



Clinical Drug Development in Developing Countries – Theory and Practice, Myths and Realities

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Abstract – Development of new drugs, new formulations of old drugs for existing and new indications, and their consequent promotion, are parts of a balanced and disciplined structure in almost all developed countries. This structure is dependent on the responsible and reconcilable role of each of its four important segments – doctors, consumers, governments and pharmaceutical companies. The evidence hitherto available from many developing countries suggests that the contribution of each of the above important and interdependent balancing influences on drug development falls far short of its obligations to the population at large and to responsible health care. Examination of the Indian scenario confirms beyond doubt this regrettable observation.

Although drugs do not guarantee health, availability of essential drugs at affordable prices, elimination of all irrational and hazardous drugs and drug combinations, cessation of indiscriminate proliferation of an already bewildering array of many thousands of formulations, and availability of information on drugs to the public, are mandatory changes long overdue in all developing countries, including India. Furthermore, the enforcement of Good Manufacturing Practice (GMP) and Quality Assurance (QA), by statutory measures, if necessary, and implementation of guidelines of Good Clinical Practice (GCP), are the needs of the hour. These and other related issues will be discussed in this paper.

INTRODUCTION

Medicines were first subjected to quality control and prescribed standards in Europe at the School of Salerno, Italy in the 13th century. Later, in the 15th and 16th centuries, quality requirements for medicines were laid down in England, France and Scotland. London had its first 'Drug Inspectors' in

the early 15th century. The Therapeutics Substances Act was passed in England in 1925 to control medicinal products of biological origin, long before the ever-increasing therapeutic armamentarium exploded on the practising physicians after the second World War¹.

The thalidomide tragedy of the late 1950s and the early 1960s provoked the legislation of safety of medicines, to be followed later by the introduction

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of statutory requirements of efficacy in addition to safety and quality within the next few years. Since then, governmental regulatory authorities have been set up in many countries around the world, both developed and developing. The standards of these authorities vary widely. Attempts are being made in Europe to harmonise the requirements of the member states to ensure uniformity and higher standards. In many developing countries, the drug regulatory requirements are based on those of the Food and Drug Administration in the United States of America – the FDA. However, in reality, the regulations are either unimplementable because of obvious local inadequacies or, when implemented, leave a lot to be desired. Notwithstanding these facts, there is no alternative to controlled evaluation of safety, efficacy and quality of drugs in the local environment. Further, this must be tailored to fulfil certain essential and mandatory minimal requirements, particularly in the clinical setting so that data generated are reliable and relevant.

DRUG DEVELOPMENT

As the process of discovering and developing new medicines is expensive, risky and time-consuming, basic and applied research for this purpose is seldom, if ever, undertaken, in developing countries. So-called research is, therefore, invariably confined to pharmaceutical re-formulation of drugs already extensively tested, and clinical trials of these formulations on patients which are, at best, inadequate replications of numerous double-blind randomized studies performed and approved, in the West.

The drug regulatory authorities in developing countries, as of now, accept reports of extensive pre-clinical studies, e.g. animal pharmacology, animal toxicology, teratogenic, perinatal and reproduction, mutagenicity and carcinogenicity from recognised laboratories and institutes in developed countries. The requirements are similar to those in developed countries. In India, applications for permission to import a new drug have to be made in writing to the licensing authority and an Import Licence granted, prior to repeating some of the pre-clinical and clinical studies stated above.

DEFINITION OF NEW DRUG

The definition of a new drug, in accordance with the statutory requirements of the Ministry of Health and Family Welfare of September 21, 1988,² is as follows:

- A new substance of chemical, biological or biotechnological origin: in bulk or prepared dosage form; used for prevention, diagnosis or treatment of disease in man or animal; which except during local clinical trials, has not been used in the country to any significant extent; and which, except during local clinical trials has not been recognized in the country as effective and safe for the proposed claims.
- A drug already approved by the licensing authority for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration.
- A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz. indications, dosage form (including sustained release dosage form) and route of administration.

For the purpose of this rule, all vaccines shall be new drugs unless certified otherwise by the licensing authority. Furthermore, a new drug shall continue to be considered as a new drug for a period of four years from the date of its first approval or its inclusion in the Indian Pharmacopoeia, whichever is earlier.

CLINICAL TRIALS

Permission to initiate clinical trials may be obtained along with the permission for a test license to import or manufacture the drug, if the protocol for the proposed clinical trials, case record forms (CRFs) to be used in the trials, the names of investigators and institutions are submitted and approved.²

The clinical trials required to be performed in the country before a new drug is approved for marketing depends on the status of the drug in other countries. If the drug is already approved/marketed, Phase III clinical trials are required². If however, the drug is not approved/marketed elsewhere, clinical trials are generally allowed to be initiated at one phase earlier to the phase of clinical trials in other countries². In actual fact, if the drug is approved for marketing in the UK and/or the USA, it is looked upon more favourably than otherwise. For new substances of therapeutic potential discovered in India, clinical trials are mandatorily required to be performed from Phase I.

Other clinical trial requirements such as ethics committee approval of proposed studies, suitably experienced and qualified investigators (clinical trialists), monitoring trial procedures, etc. are similar to those demanded in developed countries.

DISCUSSION

The reader will be impressed by the regulations and guiding principles enunciated so far. **However, there is a yawning gap between theory and practice.** It is beyond the scope of this paper to discuss every aspect of the complex and confusing manner in which drug development and production are undertaken in India. If one starts with the universally accepted twin basic concepts of health being a fundamental human right in modern society, and medicinal products being an important segment of health care, an examination of the Indian scenario yields depressing results. First and foremost, these concepts do not receive the attention they deserve. Secondly, policies and priorities do not take into account urgent national needs. Instead, they serve the vested interests of those in the corridors of power and their cronies. Health has not figured as a critical parameter for various post-Independence Indian governments, whatever their political hue. This is reflected in the dismal allocations of funds, two per cent or thereabouts, of GNP, for health care in successive five-year plans. Scant attention is paid to the quantity and quality of medicines required to satisfy the health care needs of the majority of the population. In contrast to the World Health Organisation's recommendation that 250 essential drugs are adequate for the treatment of more than 80 per cent of diseases that afflict human beings around the world, the Indian pharmaceutical market flaunts 60,000 (or more) formulations which cost the exchequer in excess of 25 billion rupees. And, in spite of these enormous costs, most essential drugs are either in short supply or not available.

The regulations governing drug development and production are largely confined to the statute books. No serious and/or sustained attempts are made to stop the indiscriminate proliferation of an already bewildering array of many thousands of formulations. Product licenses for life-saving drugs and drugs for serious illnesses are granted to pharmaceutical companies without ensuring their strict compliance with statutory Indian Good Manufacturing Practice (GMP) and Quality Assurance (QA) requirements. This, in itself, is an error of omission which can have grave consequences. As Smith writes in his paper³, 'the introduction of Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) in 1962 and 1979 respectively, in the USA, have provided consistency and served to maintain quality and protect against unscrupulous or careless manufacturers'. He also notes that there has been a reduction in the number of ineffective medications and/or combinations of medications³. In the developing countries, particu-

larly in India, the system of implementing GMP and QA is woefully inadequate, and accountability and penalties for those violating statutory requirements are almost non-existent. These are matters which merit urgent attention and action, not mere rhetoric.

There are no regulations governing Good Clinical Practice. The principles to ensure acceptable and reliable standards of Good Clinical Practice (GCP) which are pertinent to all phases of clinical investigation of medicinal products are often ignored, thus, at best rendering the data generated from many clinical trials suspect. Rondel⁴ puts it simply: 'Good Clinical Practice is about establishing procedures for conducting clinical research to the best international scientific and ethical standards'. The basic measures that he advocates to implement GCP⁴, are reasonable and do not need the gadgetry of high technology medicine. In fact, the principal ingredient is the 'culture of clinical research'. This is sadly lacking in the Indian environment⁵ and in other developing countries. Booth⁶ has eloquently and persuasively argued: 'We need clinical research for four main reasons. Firstly, it contributes to . . . scientific knowledge from studies of man in health and disease. Secondly, it develops and applies advances in basic sciences and technology to effective investigation and treatment of human disease. Thirdly, it . . . assesses both new and existing methods of clinical practice. Finally, it ensures that undergraduate and post-graduate teaching do not degenerate into dogma'. In the specific context of drug development, clinical research is capable of generating good clinical trial data of acceptable international standards, both from the ethical and scientific standpoints. This, in turn, can be of immense commercial value. Thus, GCP is cost-effective and accelerates the process of international acceptance of the drug. Developing countries are best advised to formulate guidelines to ensure reliable clinical data from local studies which will benefit all concerned.

The regulations currently governing clinical drug development in many developing countries, constitute nothing more than inadequate, inappropriate and irrational adaptations of models of the developed world, particularly the U.K. and U.S.A. as far as India is concerned. This policy is fundamentally flawed because it fails to take into consideration the basic norms of clinical trial methodology on the one hand and the paucity of expert and experienced clinical trialists with the required clinical and laboratory facilities in the country, on the other. The statutory requirements are absurd and incongruous if one takes into account the number of drugs being approved and the number of trials required for each of the drugs by the regulatory authorities. Let me illustrate

this point by quoting the requirements as stated in The Gazette of India; Extraordinary²: 'If the drug is already approved/marketed in other countries, phase III data should generally be obtained on at least 100 patients distributed over 3–4 centres to confirm the efficacy and safety of the drug in Indian patients when used as recommended in the product monograph for the claims made'. It need hardly be added that such data, even if obtained from completed studies, cannot provide meaningful – let alone conclusive – evidence of safety and efficacy. Furthermore, 'if the drug is a new substance, discovered in India or elsewhere, and not marketed in any other country, phase III data will have to be generated on at least 500 patients distributed over 10–15 centres and data on adverse reactions should be collected in 1000–2000 patients'². The infrastructure required to perform such studies is available in very few centres and it cannot but be surmised that the data submitted to the regulatory authorities may not be of an acceptable standard, if scrutinised. This leads to the next valid observation that the regulatory authorities are ill-equipped, understaffed and unable to provide the required standard of discerning evaluation. The result of this charade is the worst of both worlds. As Smith³ states bluntly but accurately: 'Slavish adaptation of developed-world models won't work. What is happening more often than not is that the worst aspects of these systems are being adopted'. This is being effectively illustrated by the following example. The drug regulatory authorities in India routinely request data on 100 patients from three or four clinical trials of a test-drug approved/marketed else-where. Such trials will almost certainly produce inconclusive data on safety and efficacy, although a bureaucratic requirement may be fulfilled. Instead, one well-designed, dose-finding, pharmacokinetic/bioavailability study will give far more useful information on the drug, its unit dose and daily dosage in the local population. It is well known that lower body weights, nutritional status and genetic differences influence the dosage of drugs. Even more ridiculous and indefensible is the fact that clinical trial data are not required for approval of a herbal medicine.

It is about time that India, as one of the leaders of the developing world, after almost four and a half decades of independence, unequivocally accepts the gross incongruity of the present drug regulations and reverts to the drawing board to create a model of drug development, evaluation and approval as part of a comprehensive health care system which takes into account the needs of the people. It is abundantly clear that policies of successive governments have failed to yield desirable results. Essential drugs of consistent quality, in required quantities and at afford-

able prices are not yet available. Hazardous and irrational drugs and drug combinations continue to be manufactured and marketed. Indiscriminate proliferation of an already bewildering array of many thousands of formulations, continues unabated.

THE FUTURE

Clinical drug development in developing countries must be based on models relevant to the health problems and therapeutic needs of the people. Essential drugs of consistent and reliable quality, manufactured in adequate quantities, and at affordable prices to the majority of people must always take precedence in developing countries over indiscriminate and irrational proliferation of drugs acquired from developed countries at considerable expense. The WHO essential drugs programme should be used as a model to encourage controlled clinical development of drugs and good prescribing habits. The limited financial resources allocated to health care in developing countries merit urgent review and suitable increases for optimal use in the prevention and treatment of illnesses primarily responsible for mortality and morbidity, and to improve existing therapeutic modalities. Good Manufacturing Practice (GMP) and Quality Assurance (QA) must receive significantly greater attention than at present, to ensure high quality drugs. Defaulters must be accountable and appropriately penalised. Regulatory authorities should be strengthened, subjected to the same scrutiny as those whom they regulate, and held responsible for lapses on their part and/or if they compromise standards. Guidelines for Good Clinical Practice (GCP) should be introduced so that clinical trials improve in quality and yield meaningful results.

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