



Drug Development and Health – How Relevant is the U.S. Model

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Abstract – *The achievement of systems for the effective, health-promoting regulation of pharmaceuticals in developing countries is a multifaceted and complex problem. Many countries are looking to the U.S. drug regulatory system as a model. However, a review of the U.S. system, while it reveals many positive aspects, leads to the conclusion that this system is not suitable for the developing world. Rather, the developing world must take on a leadership role, devising its own drug regulatory systems. These systems should not be negative compromises, but forward-looking, innovative, need-appropriate and cost-effective approaches. If they can be developed, world health will be the beneficiary.*

INTRODUCTION

The regulation of pharmaceuticals in developing countries is an important, but difficult problem. At issue are several sub-problems. The first is ensuring the availability of 'essential drugs' as defined by WHO¹. A related problem is obtaining necessary therapeutic agents at the best possible cost (which, in many cases, means minimising the drain on foreign exchange reserves). Quality, consistency of manufacture, and stability over time must also be assured. Drug distribution constitutes yet another major task. Physicians, nurses, community health workers and patients must be educated to use the drugs properly, and a system to monitor drug usage and adverse effects must be set in place. Provision for identifying new, more effective therapeutic agents must also be

made. All of this must be done with a minimum of economic resources.

Many countries have looked (and are looking) to the industrialised world for examples of how to carry out these drug regulatory and development tasks. Both the U.K. and the U.S. drug regulatory systems are highly regarded and frequently drawn upon not only for specific information on therapeutic agents, but also for regulatory standards and structure. But are they suitable models? It is the purpose of this paper to examine this question in relation to the U.S. model.

DRUG REGULATION IN THE UNITED STATES

The U.S. drug regulatory system has undergone many changes over the years. In its infancy, in the early

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1930s, there was little or no regulation. In 1938, a series of fatalities resulting from a change in the solvent for sulphonamide drugs by one pharmaceutical company led to the formation of the Food and Drug Administration and the requirement that all therapeutic drugs be tested and approved for safety.

Twenty-four years later, in 1962, a series of birth deformities associated with the use of a sedative drug, thalidomide, in pregnant women in Europe led to much more stringent regulation. Now, according to the Food, Drug, and Cosmetic Act of 1962, both safety and efficacy for any new drug had to be established.

Actually the thalidomide story only brought together a series of threads leading to more government regulation of pharmaceuticals. A series of Congressional hearings was conducted by Senator Kefauver in 1959 to explore drug company profits and collusion. Other issues identified by a variety of witnesses from industry, academia and government included the need to certify the quality of batch antibiotic production; the irrationality of fixed-ratio combinations of antibiotics; the need to instruct physicians in the use of a drug (package inserts); the quality of safety and efficacy data needed for approval; the lack of informed consent procedures in the investigation of experimental drugs; means of speeding drug development; the costs of drug promotion; compulsory cross-licensing for patent protected products; and the relationship of the FDA to industry.

Catalyzed by the thalidomide tragedy, the Food, Drug and Cosmetic Act of 1962 was passed. A crucial feature was the scope given to the FDA to draft regulations that, in effect, set policy. Some of the issues over which the FDA had authority were of major importance to the future shape and direction of U.S. drug regulation. Initially, the FDA had to define its role. Was it to protect the public or, more broadly, to promote the health of the public? The FDA chose to emphasize the former as a regulatory agency. Recently, then-Commissioner Frank Young undertook to speed up the regulatory process to make it more responsive to health needs such as those of AIDS, but the emphasis of the FDA continues to be on protection.

Another critical issue was whom the FDA regulated. A clear target was the pharmaceutical companies. The FDA had authority to determine drug approval for specific indications, thus establishing the indications for which a company can market and advertise a drug. Not clear was whether this authority extended to the practice of physicians, i.e. if an indication for a given drug was not listed by the FDA, was the physician permitted to prescribe it for that purpose? Initially the FDA felt that prescriptions could only

be written for approved indications, but the practicalities of policing such a restriction were enormous and the policy was vigorously resisted by the medical profession. In the *FDA Drug Bulletin* of 1982, the FDA said,

'The Federal Food, Drug and Cosmetic Act (of 1962) does not limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labelling. Such 'unapproved' or, more precisely, 'unlabelled' uses may, in fact, reflect approaches to drug therapy that have been extensively reported in the medical literature².

Despite this clear statement of FDA policy, the 'approved' (listed) indications for a drug carry substantial weight with physicians, especially in the highly litigious medico-legal climate in the U.S. today. Physicians simply feel that it is safer not to stray from what the FDA has determined can be listed.

A third major area of the 1962 FD&C Act was its requirement of evidence of both safety and efficacy prior to FDA approval for marketing of a drug. The language of the act specified that there must be 'substantial evidence' of efficacy for approval. The FDA was left to define what 'substantial evidence' was. The definition was cast in terms of adequate numbers of randomized, double-blind, placebo-controlled studies. Comparative efficacy, i.e., the effectiveness of the test drug compared to that of a standard therapy, also became an issue. Beyond its definition of 'substantial evidence,' the FDA extended its involvement to the actual design of drug investigation protocols and a determination of their safety. Thus the FDA's various divisions became active participants in the drug approval process.

Over the years since 1962, with the latitude and authority given to it by the 1962 legislation, the FDA has defined and redefined the entire process of drug development and approval. There have been many positive results of this process. The introduction of good manufacturing practice (GMP) and good laboratory practice (GLP), in 1962 and 1979 respectively, have provided consistency and served to maintain quality and protect against unscrupulous or careless manufacturers. There has also been a reduction in the number of ineffective medications and/or combinations of medications that plague many developing countries. Arguable, but less easy to establish, is the case that the public has also been protected from the too-rapid introduction of new drugs with potential, and perhaps unexpected and dangerous, side-effects. Finally, it may be added that the evidence for efficacy of any new drug reaching the market is better established now than ever before.

The beneficial elements of the system cannot be denied. However, there is a down side. The result of the FDA's approach to these critical issues within the FD&C Act of 1962 has been an enormously complex and expensive drug development and approval process.

Typical figures for the time requirements of each stage of the process for a new chemical entity are as follows³:

Chemical lab (synthesis, purification)	0.5 yr.
Pre-clinical (pharmacology, toxicology)	3.5 yr.
Clinical development (phase I,II,III)	6.6 yr.
NDA approval	2.7 yr.
Total	13.3 yr.

One consequence of this lengthy process is the loss of useful patent life for a new chemical entity. Recent legislation has tried to alleviate this problem (the U.S. government returns part of the IND development time and most of the NDA review time back to the manufacturer when the drug is approved), but it is difficult to eliminate it when the drug development and approval process is so long.

The analysis of the effectiveness of any drug regulatory policy must be assessed in risk-benefit terms. One criticism of the current U.S. system is that, rather than protecting patients, it actually harms them by denying them access to new therapeutic agents in a timely manner. Critics point to the drug lag, the lag between the availability of a drug in the U.S. compared to the United Kingdom or other European nations. A clear example is that of the anticonvulsant valproic acid or sodium valproate, which was in very effective clinical use in Europe for 13 years before it was approved in the United States. There are other examples.

Time is not the only issue. Cost is another major factor. According to recent figures from the Center for the Study of Drug Development⁴, in 1990 the total cost of development of a new drug from initial synthesis through FDA approval for marketing is US\$ 231,000,000 and the time required for the process is 12–13 years. This is up from US\$ 54,000,000 in 1979, and 10 years and US\$ 125,000,000 in 1986. The process is not only expensive, but also risky. According to the Pharmaceutical Manufacturer's Association only 5 of 4,000 compounds screened in pre-clinical testing make it to human testing and only one of 5 tested in people are approved. Despite all this, and perhaps in part because of it, the U.S. pharmaceutical industry will invest US\$ 8,200,000,000 in drug research and development⁵. This figure represents 16.8% of total sales.

An important footnote to this discussion is that, despite all the time and money spent on drug develop-

ment in the U.S. model, there are still holes in the system. According to a recent U.S. government agency report⁶, 'serious' post-approval drug risks were identified for 41% of the new drugs approved between 1983 and 1985.

It is easy to be critical of a ponderous bureaucracy. All the problems are not the FDA's fault. Much of the over-regulation has resulted from an increasingly litigious U.S. society which feels that there should be no risks in health care.

Whatever the sources of the problems, the U.S. system for bringing medicines to the public is flawed. Some flaws are to be expected, and many can be tolerated. However, the cost of the process mandates change. With the U.S. already spending close to 11% of its gross national product (GNP) on health⁷ it is estimated that, at the current rate of increase, in 60 years the entire GNP will be taken up by health care costs⁸. With talk of rationing health care in the U.S. because of cost, the FDA system is going to have to change. The question is not 'if', but 'how soon'.

DRUG DEVELOPMENT, REGULATION AND HEALTH IN THE DEVELOPING WORLD

If the U.S. cannot afford its drug development and regulatory process, then developing countries with a host of basic structural and logistical problems to solve can certainly not afford it. And the issue is not just one of direct cost; poor health is enormously costly to society as a whole. Promoting health and providing better health care are national imperatives everywhere.

Having said that there are useful elements in the U.S. system, what approach should developing countries take to drug development and regulation? Certainly the point is not to create lesser systems, but rather systems that are realistic, practical, and of first quality. A critical and very basic step has been the adoption of the WHO Essential Drug List. This is a good example of optimal utilisation of available knowledge for the common good. Furthermore, it is cost-effective. However, adoption of this important policy only addresses part of the problem. New therapeutic agents and modalities are needed to deal with a wide variety of pressing problems. How are such agents developed or introduced to the system? How does a country with limited economic resources promote the health of its people in this respect?

One frequently-used approach is to allow the industrialised nations to lead the way. In this scenario a developing country only approves drugs that have already been approved in the U.S., the U.K. or Europe. While there are arguments and realities that favour such an approach, there is also the fact that

the drug development priorities of the industrialised world are frequently not those of the developing world. The economics of drug development in the industrialised world also push pharmaceutical companies to develop expensive, patent-protected drugs which will return their very substantial investment. Tropical diseases are generally not the subject of intense interest or investment. In other words, this approach, although of some value, is simply not sufficient for the developing world.

The only alternative is for the developing countries to take an active, leadership role in the drug development and regulation process. Is such a plan realistic or is it just empty talk? It can be made realistic, but slavish adaptation of developed-world models won't work. Unfortunately, the latter seems to be the trend. What is happening more often than not is that the worst aspects of the systems are being adopted. Instead, the developing world should create its own models. The following are suggestions for such systems:

- **Careful planning and prioritising:** Good epidemiologic data defining just what, and how extensive, the critical health problems are, is essential. What disorders should be attacked first? Where are these problems most severe?
- **Essential drugs:** Based on the picture of diseases and symptoms defined above and the WHO Essential Drug List, an appropriate National Formulary must be established. The currently available drugs need to be examined critically. The WHO Essential Drug List contains approximately 250 entries. Some countries have as many as 16,000 pharmaceutical agents and combinations of agents available on the market. Many of these are ineffective or even harmful.
- **Drug supply and distribution logistics:** The national health/disease priorities defined above must be matched to national economic resources and pharmaceutical manufacturing capability. Importation of drugs may be necessary in many cases, but minimizing this is clearly desirable. Whatever can be done in-country, such as final encapsulation or packaging of imported bulk materials may be options to consider to encourage the development of a national industry. For the existing national pharmaceutical industry, collaborative efforts between the public and private sectors or within the public sector should be targeted at redirecting production to meet the needs and priorities defined above. Finally, careful thought, and sufficient funds, must be devoted to setting up a satisfactory distribution system.
- **Quality control:** Good Manufacturing Practice (GMP) as required by section 501(a)(2)(b) of the

U.S. FD&C Act, whether of externally or internally produced drugs, needs to be assured. This means licensing and ongoing monitoring of manufacturing facilities. Where two or more generic equivalents of a drug are available, bioequivalency must be established or, at the very least, instructions given to exercise care in shifting from one drug to another. To avoid costly re-duplication of facilities and databases, arrangements for sharing information with other countries should be developed.

- **Communication and education:** An ability to tap into national and international therapeutic databases such as MEDLINE and TOXLINE from the National Library of Medicine in the U.S. or European or multinational databases must be made available. This availability must extend in one or another form to physicians and other health professionals in the rural as well as urban areas. The advent of the newer computer and satellite technologies makes it possible to think of new two-way communication systems that should make up-to-date medical advice and information accessible almost everywhere. Continuing education and support for physicians, nurses, and other health workers should be much easier now and cost-effective than it has been in the past.
- **International collaboration:** Working closely with other nations, both developed and developing, is a must. With the world's resources for health extremely limited, and the problems especially acute in the developing world, collaborative efforts are the only way.

Both regional and more distant networks of co-operation, which involve sharing clinical data and experience, as well as basic clinical pharmacologic information and quality-control data, should be formed. Such networks can also pool information and resources about basic health problems and how they might be approached therapeutically. Collaborative clinical research efforts can be initiated.

There are vehicles such as WHO through which international efforts can be channeled. Links of the various states or regions within a country such as India or Ghana should also be feasible. New linkages between industry, government, academic and private or non-governmental organisations need to be formed as well. A given nation's best and most idealistic talent needs to be engaged in this work.

When all is said and done, two principles emerge. Whatever the details of the system or systems planned, improved health must be kept clearly in sight as the goal. The system is not the goal, nor should it be allowed to take over or obscure this goal — 'Health for All'. The second overriding principle is that we must optimize the use of resources available to us

now. There is a tendency to say that we could do more if only we had more resources. There is nothing wrong in hoping for more resources, resources diverted from military spending for example, but we cannot be paralysed in the absence of these resources. We can do much more with what we have.

CONCLUSION

In conclusion, there are many good things about the U.S. system for drug development and regulation, but the system taken as a whole is not suitable for the developing world. Keeping the good parts, the developing world must devise new systems suited to their needs and realities. These new systems should not be negative compromises, but forward-looking, innovative approaches that, in the end, will teach the industrialized world how to accomplish more with

less, a lesson it too must learn. World health will be the beneficiary.

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Vitamin A and Children's Mortality

India has approximately half the world's children afflicted with various degrees of vitamin A deficiency. This means that children with mild to severe vitamin A deficiency in India comprise a staggering figure of up to 20 million. Vitamin A deficiency contributes significantly to the morbidity and mortality of children in India. In the light of these facts, a controlled, masked, randomized clinical trial involving 15,419 pre-school-aged children was done in South India. The children were allocated to two groups, one of which received 8.7 micromol of vitamin A (8,333 IU) and 46 micromol of vitamin E (20 mg), the other which served as a control group received just vitamin E for 52 weeks. The baseline characteristics of the children were similar. The incidence of vitamin A deficiency and malnutrition was high in both groups. Community health workers delivered the vitamin supplements weekly for the entire period of the study and recorded morbidity and mortality. The results of a regular provision of vitamin A supplement equivalent to that obtainable from foods in children with vitamin A deficiency demonstrated a significant reduction in mortality (average: 54 per cent). Although the evidence supports the immediate implementation of vitamin A programmes in populations with confirmed vitamin A deficiency and protein-energy malnutrition, such programmes will be beyond the resources of many of the developing countries.

Excerpted from Rahmathullah L, Underwood B A, Thulasiraj R D et al. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A.

The New England Journal of Medicine 1990; **323**: 929–35.

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"The works of the great painters, musicians, and scientists of the past are surely no greater a reflection of the nobility of the human spirit than are the scientific and technical achievements of modern medicine. There is no human endeavour, other than the feeding of the hungry, to which the ingenuity of man can be better devoted".

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