CONTROLLED DRUG BIOAVAILABILITY

Volume 2: Bioavailability Methodology and Regulation

Edited by Victor F. Smolen
Lu Ann Ball

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VOLUME 2
BIOAVAILABILITY METHODOLOGY AND REGULATION

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Controlled Drug Bioavailability

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Series Preface

The purpose of this newly established continuing series of monographs is to provide a forum to disseminate current knowledge that contributes to expediting the design, development, evaluation, manufacture, control, marketing, and clinical use of increasingly safer and more effective drug products at lower costs. A critical problem with the entire health care industry is the high and rapidly escalating costs. A significant contribution to this problem is the cost of drugs. Not only is the research for the development of drug products expensive, but so is the process for the establishment of their quality, safety, effectiveness, and manner of use. It has been estimated that it presently takes an average of seven years and in excess of $50 million to gain approval of a single new drug in the United States by the Food and Drug Administration (FDA). Briefly, a promising new drug must first be tested in up to thousands of animals to assess its possible toxicity. That done, it must then be used in multiphasic tests before the dosage form(s) and dose levels, safety, effectiveness, and possible side effects can be determined. These human subjects must be under the almost constant surveillance of high-priced specialists, and the results of all these studies must be analyzed by statisticians and reported. Finally, this mass of data must be reviewed and approved by drug regulatory agencies such as the FDA before permission to market the drug can be given. It is obviously imperative that the most current knowledge be effectively applied to reduce the costs of drug product development and accelerate the availability of new therapies and improved products to the patients needing them.

In all approaches to drug development it cannot be overlooked that drugs are never used as the pure chemical substances whose molecular structures are responsible for their intrinsic pharmacological activities. Drugs are always put into delivery systems, such as liquids to be injected by mechanical or electromechanical devices, or are formulated into dosage forms such as tablets, capsules, suppositories, and so on, and recently even into patches placed on the skin's surface; such dosage forms become the marketed drug products themselves. In practice, the dynamics of the manner by which a dosage form releases its drug to become available to its site(s) of action in

the body is equally as important in determining the safety and effectiveness of the course of drug therapy as is the intrinsic pharmacological activity of the chemical substance that the drug product contains.

The formulation and manufacture of drug dosage forms, as well as how drug delivery devices are designed and operated, has a profound influence on the manner in which drugs access their site(s) of action. In recent years it has become widely recognized among pharmaceutical scientists, clinicians, and government regulatory agencies that drug bioavailability, defined as the time course of the rates and extents of drug entrance into the body or release to its sites of absorption prior to entering into the body, is of the most fundamental importance to the design, development, evaluation, and clinical use of drug products. This importance becomes apparent from simply considering that once a drug enters into the body (i.e., becomes bioavailable), the course of its therapeutic and toxic effects becomes entirely determined by the intrinsic dynamics of the drug's disposition and actions in the body. Since targeting of drug molecules to specific sites of action is not yet achieved, there is presently virtually nothing that can be routinely and effectively done to alter the course of these effects. Therefore, selection of or otherwise affecting the manner in which the drug is allowed to enter the body in the first place (i.e., the bioavailability input of the drug) provides the only practical means to control, or inadvertently alter, the safety and effectiveness of drug products. A potential basis for drug product design and development must, therefore, always consider the relationship between the drug bioavailability inputs that a product will deliver and the resulting time course of pharmacological effects and body fluid drug levels that ensue. Products having the same bioavailability inputs can be considered bioequivalent. Pharmacokinetics, defined as what the body does to the drug (i.e., absorb, distribute, metabolize, and eliminate it), and pharmacodynamics, defined as what the drug does to the body (i.e., elicit pharmacological effects), provide the theoretical and computationally practical means of relating drug bioavailability inputs to the drug level and pharmacological responses that underlie the safety and clinical effectiveness of a drug's usage.

Even though the development of new clinical drug entities—which was incipient and flourished after World War II—continues to produce new and exciting progress, there is presently a rapidly increasing awareness that the drug industry has entered a new era of even greater precision in drug therapy based on controlled drug bioavailability. As is the case with all trends in our society, circumstances of politics, law, and economics, in addition to developments in science and pharmaceutical technology, are providing a strong impetus to the growth of precisely controlled bioavailability. This can be understood from considering the regulatory law requirements and economics of new drug entity development relative to the inordinately lower

costs of developing and marketing better drug delivery systems for generic drugs whose intrinsic safety and effectiveness have already been well established.

Generic drugs are those for which patent protection has expired, allowing them to be sold by other manufacturers in competition with the original patenting pharmaceutical company. In 1979 the U.S. market in generic drugs was an estimated $4.37 billion, representing 43% of the total pharmaceutical drug market in that year. A recent Frost and Sullivan report on the generic drugs market forecasts generic drug sales to reach nearly $10 billion by 1989 in the United States alone. Others forecast $10 billion generic sales to be reached by 1985. Significant factors in this growth are the expiration of patents of 48 of the major pharmaceuticals (which had combined sales in the United States of $2.2 billion in 1979) and the time, difficulty, and expense of developing new ethical, patented drugs. Therefore, the competition by both ethical and generic drug companies to retain and capture market shares can be projected to become increasingly fierce. Successful competitors can be expected to offer superior drug products that provide therapeutic advantages. The leveling of competition between multisource suppliers of the same generic drug entity should provide the economic impetus to develop drug products that are not merely satisfactory but have a therapeutically optimal, controlled drug bioavailability. The development of such products would contribute to even more rapidly advancing the pharmaceutical sciences as well as being of obvious benefit to drug-consuming patients. It is to these objectives that this series of monographs is dedicated, through presenting current information relating to the theory and practice of controlled drug bioavailability.

The present and subsequent volumes are devoted primarily to those topical areas whose interaction is requisite to the development of drug products of optimal therapeutic benefit. Most broadly, these topics include (1) pharmacokinetics and pharmacodynamics that provide the theoretical and computational means necessary to relate the dynamic manner in which a drug must be allowed to enter the body to elicit optimally sought pharmacological effects (the performance criteria, on which to design the drug release dynamics of drug products to achieve optimal therapeutic benefits can be determined); (2) methodologies and drug regulatory considerations for the bioavailability–bioequivalency requirements and the evaluation of drug delivery systems; (3) the specific design, development, properties, manufacture, control, and factors that affect the bioavailability of particular types of drug delivery system that most broadly are chemical, mechanical, or electromechanical devices; and (4) the marketing and promotion of drug products. The projected market success of a controlled-release drug product is of course the initiating factor for its development. The man-

ner of promoting a uniquely new product will include a need to educate the physician, pharmacist, nurse, and patient in order to gain its acceptance; therefore, the promotion of a new and novel drug delivery system is even more important than the otherwise unrealized potential therapeutic benefits such products can provide. For example, there is clearly a need for controlled-release drug products that allow for a once-a-day dosing schedule to always be maintained for all the drugs a patient is taking in order to achieve maximum patient compliance and therapeutic benefits. This must be done while permitting the dosage for many of the most important drugs to be readily adjusted to a patient's individualized needs. These objectives would necessitate that the drugs be supplied in unconventional forms. The marketing and promotion of new drug product forms would require the application of both a clinical pharmacokinetic and educational support program to ensure the proper and most successful usage of such products. This example serves to illustrate the need for the integration of all the relevant topics and themes of this series to deliver a maximum therapeutic benefit to patients in what is envisaged to continue to be an era of increasing improvements in controlled drug bioavailability.

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Preface

In the development of a new drug product, an immense amount of time and money is spent testing for safety, effectiveness, and reliability. The abundance of results obtained must be reported to and approved by the Food and Drug Administration (FDA) before the drug product can be marketed. To minimize the overall effort, it is important to use effective in-vitro and in-vivo testing methods in animals and in humans. Volume 2 in this continuing series on controlled drug bioavailability is of particular value to the pharmacokineticist who designs effective testing methods and reports the results to the FDA. Chapter 1 is concerned with factors that influence the results of a bioavailability/ bioequivalence study performed in humans. Bioavailability testing in animals is the topic of Chapter 2. Chapters 3 through 5 address in-vitro methods for assessing drug product bioavailabilities. Chapter 3 discusses the correlation of in-vitro dissolution test results with in-vivo bioavailability parameters. A method for computationally converting in-vitro dissolution results into a time course of in-vivo response is reported in Chapter 4. Chapter 5 looks at various dissolution testing methodologies, including a computer-controlled dissolution testing apparatus that can, when programmed with in-vivo results from a pilot study, substitute for a panel of human subjects in the determination of drug product bioavailability/bioequivalence. Chapter 6 suggests an approach to effectively reporting in-vitro and in-vivo results and conclusions to the FDA. Poorly written reports can prolong the drug product review process and delay its subsequent approval for marketing. A method for obtaining pharmacokinetic data by computer resolution of recorded physiological signals is discussed in Chapter 7, and an example is shown for organic nitrates.

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CHAPTER 1

Experimental Factors Influencing the Results of Drug Product Bioavailability/Bioequivalency Studies in Humans

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To determine relative bioavailability or bioequivalence, various formulations of two or more preparations are compared under identical trial conditions. These conditions are particularly suitable if they permit clinically relevant statements to be assessed economically. We can select suitable experimental conditions and factors only if we know how these factors influence the bioavailability of drugs.

The knowledge and consideration of all experimental factors that can modify the bioavailability of drugs is also important for a safe and effective drug therapy. Experimental factors are those that may affect drug bioavailability and can be influenced by the investigator planning a study with a given substance and formulation. They include the *external trial conditions* and the *physiological and biochemical characteristics* of normal subjects or patients. The second point is especially important when a trial design with independent groups of volunteers or patients is used.

Many relevant factors have been identified and their importance documented and reviewed during the last 15 years (1–17), although some had already been identified in the "Old German Literature" (18). Tappeiner (19) wrote in 1899:

> The common route which is chosen for the application of drugs is that through the mouth. The digestive canal is perfectly equipped for the nutrition business but it has many disadvantages for the use in therapy. First of all, the stomach is not at all an excellent absorption organ. In this respect the stomach is by far inferior to the gut. Secondly, the state of filling often implies a great delay in absorption and in any case uncertainty with respect to its beginning. Thirdly, many substances are decomposed in the digestive canal and thus rendered ineffective, others will not at all be absorbed, and at the end fourthly, even after the uptake into the blood the drug must pass through the liver which is—as is well known—able to chemically convert or retain many substances. All these conditions imply great uncertainty. To this adds, that even in the most favorable cases presumably the first molecules will be already absorbed after 5 minutes and even pass into the secretion, but the main portion will arrive after 10–15 minutes and the last remainder will arrive only at a time when the first have been already excreted a long while ago. Therefore the administered dose will never be entirely present in the blood at the same time to be active in the organs. The effect, therefore, only reaches a certain extent which will gradually be gained and just so gradually abandoned again. [author's translation].

The aim of this chapter is to review concisely all possible influences of experimental factors on the results of bioavailability/bioequivalency studies, including a compilation of relevant references.

A pragmatic *classification of the experimental factors* can be established as follows:

1. External trial conditions.
   a. Subject related.
      i. Intake of food: time relative to intake of drug, quality, quantity, temperature, and spices (20).
      ii. Intake of fluid: time relative to intake of drug, quality, quantity, and temperature.
      iii. Social drugs: coffee, tea, tobacco, and ethanol.
      iv. Posture and physical activity: supine, rest, and exercise.
      v. Psychic stress: specific, necessary inconveniences of the protocol (e.g., duration and physical inconvenience) and situations producing tension or anxiety.
   b. Environment related.
      i. Climatic variations: temperature, atmospheric pressure, weather condition, and humidity.
      ii. Chronobiologic factors: circadian and seasonal variations and chronopharmacokinetics.
      iii. Atmosphere of the clinical environment: the surroundings, recreational facilities, contact with the staff, and conflict and tension-producing situations independent of the protocol.
2. Characteristics of volunteers.
   a. Somatic characteristics.
      i. Anthropometric data: race, sex (pregnancy), age, height, weight, and ponderal-index (height-weight-relation).
      ii. Physical state: physical examination (nutritional and physical state) and laboratory data (clinical chemistry, hematology, urinalysis, and hemostaseology).
      iii. Special physiological functions: liver, stomach, thyroid, kidney, and GI-tract (genetic constitution, pharmacogenetics, and ethnopharmacokinetics).
   b. Psychic characteristics.
      i. Personality traits: level of neuroticism and anticipation anxiety.
      ii. Tolerance for stress, personal trial experience.
      iii. Attitude toward the trial: motivation, cooperation, and compliance.

c. Habits and conditions of living (not the *external* trial conditions *during* a study, but individual habits and conditions of living and environment that have *persistently* affected the *internal* milieu of a subject *before* a study).

i. Dietary factors: feeding habits, meal times, quantity and composition of food, and fluid intake and volume.

ii. Social drugs: tobacco, alcohol, and coffee or tea (type and quantity).

iii. Drugs (common self-medication): contraceptives, laxatives, antacids, vitamins, analgesics, and sedatives.

iv. Micturition: deliberate control.

v. Defecation: normal frequency.

vi. Physical activity: state of training.

vii. Employment: occupational exposure.

3. Special characteristics of patients.

a. Pathophysiologic conditions (disease): of stomach, GI-tract, liver, kidney, thyroid, GI-flora, plasma proteins, body temperature, and cardiovascular system.

b. Interaction with other drugs: antacids, anticholinergics, etc.

1. EXTERNAL TRIAL CONDITIONS

The external trial conditions listed above usually modify bioavailability because they influence one or more *physiological factors* such as (3, 5–7, 12, 21–40): hydrogen ion concentration in the GI-tract (secretion and buffering), gastric juice (volume and viscosity), gastrointestinal motility (pyloric passage and GI-transit time), blood flow rate (mesenterium and liver), GI-endocrine system, flow rate of bile and pancreatic juice, and microflora of the GI-tract.

1.1 Subject Related

1.1.1 *Intake of Food*

The influence of food on the bioavailability of drugs has often been described (41–48), but it is not yet possible to make many general statements. Therefore, the individual results are listed pragmatically in Tables 1–4, as proposed by Welling (14, 49, 50) and Toothaker and Welling (51), who

reviewed this topic. The data are supplemented by the results of Weber (52), Melander (53), Beerman (54), Leopold (55, 56),* and others.

Food influences the bioavailability of drugs by modulating physiologic functions of the GI-tract, except in cases exhibiting a direct interaction with food constituents (e.g., formation of poorly soluble salts, chelation, adsorption, etc.). Because of its large surface, drugs are better absorbed in the small intestine than in the stomach (6). Therefore, the moment of passage through the pyloric sphincter is especially important for the enteric absorption of drugs. A delay in gastric emptying often implies a delay of absorption. The rate of gastric emptying can be raised by increasing intragastric pressure; the relevant baroreceptors are located in the gastric wall (57, 58). A delay of gastric emptying can be effected by the impulses of three types of receptors in the duodenal mucosa and by the action of hormones. The receptors exhibit a selective sensitivity to hydrogen ions, fatty acids, or osmotic changes. When ingested food or fluid of low pH, high fatty acid content, or high osmolarity reaches the duodenum, a reflex inhibition of gastric emptying occurs. The inhibition of gastric motility by hormones (gastric inhibitory peptide [GIP], enterogastrin, cholecystokinin-pancreozymin, and motilin) is also triggered by low pH and fatty acids in the duodenum. These inhibitory mechanisms protect the epithelium of the small intestine (59, 60). Furthermore, the higher the temperature of an ingested meal or drink, the more solid a meal, and the more viscous the gastric contents, the stronger the inhibition of gastric emptying will be (61–64).

The regulation of gastric motility is tightly connected with the gastric secretion. Psychic-neural as well as gastric and intestinal influences play a role. Gastric secretion is mainly stimulated by gastrin liberated by distension- and chemo-receptors (e.g., those sensitive to protein fragments). Gastric secretion is inhibited by secretin, cholecystokinin-pancreozymin, and GIP, which are liberated in the duodenum by fatty acids and hydrogen ions. The secretion of pancreatic juice is regulated by secretin and cholecystokinin-pancreozymin.

The production of bile is enhanced by secretin; the contraction of the gall bladder is triggered by reflex or by cholecystokinin-pancreozymin (36, 59, 60).

The blood flow rate in the splanchnic region is increased during a meal and postprandially; the extent depends on the type of food. After a high-protein meal the blood flow rate increases significantly and normalizes only gradually,

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