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PREFACE

The tripolar base of drug manufacturers, regulating and enforcing agencies and the public is essentially germane to the co-ordinated health needs and well being of mankind. The three partners may not be working at cross purposes but do have particular interests distinctly different. A forum like the present one has attempted to bring together different view points concerned with the necessity of laying the common ground work; and perhaps the present monograph may serve to justify this expectation.

From the humble beginnings of vitrually no regulation and safety measures for food and drugs, there has been a sea change today. The impact of growing technology, experiences of adverse side effects of drugs, the concept of quality control and bioequivalence, among others, have brought in its vogue the necessary laws and methods to achieve optimisation. Section I sets the pace by giving a glimpse of the historical perspective of the evolution of food and drug laws, the problems and remedial measures that need to be tackled and some idea of the responsibilities, organisation and working of the government food and drug enforcing agencies as also concrete suggestions for preparing and processing of requests by drug manufacturers.

Terms like bioavailability and bioequivalence have remained not explicitly answered or understood. Bioequivalence problems and requirements have, inter alia, some local overtones. For instance, the Canadian experience may reveal aspects different from the Indian context. These and other features like current status contrasted with concepts in traditional system of medicine are ably addressed in Section II.

Section III deals with the evaluation of bioequivalence studies in their proper perspective and covers *in vitro* dissolution methods, statistical dimensions and non-linear pharmacokinetics of specific drugs.

How the proper understanding of bioavailibility, bioequivalence and pharmacokinetics help improve the production of right drugs with right dosage forms, minimal side effects and cost-effectiveness is illustrated in Section IV. Development of drugs for groups of diseases like tropical diseases, specific drug development as anti-infective agents, transdermal and ophthalamic drug delivery systems and comparison of slow releasing Diclofenac *vs* enteric coated tablet and Voltaren retard preparation, are some examples to show the implications of such understanding.

It is hoped that the monograph would be of interest to a wide specturm of the society ranging from the pharmaceutical scientists to government controlling

and regulating agencies, companies and institutions involved in drug research and development, and lastly but not the least – the consumer.

The monograph is based on the First Indo-US Symposium on "Generic Drugs, Bioequivalence and Pharmacokinetics", held in Delhi in February, 1988, and its publication has been supported under Special Foreign Currency Funds. The active interest of Dr. S.V. Dighe and Dr. R.M. Mhatre of United States Food and Drug Administration, Dr. D.L. Madden, S&T Counsellor, American Embassay, Delhi and Mr. M.M.L. Saxena of the same office and the ever willing help from our colleagues in UCMS is greatly appreciated. Drs. Prabha Mahajan and Pramod Mediratta need a special mention for their untiring efforts in going through the manuscripts.

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The US Food and Drug Administration: Responsibilities, Activities and Organization

WALTER M BATTS

Responsibilities of FDA

As a consumer protection agency, FDA's mission can be characterized simply as helping people protect themselves in ways in which they cannot protect themselves alone. The vast range of products regulated by FDA include not only human foods and drugs, but foods and drugs intended for animals, as well as cosmetics and most types of medical equipment.

FDA's activities contribute to prevention, diagnosis and treatment of disease. This is achieved by a variety of functions, ranging from new product review to educational activities designed to promote the safe use of product in the market.

Authorization for FDA to perform its various functions comes from the US Congress through the legislative process and the passage of laws. The roots of FDA's responsibility began with the passage of the 1906 Pure Food and Drug Act, which prohibited misbranded and adulterated foods, drinks and drugs in interstate commerce. However, the inadequacies of the 1906 Act were painfully revealed when, in 1937, elixir of sulfanilamide killed over 100 people. This tragedy ignited the US Congress to pass the Food, Drug and Cosmetic Act of 1938 (FD&C Act) which required, among other things, that drugs be proven safe before marketing and that FDA perform factory inspections.

The FDA has grown in the last 20 years via amendments to the 1938 act and the transfer of many responsibilities to the FDA. Generally, the act gives FDA authority to regulate only those products that move in interstate commerce, i.e., move from one state to another. Products offered for import into the US are considered to have moved in interstate commerce and therefore are also subject to the FD&C Act.

Activities to carry out responsibilities

The FDA issues *Standards and Regulations* to implement the laws passed by Congress. These include good manufacturing practices to assure sanitary/sterile processing and quality control; labeling standards for ingredients, nutritional information, and drug use instructions; and monographs for OTC drugs which specify ingredients, amounts, and labeling.

Pre-market approval activities allow FDA to protect the consumer by reviewing data on product safety and efficacy before the product may be marketed. These

pre-market reviews are conducted for drugs and biologics, class III medical devices, and food and color additives. It is important to note that the law does not require pre-approval of most medical devices, cosmetics, and food substances other than additives.

The FDA's activities don't stop once a product is approved for marketing. In some respects, the job has just begun. Because initial testing only involves a relatively small number of subjects, we must maintain an effective *postmarketing surveillance* system. As part of this system, adverse reactions are reported by physicians voluntarily, manufacturers mandatorily, and selected hospitals and states under special agreements. The FDA uses automated systems to track the approximately 95,000 adverse reaction reports received yearly.

The law also recognizes the need to *monitor* the market place constantly to assure the safety and quality of products. The statutes provide FDA the authority to inspect establishments, examine samples and conduct investigations to see that product quality standards are being met at every stage of the commercial system.

Although FDA strives to promote voluntary compliance with the law, legal actions such as regulatory letters, seizures and prosecution can be taken if necessary. Where, there is a clear health hazard, manufacturers can usually be convinced by the FDA to conduct recalls voluntarily.

FDA's organization

Now, how is FDA organized to carry out its responsibilities in an efficient and effective manner?

First, FDA is not an independent regulatory agency; it is a component of the Public Health Service (PHS) within the Department of Health and Human Services (DHHS). Most of the agency's approximately 7,000 employees have scientific background, and many work in areas as diverse as veterinary medicine, engineering, entomology, chemistry and medicine. The FDA is headed by a commissioner who is supported by both line and staff personnel.

There are seven associate commissioners who are responsible for specific aspects of FDA affairs. These include regulatory affairs, health affairs, management and operations, planning and evaluation, legislative affairs, public affairs and consumer affairs.

The headquarter's Line Organizations include five centers:

The Center for Food Safety and Applied Nutrition (CFSAN)
The Center for Drug Evaluation and Research (CDER)
The Center for Biologics Evaluation and Research (CBER)
The Center for Veterinary Medicine (CVM)
The Center for Devices and Radiological Health (CDRH)

Center for food safety and applied nutrition

The center for food safety and applied nutrition is responsible for FDA's regulation of foods for human consumption and of cosmetics—regulation designed to ensure that foods are pure and wholesome, safe to eat and produced under sanitary

conditions; that cosmetics are unadulterated and made from appropriate ingredients; and that the labeling of foods and cosmetics is truthful and informative. FDA's responsibility for foods covers essentially all foods in interstate commerce except meat and poultry product, which are regulated by the US Department of Agriculture (USDA).

Center for drug evaluation and research

The center for drug evaluation and research (CDER) evaluates and approves new drugs for marketing on the basis of safety and effectiveness, and also assures that these drugs are properly labeled. The approval process involves two stages, called the investigational new drug (IND) and the new drug application (NDA) stage. FDA has recently completed a massive revision of the regulations governing both the IND and the NDA process. These revisions are intended to facilitate and streamline the development and review of new and benefical drug products.

Center for biologics evaluation and research

The center for biologics evaluation and research (CBER) is responsible for regulating vaccines, toxoids, allergenic products, blood and blood products. Before a new vaccine or allergenic can be marketed, the manufacturer must send the center test data that demonstrate that the product is safe and effective and CBER must licence the product (in contrast to approving an NDA for a drug product) as well as the establishment producing the product. For some products, the center also tests each batch manufactured, to assure that important standards are met.

Center for veterinary medicine

In a process similar to that for new drugs and biologicals, the center for veterinary medicine reviews animal drugs on the basis of safety and effectiveness. Sponsors of a new drug file an investigational new drug application (INDA) before they begin testing the product on animals. Following the test, but before marketing, the sponsor seeks FDA approval of a new animal drug application (NADA), which contains the necessary data on safety and effectiveness. If the drug is to be used in food producing animals, the NADA must also contain data on drug residues in edible tissue, since they affect human safety.

The center for veterinary medicine also reviews food additive and generally recognized as safe (GRAS) petitions for substances to be used in animal feed, drug experience reports, and information derived from inspections by FDA field personnel.

Center for devices and radiological health

The center for devices and radiological health is responsible for ensuring the safety and effectiveness of medical devices, as provided for by the 1976 medical device amendments of the Act; and eliminating occupational, and consumer products, as provided for by the radiation control or health and safety (RCHS) Act of 1968. Through its regulatory and educational mechanisms, the center deals with the public health issues involved in medical device and radiological health products.

There are two additional major units within FDA, the National Center for Tox-

icological Research (NCTR) and the field force. The NCTR is a research arm of FDA charged with studying the biological effects of potentially toxic chemicals. The center's mission encompasses four main program areas, 1) testing the assumptions underlying risk assessment of toxic chemicals; 2) defining the biochemical markers involved in carcinogenesis; 3) investigating the modulators of toxicity; 4) studying the reproductive and developmental effects of toxic agents.

FDA's field force consists of over 2,600 people located in offices throughout the United States. FDA's district offices are responsible for all inspections, investigations and contact with industry and public in their geographical area. The district office includes management and administrative support, compliance officers who review enforcement actions and the consumer affairs officers who deal with the public and consumer groups. Most district offices include laboratories that provide prompt testing of product samples.

Drug development and regulation

Since this symposium is focused on drug issues, it would be more appropriate to go into more depth about the activities of the center for drug evaluation and research (CDER) and role FDA plays in the drug development process. To expand on the earlier description of the activities of CDER, they include:

New drug evaluation,
Generic drug evaluation and standards,
Over the counter drug evaluation,
Prescription drug advertising and labeling,
Drug quality assurance,
Post-marketing surveillance,
Health fraud.

Generally, the drug development process in the United States begins with the discovery of a drug by a sponsoring drug firm. These firms discover biologically active new molecules mainly by screening large numbers of synthetic compounds and natural products for various types of pharmacological activity. Those compounds that look promising are then subjected to short term toxicology testing in animals (one week to three months, depending upon the compound) before being studied in humans. If the results are promising, the data is assembled in an Investigational New Drug Application (IND) and submitted to the Food and Drug Administration (FDA). The firm must wait 30 days before beginning human tests, during which time FDA reviews the accumulated data. If not placed on hold by FDA, the firm may proceed with studies in humans. Also, regulations issued by FDA require that all research involving FDA-regulated products be reviewed by an Institutional Review Board (IRB) before tests on humans can begin. Clinical trials on new drugs are conducted by academic physicians working in University Medical Centers and by physicians in private practice. These trials are paid for by the sponsoring drug firms, and the results are commonly published in the medical literature. If the drug continues to look promising and no undue risks are discovered, the manufacturer conducts additional tests necessary for marketing. These include tests in animals for teratology and, for drugs to be administered chronically, carcinogenicity. In addition, broader clinical trials are conducted to assure the