to a predisposition to benefit or a predisposition to harm, need to be pursued method-

ically to see whether such suggested predisposition is spurious or valid.

If pharmacokinetic and pharmacodynamic studies on the elderly, or on patients with renal or hepatic insufficiency have not been done prior to registration, these may be required after registration.

The profile for adverse drug reactions delineated prior to registration may require further studies to see whether the profile elucidated primarily in controlled clinical trials will be borne out in actual practice. The same will apply to adverse reactions that were suspected in pre-registration studies but not definitively nailed down.

Studies will at times be required of the incidence and nature of adverse drug reactions as a function of duration of therapy.

For extremely rare suspected adverse reactions, it may be necessary to do case control studies, since prospective studies or controlled clinical trials will be incapable of providing the required information.

Finally, studies may be desirable in the area of physician error. If a physician prescribes chloramphenicol for what the takes to be typhoid fever, which would appear to be a sensible recommendation, but in fact the patient's fever and splenomegaly are due to bacterial endocarditis, there would be an instance of a perfectly good drug being given for an inappropriate indication. Again, physicians may err considerably in the way they approach perioperative prophylaxis, usually in the direction of giving antibiotics for a much longer period of time than is recommended by the antibiotic experts. There is also a lack of sophistication in the prescribing of analgesics, with the tendency being to underprescribe in regard to both dosage and dosage interval.

Some special problems that need attention include the need for intensive follow-up of serious adverse reactions, such as fatalities (since meticulous scrutiny of the records will be necessary to validate the report), re-examination of the optimal dose for drugs (since in the area both of cancer chemotherapy and cardiovascular diseases, it is not uncommon for the doses recommended at the time of registration be higher than optimal), cost-benefit studies in regard to both economic benefit, and changes in the quality of life as a function of treatment, and the use of biological endpoints as substitutes for full scale randomized controlled clinical trials.

This last-named problem has to do with the fiscal and other difficulties involved in carrying out complicated, lengthy, and expensive trials in areas such as hypertension, diabetes mellitus, or atherosclerosis. It is not difficult to show that a drug causes short-term drops in blood pressure in hypertensive patients, or even persistent drops in blood pressure in such patients, but proving that such drug-induced hypotension has a desirable impact on the occurrence of cardiovascular events is quite another matter. Similarly, it is relatively easy to find out whether a drug lowers serum cholesterol, serum triglycerides, or blood sugar, but to prove that such biochemical alterations are accompanied by significant clinical benefit is considerably more difficult.

Society cannot afford to put every drug to the "gold standard" type of test, so we have to ask ourselves in what way can we match cases and study outcome so as to end up with a justifiable faith in the ability of drugs to achieve what is the ultimate purpose, not simply the intermediate one.

## Conclusions

Let us conclude with a number of principles which are fundamental.

1. Post-registration research is the largest methodological challenge facing us; by contrast, the methodology for doing controlled clinical trials is in most therapeutic areas reasonably well-established.

2. Since this post-registration methodology is not well worked out, there is a need for intelligent,

imaginative, and creative professionals to tackle the problems and the challenges; we do not need amateurs at this game.

3. The work that needs to be done cannot be performed adequately by any one segment of society; we need collaboration between industry, academia, and government, with a pooling of the requisite talents.

4. We cannot depend on any one technique for addressing all of the problems.

5. We need an epidemiological approach, because qualitative assessment of benefit or harm will not be good enough. It is in some ways very easy to know that a given drug can produce a given adverse reaction in a given patient. But such information may be trivial, when we really want to know what the picture is for all the patients treated with the drug, not simply one or a few. The field of pharmaco-epidemiology therefore needs to be supported and sustained.

6. Pharmaco-epidemiology systems have to be in place and ready to respond in a timely fashion when drug problems surface, because the pressures from the media and the political arena will be difficult to resist for the period of time required to accumulate data if such systems are not already in place.

7. For the optimal practice of medicine, we need to know the probability for good or for harm of diseases or symptoms, if they are left untreated, as well as the probabilities if one uses any and all of the therapeutic modalities available for treatment. We also need to know these probabilities as a function of age, gender, etc. Much of this information will have to come post-registration.

These, then, are goals to be addressed by society. We are far from achieving the desired goals for any disease and for any drug, but here lie our challenges, and here, ultimately, is where the health professions and the sick will derive either satisfaction or disappointment.

Finally, those who believe that the main reason for post-marketing surveillance is to remove dangerous drugs quickly from the markets should keep in mind that the public is harmed not only when an intolerably toxic or ineffective drug remains on the market, but also when a useful drug that is not intolerably toxic or ineffective is wrongly deprived of its license.

## References

(1) Griffin, J.P., Weber, J.C.P. *Voluntary systems of adverse reaction reporting.* Part II. Adv. Drug React. Ac. Pois. Rev., 1, 23, 1986.

(2) Inman, W. *Drug Surveillance Research Unit: University of Southampton.* PEM News, August 1983.