

Personal Perspectives

Fifty years of drug regulation: solid accomplishments and an important future

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This year, the World Health Organization celebrates its fiftieth anniversary. Throughout this time, WHO has been witness to an era of astonishing advancement in therapeutics. Drugs, vaccines and medical devices undreamed of a half century ago are now commonplace. Infectious diseases, whilst still a threat, are no longer the scourge they once were. Smallpox is gone and many terrible infections such as poliomyelitis and leprosy are on the way to elimination.

The control of cardiovascular disease, the major cause of death in industrialized countries, is now possible thanks to healthier lifestyle and effective drugs for the treatment of hypertension and lipid disorders. People with gastric ulcer, leukaemia, deafness, osteoporosis, schizophrenia, HIV infection, or asthma have all been helped by new treatments developed by physicians and scientists, many of whom are still involved in research today.

This therapeutic revolution has been born of the life sciences and the technological successes of scientists and the pharmaceutical industry. It has been stimulated by a continual demand for better health care. Notwithstanding these advances, this miraculous half century could not have taken place without the establishment of sound regulatory standards to provide an infrastructure conducive to ethical drug development.

Worldwide adoption of ethical standards for the conduct of clinical research

The requirement for voluntary consent was the first principle set out in the Nuremberg Code of 1947. This principle has since been universally applied by governments, and is codified in international law as Article 7 of the United Nations International Covenant on Civil and Political Rights. The second principle of ethical clinical research is the require-

ment for independent ethical review of each research proposal, as reflected in the Declaration of Helsinki. These two basic ethical requirements, as adopted by governments worldwide, serve not only to protect patients participating in clinical studies but to stimulate public trust in the enterprise of medical research. Without these standards, the development of new drugs and devices could not have flourished during the past fifty years.

Adequate and well controlled trials

The requirement for adequate and well controlled trials, which was first adopted by US Congress in the Food, Drug and Cosmetic Act amendments of 1962, was written into law with little debate and hardly any appreciation — at that time — of the profound impact that it would have on the future of medical research. But it has transformed the scientific culture of the pharmaceutical industry and researchers. Well-planned clinical trials, rather than anecdotal evidence and uncontrolled studies, became the norm, and from this change came about the current system for designing, conducting and evaluating clinical studies on new drugs. Slowly and inevitably, controlled clinical trials became the scientific standard for evaluating new drugs, new devices, and biologicals and have now been extended to include medical practices and treatment strategies. No regulatory standard has done more to improve the quality of therapeutic products than the requirement — adopted thirty-six years ago — that approval should be based on the evaluation of adequate and well-controlled clinical trials.

Development of spontaneous adverse drug reaction reporting

Assuring drug safety is the single, most important responsibility of regulatory agencies throughout the world. In spite of the best efforts by manufacturers to evaluate the safety of each new drug prior to marketing, the fact remains that between one and three per cent of newly approved drugs are eventually removed from the market because of unacceptable adverse reactions. Furthermore, many new products will be subject to labelling changes and possibly new warnings in the light of reports from post-marketing surveillance. This kind of safety experience can only be obtained from population use. Many nations, each in different ways, have

pioneered to support adverse reaction reporting and pharmacoepidemiology. Over the years, an international network of reporting systems and data bases has matured — many in collaboration with the World Health Organization. These various systems represent a major achievement in assuring the safety and accurate labelling of all marketed drugs. Without the network of scientists and physicians who diligently report individual adverse reactions, there would be little information to warn the medical profession, the pharmaceutical industry or the public of possible, sometimes serious, adverse reactions.

Adoption of "good practices"

Good manufacturing practice, or GMP, was a policy invention of the 1960s and the first WHO good manufacturing practices text was published in 1968. The key innovation in this regulatory approach was the concept that pharmaceutical products should be produced only by manufacturers who maintain independent quality control units and are regularly inspected by the authorities. The latest WHO GMP text additionally sets out general guidelines and standards to be applied during the manufacture of pharmaceutical products (1).

Later, in the 1970s, a similar proposal concerning good laboratory practices, GLP, became common practice to assure the quality of data in toxicology studies. More recently, the WHO good clinical practices (GCP) guidelines have been published (2), and adherence will assure clinical trial data which is adequate for regulatory purposes. The general approach of requiring companies to bring independent internal auditing and quality control to the essential data in drug dossiers has vastly improved the evaluation process and has established trust in the accuracy of information in these dossiers.

Constructive collaboration

In the 1960s and 1970s, the development of new therapeutic agents was, in many ways, dominated by an adversarial attitude between manufacturers and regulatory authorities. In order to improve the situation, both parties invested heavily in activities designed to improve both the science and policies of drug development. As a consequence of the thalidomide tragedy, manufacturers were faced with a severe regulatory environment which led them to adopt clinical development programmes of quality. This move towards more disciplined research slowly transformed the quality of applications.

Regulatory authorities responded by providing guidelines to clarify regulatory requirements, and many began to offer assistance to manufacturers in the planning of their drug development programmes. Of particular importance at this time was the establishment of open advisory committee meetings by the US Food and Drug Administration (FDA). These meetings are primarily called to advise the Agency on drug and device approval requests, but have become very useful to pharmaceutical manufacturers as an educational forum. They are regularly attended by industry representatives, not only from the United States but also from Europe and Japan.

Slowly but surely throughout the past two decades, the culture of drug development has evolved towards a carefully distanced partnership between industry and regulators, with the mutual intention of bringing useful new drugs more rapidly into medical practice. This trend has been stimulated by a shift in the tenor of consumer activism from a once overriding concern with drug safety during the 1970s, to a call for the rapid release of effective new treatments for serious and life-threatening illnesses such as AIDS. With such an environment in place, the advice of regulators can be of great benefit during the development process of new drugs, and will work to facilitate access to those in need.

International harmonization of regulatory requirements

Drug regulatory legislation tends to be country specific, and this means that drug development by multinational companies is a complex business. It may also create a situation where regulatory authorities can surprise each other with conflicting decisions. The World Health Organization takes credit for beginning a broad harmonization process which began in the 1970s, when regulatory officials were invited to consult on matters related to drug development, the rational use of drugs, scheduling of narcotic and psychotropic substances and recommendations on the safety, efficacy and quality of pharmaceutical products. Regulators of many countries met and came to know one another at the International Conferences of Drug Regulatory Authorities (ICDRA) which were initiated in 1980 in Annapolis, USA. The ICDRA continues to be held every two years and provides a forum to discuss issues of importance and to promote collaboration among drug regulatory authorities from both developed and developing countries.

The beginnings of international regulatory harmonization are rooted in the creation of the European Union and the need by countries within Europe to standardize procedures. This process has spread to include the United States and Japan in a consortium known as the International Conference on Harmonization (ICH), which is made up of a partnership of regulators and industry representatives from these three regions. Members of the ICH have worked hard and effectively to bring about the harmonization and mutual recognition of many guidelines including those on the content and format of new drug dossiers, and the conduct and analysis of clinical studies. Although we are not yet one world in terms of requirements for drug development, we are far closer than we were only a brief five years ago thanks to the ICH and the efforts of its members.

The future

The drug regulatory systems of many developed nations are now mature from a policy viewpoint. Standards exist for the safety, efficacy, labelling, advertising and manufacture of pharmaceutical products, and mechanisms are in place to assure the quality and accuracy of the data contained in the new drug dossiers. Extensive scientific and procedural guidance to the industry is available in the form of regulations, guidelines and fora. At last, it would seem that no major new requirements are of immediate necessity.

The expanding drug markets of the near future will be in countries such as Brazil, Mexico, India, China, Republic of Korea and the newly independent states, such as those of the former Soviet Union. Pharmaceutical manufacturing is already well established in these nations and clinical research is expanding. The innovation of new therapeutic agents cannot be far behind. The establishment of regional consortia of regulatory authorities to evaluate new drug applications submitted by member countries seems set to continue. Thus, while preserving its own independence, each country may no longer need to invest in a separate detailed review process and evaluation of the complete dossier. Since drug application review is labour-intensive, there is a real desire for cooperation in this area. Regional grouping may also be helpful in assisting poorer countries within the region whose public health resources could then be spent on priority issues of prevention and treatment.

The clearest immediate challenge to future regulators would seem, then, the need to keep abreast of

advancing technologies in gene therapy, materials science, and even nanotechnology. How will these interventions be categorized? What form will future therapeutic innovations take? How will regulators be called on to deal with control of these new methods?

As diagnostic medicine advances, new methods of measuring efficacy endpoints will continue to appear. It is also likely that more patients will participate in large clinical studies of simple design which are set up by networks of investigators. As the new millennium unfolds, new information technology will influence the sale and advertising of products, and drug regulation will evolve in line with these new demands. Although revolutionary computer technology will assist regulators in dealing with complex applications, final decisions will remain those of dedicated and experienced people.

A major ongoing challenge to future regulators will be to protect the integrity of the drug regulatory system. Regulation is a political target — which is as it should be in a free society. But the message must be reinforced that drug regulation provides a fundamental public health benefit. The drug regulators of the industrialized world, in spite of some occasional political criticism and a few celebrated errors and lapses, have a generally commendable and constantly improving record of evaluating important new therapies without undue delay. They also have an excellent record of dealing promptly with safety problems that threaten public health.

Public awareness of pharmaceutical development is at an all-time high as can be seen on many television news programmes and as evidenced by national expenditure on drugs. The pharmaceutical industry is flourishing, both financially and scientifically. This situation has come about from a propitious meshing of scientific knowledge, technical innovation, medical need, commercial demand and high regulatory standards. The result is a therapeutic revolution beyond the imagination of anyone practising medicine at the birth of the World Health Organization fifty years ago.

References:

1. World Health Organization. *Good manufacturing practices for pharmaceutical products*. Technical Report Series, No. 823, 1992. Annex 1.
2. World Health Organization. *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products*. Technical Report Series, No. 850, 1995, Annex 3.