DRUG DEVELOPMENT COMMUNICATIONS, 1(5), 389-400 (1974-1975)

DRUG REGISTRATION - THE INTERNATIONAL SCENE*

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In the early years of this century the safety of medicines was entirely in the hands of the dispensing pharmist. With the discovery of the newer drugs and newer dose forms that require expensive plant and facilities beyond the capital resources of the small operator, the ultimate responsibility for quality and safety passed from the retail pharmacist to the drug companies.

Governments exercising control over drugs and drug products, insist that this responsibility still rests with the manufacturer and that the right of an injured consumer to proceed against the manufacturer remains unchanged. The government authorities in all countries are careful to point

*Based on a talk given at a symposium on New Product Registration at the Victorian College of Pharmacy, Melbourne, Australia on July 31, 1974.

out that they do not lift legal responsibility from the manufacturer, but merely ensure that he carries out his responsibility.

One can discern many reasons for governments standing over drug companies. One reason is that the government feels an obligation to its own agencies to check the quality of drugs bought or paid for by those agencies. Another motive, much more important for both good and bad reasons, is to allay public anxiety about drugs.

Sweden was the first country to establish a drug control laboratory with the motive of ensuring the quality of medicines, supplied as part of the welfare programme started in the 1930's. Since then, many countries have established drug controls for the same reason.

Drug technology and the associated chemistry and biology are very involved subjects usually beyond the understanding of even educated people. Though very important in everyone's life, drugs economically speaking represent a small part of total effort so that the number of people occupationally involved and hence informed, is small. The community at large is often given a mixture of truths, part-truths and untruths superimposed on a background of preconceived notions of obsolete medical theories, dishonest dealers in drugs, political corruption and the general unhealthiness of modern science.

To the extent permitted by the law of libel in a country, any struggling journalist or public affairs commentator can easily arouse public animosity against someone providing a useful public service, as well as against those dishonestly exploiting the hopes of the sick. These "stirrers" are always armed with a little more than a germ of the truth, as the drug recalls, the history of drug disasters and some public inquiries, will testify. Unfortunately over-reaction by panicky politicians often results.

Where the parties injured by drugs are emotion-generating people, such as foetuses, or if the injury is a fearful disease, such as cancer, then the hostility can be extreme and may result in the total banning of useful substances, like thalidomide and cyclamate.

Bizarre effects are sometimes produced as when an army of diet fadists marched on the FDA offices to protest against the withdrawal from the market of a cheap, highly advertised multivitamin tablet, withdrawn because of an unbalanced formulation and absence of stability data.

This motive of allaying public anxiety is, to a great extent, behind drug controls in all countries where they exist, but is most marked in the U.S.A., because of loose libel laws. The officials in the FDA have no protection from adverse publicity except secrecy. If there is a con-

templated drug recall or an adverse analytical report of even a minor nature the matter is kept under tight security, lest rash action is politically forced.

The FDA came into existence in the first place because of the sulphanilamide elixir disaster. At first the legislation was aimed at toxicity, safety and advertising, but recently it has come to be recognised that inefficacy, by replacing proper treatment, can be as dangerous as toxicity. The scope of the legislation has been widened to enable withdrawal on the grounds of lack of therapeutic properties including defective bioavailability, product stability or content uniformity.

In the U.S.A., there is more than adequate response to public pressure and Americans are as well protected against unsafe and ineffective drugs as is scientifically and organisationally possible. Recalls are relatively few and becoming fewer. Nearly all manufacturers are anxious to cooperate and the administration has a positive programme of manufacturer education. The small and hopelessly ignorant manufacturer, who contributes nothing to the health of the nation, has his products removed from the market.

The FDA has been admirably successful, even if somewhat aggressive, in tackling its task and is often held up as a model for other countries. It has now nearly completed

its work in the drug area and manufacturers are reaching such a standard that FDA controls would soon be no more than perfunctory. The officers of the FDA are now looking for other abuses in medical devices, cosmetics and perfumery.

A new and growing motive for drug controls is to maintain quality, whilst reducing prices. Governments that enter upon pharmaceutical and medical welfare programmes find that drugs are expensive and that taxpayer pressure can threaten a free or subsidised drug scheme.

There are several ways, by which prices may be reduced. A government with a pharmaceutical benefits scheme is in a powerful bargaining position as the main purchaser of drugs in the country. It can play off the originator of a drug against the usually more competitive "me-too" manufacturers. Even in the face of a monopoly, provided the drug is non-essential and provided public opinion is favourable, the price may be reduced by the government threatening to withhold purchase of the drug. The British Government has had spectular success in this way.

It is easy to reduce prices. The difficulty is to reduce or hold the price without compromising quality. The current legally enforced compendial standards are now seen to be not sufficiently high to protect patients from poor quality products. It has been the competitive situation

that has forced some companies to establish a reputation for higher than compendial quality. If the competition is to be shifted from the quality arena to the price arena, patients could suffer unless the higher standards could be enforced. This is the basis of a new motive for controls.

A powerful factor preventing price competition might be called the "trade name" factor. A manufacturer can establish a reputation for his trade name with prescribers by deft detailing. The medical profession can be relied upon to protect its right to prescribe only what it believes is best for the patient even to the point of specifying a particular brand. The exclusive right to a trade name is protected by law. When a drug is sold by several manufacturers the originator usually has a high research activity, a higher than compendial quality for his brand, hence a high reputation, a high sales volume and a high price.

The weakest part in all this is the trade mark law and it is difficult to see how the U.S. controversy about generic prescribing can be kept out of other countries. The most powerful argument in favour of trade names is the non-equivalence or the disparity between brands in the higher than compendial quality zone. So long as different brands have different bioavailabilities, different content uniformities and different expiry dates, then a brand has a real meaning for a patient. If the me-too manufacturers

can raise their quality to equal that of the originator, then the originator's reputation for putting out something better, could decline and competition would shift from the quality arena to the price arena. This is the state of affairs the Canadian Government is strenuously trying to achieve.

The Canadian Minister for Health and Social Welfare believes that if all interested parties are given regular up-to-date information on the quality and price of each brand of drug, then all manufacturers will equalize their quality at the maximum and competition will move into the price arena. The Canadian situation makes this look a feasible proposition. Firstly, with the notable exception of one company, there is no indigenous drug industry in Canada. Secondly, Canadian patent law provides no monopoly over a drug substance. Consequently, for each drug there is a multiplicity of brands, for example, there are 35 brands of diazepam, all in fierce competition.

Accordingly, the Food and Drug Directorate in Ottawa has set up an enormous product testing facility. They are systematically assessing the qualities of all the brands in a priority order based on the cost advantage to the nation. They call it the "Quad" programme. "Quad" stands for quality assessment of drugs. A regular Quad bulletin is distributed to all provincial governments, drug firms,

prescribers and purchasers. The bulletins list in simple tabular form the various brands of drugs, their relative bioavailability and other aspects of quality and the price per dose.

The methods developed for assessing the higher than compendial quality are being published in the pharmaceutical journals by the FDD and many of them may be incorporated into future editions of the world's drug compendia. It is only to be expected that different brands of drugs, conforming to future pharmacopoeial standards, would have generic equivalence. If this occurs, it will be difficult to sustain the protection of a trade name and there would be an unanswerable case for legalising brand substitution for many drugs.

The officers of the Canadian FDD are not optimistic about widespread price reductions following the Quad programme. They make the point that efficient production and fierce competition for a small market behind a tariff wall, are mutually exclusive. A large number of small competitors in a limited market cannot get the economies of scale required for low unit cost and competition will not reduce prices to cost. Drug synthesis is still a batch process so that unit cost is very dependent on batch size. Current trends in pharmaceutical technology are

toward faster production with more expensive equipment. The more competitors there are, the more advertising and promotion the purchaser has to pay for. Probably, the most costly ingredient will be the analytical and testing procedures imposed by the future compendial specifications. The establishment of formulation-to-bioavailability-to-dissolution rate relationship, the investigation of formulation and packaging to expiry date relationships and the checking of content uniformity could not be borne by a small manufacturer without a considerable rise in price.

Britain is a country with an inovatary indigenous drug industry and a large home market. The British are latecomers in drug and medicines control, but are rapidly building up controls on the scale required from the modest voluntary system that they had a few years ago. The major preoccupation at the moment seems to be to get parity with the Continental members of the European Economic Community.

A Licensing Authotiry constituted in 1968 as a result of the thalidomide disaster, answerable to the minister, is advised by the Medicines Commission, which was a small but highly qualified staff. Most of the policy is made by voluntary committees, comprising well-known people in the academic world. There is no laboratory facility and all investigations and testing are done by the Government Analyst,

the Pharmaceutical Society and pharmaceutical departments of universities.

Being in a transitionary stage, the Commission tolerates a few old non-toxic useless products for the time being. A blanket licence was given to all drug firms existing in 1968 and new ones are carefully scrutinised before licensing. There is an inspectorial system and the market is sampled. Licenses for products and for manufacturers can be withdrawn. The Commission is medically dominated and will valiantly defend the right of a medical practitioner to prescribe and have dispensed any brand he chooses. Generic prescribing is not even thought of. The government is putting the Commission to economic use in agriculture by directing it to control veterinary medicines.

In Switzerland, with a big exporting drug industry and a small home market, the registration authority is the Interkantonale Kontrollstelle für Heilmittel (IKS), in Berne. The offices and the staff are again very small. Laboratory facilities are only for chemical testing and biological testing is done by contract in universities and institutes. Drugs exported are controlled to the same extent as drugs consumed at home, which is comething no other country does. This is not simply to protect the health of foreign populations, but rather to protect the reputation of the Swiss drug industry. Medical services in Switzerland have weak

spots and are not well distributed into mountain villages. Consequently the IKS has to look after a large number of OTC's and see that they are well labelled with warnings against errors in self diagnosis. Abuses are restricted to foreign OTC's demanded by the tourist industry and some traditional herbal remedies. Their greatest difficulties are constitutional or legislative. The legal authority for the IKS depends upon a series of agreements between the pharmaceutical profession, the cantons and the federal government.

Between these four offices in the U.S., Canada, Britain and Switzerland there is communication. The staffs all know each other. They all demand similar information in new drug applications and applications for clinical trials. They have similar criteria of safety and effectiveness. In all countries, where it is legislatively possible, they license factories and warehouses handling drugs. The main variations are in the degrees of authentication. The Europeans tend to accept manufacturer's data; the Americans tend to check it for themselves. They all have substantially similar recall procedures and on-going monitoring of clinical experience after marketing has commenced. They all have a similar code of good manufacturing practice. They are all about to cover medical devices. They all have inspectorial systems and they even inspect foreign factories

making imported drugs and products. The British tend to rely more on licensing of the manufacturer, than on the licensing of his products, and so their inspectorial system is highly developed.

The various national control authorities recognise that if every country exercised its right to inspect foreign factories producing their imports, little production could ever take place because of a continuous congestion with inspectors. There is naturally a growing movement for international agreements, whereby some countries mutually recognise and accept each others reports.

One would think that all the controls could be managed by an international authority. For drug substances an international control is technically feasible. The Americans are generous with their information and even maintain a special foreign office in the FDA for this purpose. For products, international control is not a technical proposition because formulations, processes and equipment vary. It appears that each country must check its own products.