Drug Bioequivalence

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DRUG BIOEQUIVALENCE

A REPORT OF THE
OFFICE OF TECHNOLOGY ASSESSMENT
DRUG BIOEQUIVALENCE STUDY PANEL

OFFICE OF TECHNOLOGY ASSESSMENT

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LETTER OF TRANSMITTAL

Congress of the United States
Office of Technology Assessment
Washington, D.C., July 15, 1974

The Hon. Harrison A. Williams
Chairman, Senate Committee on
Labor & Public Welfare
United States Senate
Washington, D.C. 20510

The Hon. Harley O. Staggers
Chairman, House Committee on
Interstate & Foreign Commerce
U. S. House of Representatives
Washington, D.C. 20515

Sirs: On behalf of the Board of the Office of Technology Assessment, we are pleased to forward to you the following report of the Drug Bioequivalence Study Panel, which was assembled on April 12, 1974, under the chairmanship of Dr. Robert Berliner. The Panel was asked to determine whether or not the technological capability is now available to assure that drug products with the same physical and chemical composition will produce comparable therapeutic effects.

This report is being made available to your Committees in accordance with Public Law 92-484, with appreciation and thanks to Dr. Berliner and his colleagues on the OTA Drug Bioequivalence Study Pane}. “

Respectfully yours,

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terminology

Definitions of key technical terms as we have used them in this report are presented below. A comprehensive glossary of these and other technical terms is also provided on page 75.

- Drug product A dosage form containing one or more active therapeutic ingredients along with other substances included during the manufacturing process.

- Present compendia standards The official standards for drug excipients and drug products listed in the latest revision of the United States Pharmacopoeia (USP) and the National Formulary (NF).

- New compendial standards Standards to be established for active ingredients,excipients and drug products, including tests relecting the best available technology to be performed before, during and after formulation.

- Chemical equivalents Drug products that contain the same amounts of the same therapeutically active ingredients in the same dosage forms and that meet present compendia standards.

- Pharmaceutical equivalents Drug products that contain the same amounts of the same therapeutically active ingredients in the same dosage form and that meet standards to be established on the basis of the best available technology.

- Bioavailability The extent and rate of absorption from a dosage form as reflected by the time-concentration curve of the administered drug in the systemic circulation.

- Bioequivalents Chemical equivalents which, when administered to the same individuals in the same dosage regimen, will result in comparable bioavailability.

- Therapeutic equivalents Chemical equivalents which, when administered to the same individuals in the same dosage regimen, will provide essentially the same efficacy and/or toxicity.

- Interchangeable drug products Pharmaceutical equivalents or bioequivalents that are accepted as therapeutic equivalents.

conclusions and recommendations

1
Current standards and regulatory practices do not insure bioequivalence for drug products.

2
Variations in the bioavailability of drug products have been recognized as responsible for a few therapeutic failures. It is probable that other therapeutic failures (or toxicity) of a similar origin have escaped recognition.

3
Most of the analytical methodology and experimental procedures for the conduct of bioavailability studies in man are available. Additional work may be required to develop means of applying them to certain drugs and to special situations of drug use.

4
It is neither feasible nor desirable that studies of bioavailability be conducted for all drugs or drug products. Certain classes of drugs for which evidence of bioequivalence is critical should be identified. Selection of these classes should be based on clinical importance, ratio of therapeutic to toxic concentration in blood, and certain pharmaceutical characteristics.

5

Present compendia standards and guidelines for Current Good Manufacturing Practice do not insure quality and uniform bioavailability for drug products. Not only may the products of different manufacturers vary, but the product of a single manufacturer may vary from batch to batch or may change during storage.

6

New compendia standards for active ingredients, excipients and finished drug products should be developed and revised on a continuing basis to reflect the best available technology to insure quality and uniform bioavailability. Appropriate statistical procedures should be specified to make certain that the purposes of the standards are objectively satisfied. The guidelines for Current Good Manufacturing Practice should be expanded to include specific descriptions of all significant aspects of manufacturing processes from the raw materials to the final product.

7

Additional research aimed at improving the assessment and prediction of bioequivalence is needed. This research should include efforts to develop in vitro tests or animal models that will be valid predictors of bioavailability in man.

8

Current law requiring manufacturers to maintain records and make information available to the FDA is ambiguous or inadequate and should be clarified and strengthened. In particular, manufacturers should be required to submit all information relating the tests they conduct to the bioavailability data they develop in order to help provide information on the factors that modify the bioavailability of drug products. This information should be available to aid in the establishment of compendia standards.

9

Exemptions provided in current law for some drug products based on their year of introduction in relation to amendments in the Food, Drug, and Cosmetic Act (so-called grandfather clauses) have impeded improvement in the quality of these products. Such exemptions should be eliminated.

10

A single organization capable of setting standards adequate to insure the quality and uniform bioavailability of drug products should be established to replace the present USP and NF as the official standard-setting organization of the Federal Government.

1 1

A system should be organized as rapidly as possible to generate an official list of interchangeable drug products. In the development of the list, distinctions should be made between two classes of drugs and drug products:

1. Those for which evidence of bioequivalence is not considered essential and that could be added to the list as soon as standards of pharmaceutical equivalence have been established and satisfied.

2. Those for which evidence of bioequivalence is critical. Such products should be listed only after they have been shown to be bioequivalent or have satisfied standards of pharmaceutical equivalence that have been shown to insure bioequivalence.

charge to the panel

The basic charge made to the Drug Bioequivalence Study Panel* by the Office of Technology Assessment (OTA) was to examine the relationships between the chemical and therapeutic equivalence of drug products and to assess the capability of current technology--short of therapeutic trials in man--to determine whether drug products with the same physical and chemical composition produce comparable therapeutic effects.

As members of the Panel, we agreed that a review of the system of regulations and practices now used to insure quality and uniformity--the compendia standards, Current Good Manufacturing Practice guidelines, and the manufacturers' procedures for quality control and formulation--would have to be an inherent part of our assessment. After examining these factors, we would make recommendations, if necessary, for any modifications that we believed might be needed to improve the present system for insuring the therapeutic equivalence of drug products.

It was clear to us from the outset that certain chemically equivalent drug products have produced clinically important and measurable differences in therapeutic effect and that these differences were the result of differences in bioavailability. Conversely, we recognized that differences in bioavailability (bioinequivalence) among some drug products may not be a critical concern with regard to the equivalence of their therapeutic effects.

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* The Drug Bioequivalence Study Panel met for the first time on April 12, 1974 to clarify its charge and to formulate a plan for its study. A chronological review of the activities undertaken by the Panel is presented as the Appendix.

As our study progressed, it became clear to us that we should recommend a system that, through improved assurance of quality and rational scientific judgments, would insure the therapeutic equivalence of drug products.

Our conclusions and recommendations are based on considerations of current technology and of the technology that we believe could be developed within the next few years. Our report also includes a consideration of the need and potential for new research relevant to the development of that technology and to other aspects of the problems under consideration.*

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* The Panel communicated extensively with various sources, requesting information and receiving documented replies in response to questions raised. A bibliography of the documentation received and reviewed by the Panel appears on page 61.

scope of the study

Because of the limited time available to us, it was necessary to restrict the scope of our study to solid drug products (capsules and tablets, but excluding timed-release and coated products) that are administered by mouth and produce a systemic effect. These are the products for which consideration of the relationships between chemical and therapeutic equivalence is most important. In addition, tablets and capsules constitute the great majority of all drug products used in the United States.

The therapeutic effect of a solid drug product is assumed to be a function of the concentration of the active ingredient in the systemic circulation and is thus related to its bioavailability. Accordingly, we directed our attention to the principles and methodology involved in estimating and comparing the bioavailability of drug products. This methodology involves measurement of the concentration of the active ingredient in the systemic circulation, either directly in blood or indirectly through studies of urinary excretion.

We also attempted to identify the general categories of drug products for which measurements of bioavailability may be critical to the assurance of therapeutic equivalence. The therapeutic equivalence of some categories of drug products can be insured, however, without a direct assessment of bioavailability, and we tried to identify the general characteristics of such products.

Certain drug products contain the same active moieties but do not have the same salt, ester or dosage form. These products, although similar, are not chemically equivalent but may be therapeutically equivalent. For example, tetracycline hydrochloride tablets, capsules and syrup all may be expected to produce the same therapeutic effect as tetracycline phosphate capsules, but they are different in dosage

or salt forms. Drug products which are not chemically equivalent but have the same therapeutic effect may be referred to as pharmaceutical alternatives but not as chemical or pharmaceutical equivalents. We believe this distinction is significant and that it requires further elaboration; however, we did not examine pharmaceutical alternatives or the extent to which they do or do not produce equivalent therapeutic effects.

It must be recognized that beyond characteristics of drug products that influence absorption of the active drug from the gastrointestinal tract, a number of other factors have an important role in determining the therapeutic effect produced in any individual. Among these factors are the following:

1. Variations from one individual to another in absorption, metabolic conversion and excretion of the drug. Some individuals have rates of intestinal absorption and metabolism that differ markedly from the average rates, and these differences may be exaggerated by the disease state. Consequently, the concentration of the drug in the blood of such individuals may be well above or below the average, even if the drug is rapidly and completely dissolved in gastrointestinal fluids.

2. Appropriateness of tile prescriber's choice of drug.

3. Differences among patients in complying with instructions for taking the drug product.

4. The simultaneous use of other drugs that can affect or alter the action of the-prescribed drug.

Although such factors may greatly influence the therapeutic effect obtained from drug products, our major concern was directed at factors affecting the efficacy of drug products that are within the control of the manufacturer.

discussion of conclusions and recommendations

1

CURRENT STANDARDS AND REGULATORY PRACTICES DO NOT INSURE BIOEQUIVALENCE FOR DRUG PRODUCTS,

Although there is a spectrum of opinion about the frequency and importance of differences in the bioavailability of chemically equivalent drug products, there can be no dispute about the fact that well-documented and significant differences in bioavailability have been demonstrated in chemically equivalent products representing a number of drug categories.

Problems of bioequivalence have received serious investigative attention only during the past few years. In this brief period, however, a number of studies of marketed drug products containing the same therapeutic ingredient have revealed marked differences in the rate and extent of absorption. A considerable body of literature has accumulated in this period that indicates the existence of demonstrable differences in the bioavailability of products involving roughly a score of drugs. A partial list of studies demonstrating bioinequivalence of chemically equivalent drug products might include the following: tetracycline (MacDonald et al, 1969; Barr et al, 1972); chloramphenicol (Glazko et al, 1968); digoxin (Wagner, 1973; Lindenbaum et al, 1971) ; phenylbutazone (VanPetten et al, 1971; Chiou, 1972); and oxytetracycline (Blair et al, 1971; Brice et al, 1971).

Not only has bioinequivalence been shown to exist in products of different manufacturers but there also have been substantial variations in the bioavailability of different batches from the same company (for example, see Lindenbaum et al, 1971). It is difficult to determine whether differences

such as those cited are the exception or the rule, since positive results (in this case a demonstrable difference) are far more likely to be published than negative findings. Furthermore, in some studies in which several chemically equivalent products have been tested, some have been found to have the same bioavailability while others have not.

Nevertheless, the number of positive findings has been sufficient to establish that the problem of bioinequivalence in chemically equivalent products is a real one. Since the studies in which lack of bioequivalence was demonstrated involved marketed products that met current compendia standards, these documented instances constitute unequivocal evidence that neither the present standards for testing the finished product nor the specifications for materials, manufacturing process, and controls are adequate to insure that ostensibly equivalent drug products are, in fact, equivalent in bioavailability.

2

VARIATIONS IN THE BIOAVAILABILITY OF DRUG PRODUCTS HAVE BEEN RECOGNIZED AS RESPONSIBLE FOR A FEW THERAPEUTIC FAILURES, IT IS PROBABLE THAT OTHER THERAPEUTIC FAILURES (OR TOXICITY) OF A SIMILAR ORIGIN HAVE ESCAPED RECOGNITION,

The fact that drug products differ in bioavailability is not, in itself, evidence that the use of such products will produce significant practical problems in the treatment of patients. However, it is also a fact that therapeutic inequivalence has been observed among certain chemically equivalent drug products. One example of therapeutic failure arising from variations in the bioavailability of ostensibly equivalent products involved the important and highly potent cardiotonic drug, digoxin. A number of patients were observed to require unusually large maintenance doses of digoxin despite the absence of any condition that might have explained a high tolerance to the drug. Upon investigation, the patients were found to have low digoxin concentrations in their blood plasma (Lindenbaum et al, 1971). A crossover study revealed striking differences in bioavailability among four digoxin preparations available in the same hospital at the time. The peak concentration after a single dose was found to vary among the four drug products by a factor of as much as seven. It is noteworthy that the margin of safety of this drug is sufficiently narrow that serious or even lethal toxic effects can result if the dose given and absorbed is as little as twice that needed to achieve a therapeutic effect.

Another instance of therapeutic failure with a drug product meeting compendia standards was demonstrated in the case of a thyroid preparation that met those standards but was therapeutically inactive (Catz et al, 1962).

While these therapeutic failures resulting from problems of bioavailability were recognized and well documented, it is entirely possible that other therapeutic failures and/or instances of toxicity that had a similar basis have escaped attention. The variability among individuals--in the absorption, excretion and metabolic conversion of drugs; in the individual physiological or toxic response; and even in the regularity with which the prescribed dose is actually taken--is such that the source of an abnormal or inadequate therapeutic effect in an individual patient is not readily identifiable. Differences owing to the bioavailability of the administered product are likely to be recognized only when information is collected in an organized manner or effects are noted in a significant number of patients under sufficiently close observation by an unusually alert and observant physician. More important, for drugs that, because of relatively narrow margins of safety, are generally administered in doses that produce plasma levels not much higher than the minimum required for efficacy, therapeutic inequivalence must certainly occur whenever there are substantial differences in bioavailability.

Therefore, although the number of instances of demonstrable therapeutic inequivalence is small, the problem is an important one and, in the case of drugs with narrow margins of safety, assurance of bioequivalence is vital.

3

MOST OF THE ANALYTICAL METHODOLOGY AND EXPERIMENTAL PROCEDURES FOR THE CONDUCT OF BIOAVAILABILITY STUDIES IN MAN ARE AVAILABLE. ADDITIONAL WORK MAY BE REQUIRED TO DEVELOP MEANS OF APPLYING THEM TO CERTAIN DRUGS AND TO SPECIAL SITUATIONS OF DRUG USE.

The conduct of bioavailability studies in man requires that a drug product be administered to a group of individuals and that the time-course of the concentration of the drug in the blood be evaluated either directly or indirectly.* It is necessary, therefore, that there be available (1) analytical methods for determining the concentration of the active ingredient in body fluids; (2) standardized procedures for administering the drug product and obtaining appropriate blood and/or urine samples; and (3) adequate methods for statistical analysis and interpretation of the results.

ANALYTICAL METHODS

It may be necessary to measure, in a small volume of biological fluids, an amount of the intact drug that

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* In 1972, the Academy of Pharmaceutical Sciences of the American Pharmaceutical Association published the Guide for Biopharmaceutical Studies in Man, which presents a systematic approach to the conduct of bioavailability studies based on analytical determination of drug in blood and/or urine.

is only one millionth to one billionth of the dose administered. Fortunately/, such recent advances as gas-liquid chromatography, high pressure liquid chromatography, fluorescence techniques, mass spectrometry, radioimmune assays, and microbiological assays have greatly increased our capability of measuring such minute amounts of drugs. The methods used must have not only adequate sensitivity and accuracy, but also the selectivity that will make it possible to quantify the drug in the presence of its metabolizes or of endogenous compounds that may interfere with the determination of the compound in biological fluids.

In instances in which no sufficiently sensitive chemical method is available to detect the active ingredient, radioactively labeled molecules may be utilized. It must be verified, however, that the measured radioactivity is contained in the intact compound that has been separated from its metabolites. One must also be assured that the dosage form containing the radioactive drug to be administered possesses, insofar as possible, physical and chemical properties identical to those of the usual (unlabeled) dosage form.

Some of these methods are cumbersome and rather time-consuming, but they are capable of providing relatively accurate measurements at the required levels. Unfortunately, some of the early pharmacokinetic studies were based on methods subject to ambiguities. Continuing efforts, therefore, are still required to simplify and improve the existing methods and to develop new ones.

PROCEDURES FOR ADMINISTERING THE DRUG PRODUCT

The most common experimental plan for comparing the bioavailability of two drug products is a simple crossover study. In this design, each individual in a group of subjects receives both drug products (at different times) so that there is a direct comparison of the absorption of each product in the same individual. Special care must be taken to allow sufficient time to elapse between the administration of the first and second drug products so that there are no carryover effects. In order to minimize the influence of such effects on the outcome of the study, good experimental design requires that each drug product be administered initially to half of the subjects.

In some instances, more than two drug products are to be compared in a single investigation. If three products are to be studied, all three can be administered to each individual in a suitably balanced order. However, investigations involving more than three drugs may require alternative experimental designs, as it may be impractical to give more than three drug products to the same individual. A suitable way of planning such investigations is to utilize statistical experimental plans called incomplete-block designs. The statistical methodology for such experimental plans is readily available.

For some applications of some drug products, the steady-state concentration of the drug in the blood, attained after repeated administration of the drug product at regular intervals, may be a more appropriate index of bioavailability than the time-concentration curve after a single dose.

STATISTICAL METHODOLOGY FOR BIOAVAILABILITY STUDIES

The statistical methods to be used in bioavailability studies should be chosen with careful attention being given to the effect of the variations among individuals and among batches of nominally identical manufactured drug products. The planning, analysis and interpretation of these experiments are not routine problems but, rather, require considerable care, consonant with the purpose for which the data are to be used.

INDIVIDUAL VARIABILITY AND BIOEQUIVALENCE

When drug products are administered to individuals, the investigator inevitably finds differences in one or more of the variables measured. These differences are due partly to factors related to dosage form and partly to biological factors unique to each individual, since each person has his own characteristics for absorption, metabolism and excretion of each drug. Through appropriate use of statistical procedures, it is possible to identify the variations that result from differences among individuals and thus to isolate those that result from differences in the bioavailability of the drug products.

BATCH-TO-BATCH VARIABILITY AND BIOEQUIVALENCE

Some drug products may exhibit substantial batch-to-batch variation with respect to important bioavailability characteristics. If the batches are manufactured under adequately controlled conditions, then one could regard the different batches to be theoretically bioequivalent. However, one would expect the average levels of some of the bioavailability characteristics to vary from batch to batch. The measurement of the effects of batch-to-batch variations on bioavailability is important in assessing the effect of changes in the manufacturing process which may take place in the future.

The problem arises as to how to judge whether two chemically equivalent drug products are bioequivalent. The solution to this problem depends on the batch-to-batch variation of the bioavailability. A working rule for judging the bioequivalence of two drug products might be that the two are considered equivalent if the differences between them are similar to what one would expect from the batch-to-batch variation of the original product. Unfortunately, there is little information concerning the effects of batch-to-batch variation on bioavailability. Studies to examine this question have not often been carried out, since they require in vivo tests of bioavailability unless there are in vitro tests whose results have been shown to have a high correlation with bioavailability.

SAMPLE-SIZE CONSIDERATIONS

One of the most important and difficult problems in planning bioavailability investigations is the selection of the appropriate sample size. If conventional statistical tests of significance are used to analyze the data, then it is possible that studies involving small numbers of observations (subjects) may fail to yield differences that are statistically significant even if the drug products being compared are, in fact, different. Alternatively, if large numbers of observations are used, then one may find statistically significant differences between drug products, even if the real differences are small and of no pharmaceutical or therapeutic significance.

Therefore, in planning bioavailability investigations, one must determine the difference in mean values of the parameters of bioavialability that it is practically (pharmaceutically or therapeutically)

important to detect. The choice of sample size requires that the probability of failing to detect important differences be small, when such differences exist.

METHODS OF ANALYSIS

The experimental results of bioavailability studies can be analyzed statistically in many different ways. The statistical methods of analysis depend on (1) the statistical model of the concentration-time curve, (2) the statistical model of the various sources of variation (for example, person-to-person variations, or nonindependent measurements) , and (3) the experimental plan that specified how the measurements were to be made.

Perhaps the simplest way to use concentration-time curves for comparing two drug ‘products is not to compare the entire curves but to compare characteristics of the curves that are deemed important with regard to the drug product under study--for example, area under the curves, peak heights, or rates of absorption. If only a single characteristic is involved, an appropriate method of analysis is the method of paired comparisons, in which each individual generates a paired difference. There are also adequate statistical procedures for the comparison of two or more sets of variables, and these, can be used when more than two drug products are studied.

4

IT IS NEITHER FEASIBLE NOR DESIRABLE THAT STUDIES OF BIOAVAILABILITY BE CONDUCTED FOR ALL DRUGS OR DRUG PRODUCTS, CERTAIN CLASSES OF DRUGS FOR WHICH EVIDENCE OF BI0EQUIVALENCE IS CRITICAL SHOULD BE IDENTIFIED, SELECTION OF THESE CLASSES SHOULD BE BASED ON CLINICAL IMPORTANCE, RATIO OF THERAPEUTIC TO TOXIC CONCENTRATION IN BLOOD, AND CERTAIN PHARMACEUTICAL CHARACTERISTICS,

More than 20,000 prescription drug products are presently available from drug manufacturers. For only a few of these are there adequate data documenting their bioavailability in man. Because of the large number of drug products for which studies of bioavailability might be conducted, the enormous number of human volunteers that 'would be needed, and the large number of clinical investigators and other sciefitific personnel who would be needed to do the work, it is clearly not feasible to carry out studies of bioavailability in man for all drug products.

Furthermore, even were it feasible to do so, it would not, in our opinion, be ethically justifiable. The administration of drugs to man is never without some hazard, although in some cases the risk is very small. In addition, subjects always experience some inconvenience and usually some discomfort. It is axiomatic that these hazards and inconveniences should not be incurred unless they are outweighed by the prospective benefits of the studies. When studies of bioavailability are necessary to insure

the effectiveness and safety of therapeutically important drugs, such studies are ethically justified and necessary. For any lesser purpose, they will rarely be justifiable. We do believe, however, that bioavailability studies should be required for products if the active ingredient in the product has not yet been introduced on the market.

In asserting that studies of bioavailability will not be required for all drug products, it becomes important to set forth general criteria to guide the selection of those products whose bioavailability should be documented by testing in man. A necessary, albeit not a sufficient, condition is that the drug be one that serves a clinically important purpose, especially if it is used in the treatment or the prevention of severe or life-threatening conditions. However, the clinical importance of a drug alone would not be an adequate reason for conducting an in vivo study of its bioavailability.

Beyond questions of feasibility and ethical justifiability, there are other good reasons to refrain from conducting studies of bioavailability of a number of drugs, including many that are therapeutically important. Many drugs are given in fairly standard dosage with little regard to the body size of the patient or to the titration of dosage to exactly the desired therapeutic effect. Such practice reflects the fact that for many drugs there is a wide margin between the concentration of the drug in the body fluids needed to produce the desired therapeutic effect and the concentration at which undesirable toxic effects begin to appear. Thus, the standard dose is usually one that will produce in the vast majority of patients a concentration in the blood well above the levels needed for the therapeutic effect without reaching unacceptable levels of toxicity. Clearly, under such, circumstances a wide range in bioavailability could be tolerated without hazard of therapeutic failure.

For example, no one would question the clinical importance of penicillin, nor the seriousness of many of the conditions for which it is used. But the margin between its effective concentration and its toxic level is so great that the prescribed dosage can be aimed at achieving a concentration in the blood far above the minimum effective level, thus insuring a therapeutically effective level in virtually all users. Moderate differences in the concentration achieved in the blood owing to

differences in the bioavailability of chemically equivalent penicillin products would be easily tolerated.

Conversely, drugs that have a relatively narrow range between the concentration needed for the desired therapeutic effect and the concentration associated with significant toxicity would be candidates for testing of bioavailability, since relatively modest changes in the concentration achieved in body fluids might well be associated with large changes in the frequency of therapeutic failure or significant toxicity. Examples of drugs that might fall into this category include a number of cardioactive drugs (digitalis glycosides, quinidine), anticonvulsant agents (diphenylhydantoin) , some corticosteroids, and certain antibiotics (chloramphenicol and cephalosporins) .

The pharmaceutical properties of drugs and drug products affecting volubility and dissolution characteristics in gastrointestinal fluids constitute additional factors to be considered in the selection of chemically equivalent drug products for which evidence of bioavailability may be required. The drugs themselves may differ in particle size or crystal form, and these differences can affect volubility. In addition, the method of manufacture of other ingredients, such as excipients, diluents or fillers may alter dissolution characteristics. For many drugs and drug products, however, high volubility of the drug and rapid dissolution of the product make it relatively unlikely that major differences in absorption from the gastrointestinal tract will occur. However, there are certain conditions in which even these drugs may show differences in bioavailability.

Sustained-release and enteric-coated products constitute a separate problem that we have not considered in any detail, but it is clear that there is a particular need for tests of the bioavailability of many such preparations.

In summary, measurements of bioavailability may be critical to assuring therapeutic equivalence of drugs or drug products that:

- Are used for treatment or prevention of serious illness;
- Have steep dose-response curves or unfavorable therapeutic indices; or

- Contain active ingredients that are relatively insoluble or are converted to insoluble forms in gastrointestinal fluids.

In view of (1) the demand on limited resources (particularly the time and effort of trained investigators and other scientific personnel), (2) the hazards, however minimal, of exposure of volunteers to additional drugs and the associated investigational procedures, and (3) the unnecessary addition to the cost of drug products that such studies would entail, we consider it desirable that studies of bioavailability in man be carried out only in the case of drugs with characteristics such as those described above. We believe that appropriate panels of experts would have little difficulty in distinguishing between those drugs for which bioavailability studies in man should be required and those for which they should not. (See discussion on page 59.)

5

PRESENT COMPENDIA STANDARDS AND GUIDELINES FOR CURRENT GOOD MANUFACTURING PRACTICE DO NOT INSURE QUALITY AND UNIFORM BIOAVAILABILITY FOR DRUG PRODUCTS, NOT ONLY MAY THE PRODUCTS OF DIFFERENT MANUFACTURERS VARY, BUT THE PRODUCT OF A SINGLE MANUFACTURER MAY VARY FROM BATCH TO BATCH OR MAY CHANGE DURING STORAGE,

As we have pointed out, the fact that several marketed drug products that are chemically equivalent have been found to differ significantly in bioavailability is a clear indication that present compendia standards and guidelines for Current Good Manufacturing Practice (CGMP) do not insure bioequivalence. A consideration of these standards and guidelines may clarify the reasons for their inadequacy.

COMPENDIA STANDARDS

HISTORY

The official drug compendia originated independently of the Federal Government and have been maintained through a convention and committee system composed of interested health professionals. The United States Pharmacopeial Convention, Inc., (USP) dates back to 1820, and the National Formulary Board (NF), subdivision of the American Pharmaceutical Association, was established in 1888. The compendia that have been published by these organizations

since their founding were developed to help insure that drug products of an acceptable level of quality would be available to physicians. They set forth standards for drugs used in dispensing and compounding prescriptions. Later, they provided pharmaceutical manufacturers with descriptions of recognized standards for products conforming to certain criteria of strength, purity and quality.

Pharmacists in early America were responsible for identifying and establishing the quality of the raw materials they used in compounding prescriptions. In the 1880s, the pharmaceutical industry became the primary supplier of drug products and accepted responsibility for standardizing the products. However, the compendia tests for strength and purity still retained their basic simplicity, requiring minimal instrumentation and analytical skill, so that a pharmacist could still perform the assays.

Reliance on simple approaches to specifications ,of materials and the control of quality persists to this day. These shortcomings in present-day assessment of drugs particularly pertain to the tests for identity, purity and potency that form the legal basis upon which compliance or lack of compliance is established (Federal Food, Drug, and Cosmetic Act) . In some cases, physical tests and assay procedures of much greater sensitivity than" those in the compendia are known-; many of these tests are fully automated.

The FDA, at its National Center for Drug Analysis in St. Louis, has found it necessary to establish its own set of tests for monitoring the quality and uniformity of drug products. Many of these tests are also automated and reflect more advanced technology than do the compendia tests. Nevertheless if a given drug product fails to pass these advanced automated tests, the FDA is still required to repeat the analyses using official, and frequently less accurate, manual methods in order to establish a lack of legal compliance. In any case, it is difficult to defend the current selection of methods when it is apparent that they are, in some cases, inaccurate, insensitive and nondiscriminating, as can be seen by a comparison of several of the present compendia monographs with the data published in more recent sources.

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* One such current source is Analytical Profiles of Drugs, edited by Klaus Florey and (continued)

COMPENDIA MONOGRAPHS

The selection of active ingredients and finished drug products for inclusion in the United States Pharmacopoeia (USP) and the National Formulary (NF) is based primary on their therapeutic importance as judged by the revision committees; the basis for selection of excipients is not clearly specified. A large number of active ingredients and a number of excipients are not included in the compendia. Certain excipients are included, but specific tests and standards applicable to their special use as components of tablets and capsules are not listed. For excipients not described in the compendia, the drug manufacturer may set his own specific requirements or accept the specifications of the firm that supplies these ingredients to him. Since these so-called inert substances can influence the stability and/or release of the active compound from the dosage form, the lack of standards for excipients may well lead to variation in important properties of the final drug product.

The dosage form monographs contained in the official compendia deal with end products. They do not describe inactive components or processes of manufacture. Thus, they do not assure exclusion of the possibility that drugs might interact with excipients, some of which can cause decomposition, and do not exclude the formation of complexes not detectable by present official tests. There are also no specifications for the granulation or precompression mixture as a preliminary means of insuring uniformity of content and dissolution properties. Nor do the monographs include adequate tests to specify characteristics of the active ingredients needed to insure quality and standardized levels of bioavailability of the finished dosage form.

Beyond the tests for weight and uniformity of content, the most important tests included in the monographs for tablets or capsules are those for disintegration and dissolution. The disintegration tests currently called for in the compendia are relatively crude and require that an observer record the time necessary for the disintegration of six tablets. Since the average time for disintegration is about 30 minutes,

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(Continued)
published by Academic Press. TWO volumes have" been published to date, the first in 1972 and the second in 1973.

a period long enough for the manufacture of hundreds of thousands of tablets, disintegration tests are clearly unsuitable for use in the monitoring and control of the manufacturing process.

The dissolution tests, which have been specified in the compendia since 1970, are carried out in apparatus that may introduce extraneous sources of variation in the dissolution process. The test specifications for individual drug products have been established somewhat arbitrarily without sufficient consideration of the physical chemical properties of the active ingredient and of biological factors that may be critical in the dissolution process.

While uniformity in testing equipment is desirable, a single apparatus will not cover all test conditions for meaningful studies of dissolution. It should be noted that in a New Drug Application (NDA), the FDA allows the pharmaceutical industry to use all available analytical techniques and to establish unique anlytical and quality control specifications for a new drug product. Before approval of the NDA, the Washington laboratories and the district laboratories of the FDA establish their own capabilities to conduct these analytical tests, in case they should be needed for their regulatory activities. It is unfortunate that the official compendia are restricted to measurement systems with severe limitations in design.

STATISTICAL IMPLICATIONS

Irrespective of the technical soundness of the tests, the adequacy of which we have questioned above, the compendia standards for finished drug products have been established without any serious consideration of the adequacy of the statistical procedures for the detection of defective finished products. In fact, the sampling procedures are generally inadequate. No consideration is given to (1) the method of drawing the sample, (2) the rationale for specifying the number of units of the product to be tested and (3) the statistical criteria for permitting a batch or lot of a finished product to pass. Thus, current compendia standards offer insufficient protection against the possible marketing of substantial batches of defective products.

A. THE OFFICIAL TABLET DISINTEGRATION TEST

The USP and NF tablet disintegration tests require that six tablets be tested initially. If all tablets disintegrate under the conditions described, then it

is assumed that the lot or batch of tablets from which the sample of six was drawn is satisfactory. Alternatively, if one or two of the initial six tablets fail the test, then the test is repeated on 12 additional tablets. The criterion of acceptability is then that at least 16 of the total of 18 tablets disintegrate completely within the time specified. Table A summarizes the probability that the sample will meet the specified requirements as a function of the percentage of defective tablets in the batch from which the sample is drawn.

Table A. Probability of Acceptance as Function of Percentage of Defective Tablets (Disintegration Test)

Percent Defective	Probability of Acceptance
1%	.995
5%	.96
10%	.79
20$%	.39
30%	.15
40%	.004

Thus, for example, batches of tablets of which 20% are defective with regard to the disintegration tests would pass the specified disintegration test 39% of the time. This test procedure offers a high order of assurance of detecting defective lots only if the lots contain at least 40% defective tablets.

B. DISSOLUTION TEST

The USP and NF dissolution tests state that six tablets initially are to be tested for dissolution properties. If all six meet the specifications, it is assumed that the batch from which the sample is drawn is acceptable. If one or two units fail to meet requirements, then the test is repeated on six additional units. If the testing reaches this point, at least 10 of the 12 units tested must meet the requirements of the dissolution test in order to comply with compendia standards. Table B summarizes the probability of acceptance in this test as a function of percentage of defective tablets or dosage units in the batch from which the sample is drawn.

Table B. Probability of Acceptance as a Function of Percentage of Defective Tablets or Dosage Units (Dissolution Tests)

Percent Defective	Probability of Acceptance
1%	.9998
5%	.98
10%	.90
20%	.58
30%	.28
40%	.10
50%	.03
60%	.006

Note that the criteria for acceptance in this test result in even poorer protection than in the disintegration test. A batch having 20% defective tablets or dosage units will be accepted 58% of the time. Only when the percentage of defective units in a batch is 60% or greater do these requirements offer high assurance of detecting defective batches.

c. CONTENT UNIFORMITY

The requirements for satisfying compendia standards for uniformity of content are somewhat more complicated than the dissolution and disintegration tests. The standards specify the following procedures:

- Ten capsules or tablets from batch are initially assayed. The requirements are satisfied if nine or 10 of these units fall within the limits of 85%" to 115% of the content specified and all results fall within 75% to 125%.

- If two or three of the initial 10 units yield results that fall outside the range of 85% to 115% of the specified content and none fall outside the range of 75% to 125%, an additional 20 units are tested. The requirements are then met if all 30 results fall within the limits of 75% to 125% and if not more than three results fall outside the limits of 85% to 115%. Table C summarizes representative values of the percent defective versus the probability of accepting the batch from which the samples are drawn.

Table C. Probability of Acceptance Versus Percentage of Defective (content Uniformity Test)

Total Percent Defective	Percent Defective in Range 75%-85% and 115%-125%	Percent Defective Outside Range 75%-125%	Probability of Acceptance
5%	5%	0%	.97
5%	4.5%	0.5%	.92
5%	4.0%	1.0%	.88
10%	10%	0%	.82
10%	9%	1%	.72
10%	5%	5%	.56
25%	25%	0%	.25
25%	15%	10%	.17
25%	10%	15%	.13
50%	50%	0%	.01
50%	40%	10%	.009
50%	25%	25%	.006

This sampling procedure for content uniformity cannot, with any assurance, be depended upon for detecting defective batches. For example, note that a batch of capsules or tablets having 25% defective units would meet compendia standards as frequently as 25% of the time.

D. SAMPLING PROCEDURES

The compendia standards are vague with regard to how the samples of tablets or dosage forms are to be chosen for testing. If the standards are to have any utility for judging the quality of a batch, then it is essential that careful attention be given to the drawing of a sample. In order to be able to draw inferences about a batch being tested, it is absolutely essential that the sample of dosage units from that batch be randomly selected. All dosage units in the batch must have an equal chance of being selected for the sample. Yet, the compendia standards make no mention that a random sample of dosage forms is necessary, nor are guidelines given as to how the sample should be drawn.

COMPENDIA REVISION PROCESS

An examination of the USP revision process "reveals the inherent weaknesses in the development of present compendia standards. As a nonprofit, independent organization, the USP draws its membership from a broad base of organizations and

institutions concerned with drugs. Its Committee on Revision, composed of 20 medical and 40 pharmaceutical scientists, is selected once each five years by the 300 USP Convention members. Each member of the Committee on Revision draws upon the expertise of other scientists, thus expanding the number of scientists contributing to the effort to about 200. The contributions of these persons, in some cases, may be very superficial, since both the USP and the NF lack the funding and the scientific staff needed to permit serious scientific prospective searches to be conducted for potential or suspected problems.

Except for out-of-pocket expenses, all work done by committee members is voluntary. The USP (and NF) are dependent on funds derived primarily from the compulsory purchase of their published compendia by pharmacies in most states and from the sale of reference standards of official compendia substances. Major committee revisions are too infrequent to stay abreast of advancing technology. One factor that delays compendia revision and the development of test methods is the shortage of personnel to accomplish these tasks; in 1973 there was a full-time-equivalent staff of only 4.2 persons involved in the development of compendia standards. (In 1967, the corresponding figure was 1.7.) Thus, the USP and the NF both lack the internal and external resources required to develop rational and modern standards. Their continued reliance upon such limited resources is anachronistic and inadequate for the scientific activities necessary to insure pharmaceutical equivalence of drug products.

It should be noted, however, that the Food, Drug, and Cosmetic Act contains a section enacted by Congress in 1944 entitled The Revision of the USP; Development of Analysis and Mechanical and Physical Tests in which the Secretary of Health, Education, and Welfare is "authorized hereafter to cooperate with the associations and scientific societies in the revision of the USP and in the development of methods of analysis and mechanical and physical tests necessary to carry out the work of the FDA." It appears that very little has been done to implement this section of the Act during the last 30 years. We have been advised that the FDA allocated only $75,000 to the implementation of this section of the Food, Drug, and Cosmetic Act in 1974.

CURRENT GOOD MANUFACTURING PRACTICE

The regulatory measures of the FDA are based on the Food , Drug, and Cosmetic Act, as amended up to August 1972, and the FDA's supplementary regulations and guidelines established under the authority of the Act. In recent years, the FDA has established guidelines under the title Current Good Manufacturing Practice. Unfortunately, these guidelines are based primarily on the official compendia standards and are limited to rather general-statements that may be subject to wide differences in interpretation. They correctly emphasize environmental factors, including control of air supply and organization of manufacturing plants, to minimize cross-contamination of products or errors in packaging or labeling; they also focus on the integrity of quality control and production records. These guidelines have greatly improved the handling of materials, cleanliness, and consistency in production, but they do little to minimize lot-to-lot variation in the output of manufacturers generally or bioinequivalence among the chemically equivalent" products of different manufacturers.

A manufacturer of a duplicate product can request and receive approval to market his product on the basis of an Abbreviated New Drug Application (ANDA) specifying only the official compendia standards for controlling the quality of the raw materials and final drug product, including both the active . . ingredients and the excipients used in the product. Further, the raw materials can be included by the manufacturer on the basis of an identity test and a certification from the supplier of the raw materials that they passed the official compendia tests. Excipients not covered in an official monograph may be accepted from the supplier without any particular specifications at all. The manufacturer using these raw materials is expected only to assure himself that the raw material manufacturer maintains an acceptable level of quality assurance.

Current Good Manufacturing Practice guidelines do not mention preformulation tests or intermediate testing and refer only vaguely to in-processing tests. Although a manufacturer of duplicate products is required only to meet the compendia specifications, with all their limitations, the original manufacturer of the product is required to continue meeting all specifications of production and quality control described in the approved NDA. Undoubtedly, some duplicate products undergo tests and are manufactured

according to specifications that go beyond those in the compendia standards. There are, then, two sets of standards: those in the approved NDA and those established by the official compendia. It is hardly surprising that pharmaceutical equivalence is not guaranteed by the present procedures.

A million or more individual batches of tablets and capsules are manufactured each year in approximately 800 pharmaceutical manufacturing plants in the U.S. Some of these batches include several million units. Inspection of plants is required only once every two years by the FDA, although it usually is done at least once a year. The National Center for Drug Analysis in St. Louis has the capacity to test only a few thousand batches of drug products per year. The large number of different drug products and the sizes and number of batches produced make it difficult to establish assurance of quality using the present system of inspection.

In many parts of the country having very few. pharmaceutical manufacturing plants, FDA agents trained in food inspection also serve “as drug inspectors. These inspectors are often trained for their ancillary assignments in short courses in pharmacy schools; most of them are not trained sufficiently to determine whether adequate testing of the final product has been performed. The very nature of the present Current Good Manufacturing Practice-guidelines forces inspectors to concentrate on plant design and maintenance practices and to rely on inspection of records to insure manufacturers’ compliance with compendia standards.

6

NEW COMPENDIA STANDARDS FOR **ACTIVE INGREDIENTS**, **EXCIPIENTS** AND FINISHED DRUG PRODUCTS SHOULD BE DEVELOPED AND REVISED ON A CONTINUING BASIS TO REFLECT THE BEST AVAILABLE TECHNOLOGY TO INSURE QUALITY AND UNIFORM BIOAVAILABILITY, APPROPRIATE STATISTICAL PROCEDURES SHOULD BE SPECIFIED TO MAKE CERTAIN THAT THE PURPOSES OF THE STANDARDS ARE OBJECTIVELY SATISFIED, THE GUIDELINES FOR CURRENT GOOD MANUFACTURING PRACTICE SHOULD BE EXPANDED TO INCLUDE SPECIFIC DESCRIPTIONS OF ALL SIGNIFICANT ASPECTS OF MANUFACTURING PROCESSES FROM THE RAW MATERIALS TO THE FINAL PRODUCT,

The philosophy that is applied in regulating the preparation of sterile solutions for parenteral use can serve as a model in establishing the requirements for insuring the quality of drug products. In the case of parenteral solutions, it has been determined that a zero level of microbial contamination should be the standard of quality with respect to sterility. No amount of testing applied only to the final product could insure this total freedom from microbial contamination without destroying and testing every package. Instead, a series of tests and procedures has been specified for every material used and at every stage of the process of manufacture in order to minimize the possibility of microbial contamination

at each step and thus in the final package.

Similarly, rather than aiming to insure the uniformity of oral drug products by tests applied only to the final entity, uniformity of quality and bioavailability should be promoted by making as specific as possible the requirements for the characteristics of the materials to be used, the processes by which they are to be assembled, and the tests to be applied to representative samples of the final product. Testing at all stages of the manufacturing process should reflect the best available technology and should be based on statistical procedures which will insure that the purposes of the tests are objectively satisfied.

COMPENDIA STANDARDS

TESTS TO BE APPLIED TO RAW MATERIALS

Many of the present monographs of the USP and NF for raw materials in drug products contain outmoded or suboptimal procedures. Revision committees have adopted the policy of specifying only a single analytical method for determining the purity of an active ingredient, even though the Food, Drug, and Cosmetic Act clearly permits more than one such test. As we have noted earlier, the policy of the compendia bodies has severely limited the improvement of analytical procedures. Most modern analytical methods are sufficiently accurate and specific that results obtained with one can be compared with results obtained by other methods. Although for some active ingredients, a single analytical procedure may be desirable, for others, any one of a number of methods might be acceptable.

Beyond its chemical identity and purity, there are characteristics of the active ingredient that could be specified in order to increase the reproducibility of the properties of the final drug product. These might include such specifications as the distribution of particle size, a maximally acceptable particle size, requirements for a certain crystal form, compressibility and a requirement for a rate of dissolution. Certainly not all such properties need be specified for all drug products, but they might be critical to the quality of some.

Raw material test requirements for excipients should be expanded in the compendia monographs. The USP

and NF do contain tests for some excipients. These tests however, tend to be nonspecific, and tests for many other excipients are not included at all. The same degree of test specificity described above for the clinically active material is appropriate for those excipient materials that influence bioavailability of the drug product.

SPECIFICATIONS FOR INTERMEDIATE STAGES OF THE MANUFACTURING PROCESS

The properties of the final product will be more easily controlled if requirements are imposed at intermediate stages of manufacturing. One such stage is that of the precompression mix--,the stage after the active ingredients and various excipients have been mixed but before the mixture is compressed into tablets. The qualities of the precompression mix could be defined by tests such as those for bulk density, loss of weight on drying, particle-size distribution, compressibility, and rate of dissolution. Again, it is not intended that all of these tests be required for all raw materials or at all stages of the process. However, certain specifications for the intermediate stages may be very important in establishing batch-to-batch reproducibility, especially if any changes are made in the manufacturing process.

Data from such tests might make it possible to determine whether changes in processes or starting materials have caused changes in the properties of the final product sufficient to necessitate the performance of new studies of bioavailability. We have been informed by the FDA that it has no policy at present that outlines specific requirements for bioavailability testing when changes are made in size of batches, processing equipment or raw materials used in the manufacture of drug products. Instead, these decisions are left to the various divisions within the Bureau of Drugs to be made on a more or less arbitrary basis. The proposed tests for products at intermediate stages might provide the FDA an objective basis for making these decisions. Testing at intermediate stages would be useful when applied to certain very insoluble active ingredients since it is difficult to apply meaningful dissolution tests to the final product of such drugs because of the inordinate volumes of fluid needed to dissolve all of the active ingredient.

TESTS APPLIED TO THE FINAL PRODUCT

Dissolution tests should be included in specifications for the final product. The tests specified, however, should relate to the physical and chemical properties of the drug and to possible interactions with the gastrointestinal fluids. This may require changes in the solvent to simulate the events that occur as the capsule or tablet is exposed first to gastric and then to intestinal fluids. The apparatus currently in use is not readily adaptable to such changes of solvent. The disintegration and dissolution test procedures, as well as tests of deaggregation, are in need of serious reevaluation. Automated dissolution apparatus is in use in a number of laboratories and is adaptable to the measurement of deaggregation; this apparatus should also be evaluated as a possible alternative to disintegration testing. When appropriate bioavailability data have been developed for a specific drug product, it is essential that the dissolution tests for that drug product be modified so that the results bear a high statistical correlation with bioavailability. In the absence of bioavailability data, dissolution tests should be adopted for their value in quality control.

It should be noted that the present regulations for the certification of antibiotics do not include dissolution tests. The published data indicating that some preparations of antibiotics have been subject to problems of bioavailability clearly demonstrate the need for standards of dissolution.

STATISTICAL PROCEDURES

We have indicated above some of the statistical inadequacies of present sampling and testing procedures. It should not be difficult to effect a great improvement in these. Statistical procedures have reached a high degree of development and can be used in such a way as to yield a high level of assurance that defective batches will be detected. The detection of batches containing a high proportion of defective dosage forms can be substantially improved by (1) choosing sample sizes in accordance with the average quality that is deemed necessary, (2) adopting sequential sampling and inspection procedures, and (3) recognizing that the acceptance or rejection of a batch should be determined not on the basis of the individual tests alone, but on the totality of the tests on all important characteristics.

In order to utilize the appropriate statistical procedures for judging the quality of batches, it is necessary to recognize that no sampling plan can guarantee that there will be zero defective dosage forms in every acceptable batch. Statistical sampling plans can yield an estimate of the average level of quality of accepted batches and the percentage of defective dosage forms that may be present in accepted batches. Sampling plans should not be the same for all drugs but should be designed to take account of the cost of testing and the harm that might ensue when defective dosage forms are used for therapeutic purposes. Clearly, the statistical sampling plans for a drug such as digoxin should be different from tests on many of the antibiotics. Drugs that have narrow therapeutic margins and/or are capable of producing serious side effects should be more tightly controlled than drugs without these characteristics.

GUIDELINES FOR CURRENT GOOD MANUFACTURING PRACTICE

The present guidelines are too general and non-specific to insure the uniformity of drug products. For example, Section 133.8 of the Code of Federal Regulations states:

> To insure uniformity and integrity of products, there should be an adequate in-processing control, such as checking the weights and the disintegration times, adequacy of mixing, the homogeneity of the suspensions and the clarity of solutions. In-processing sampling shall be done at intervals with suitable equipment. Representative samples of the final dosage forms shall be tested to determine their conformity with the specifications of the product before distribution.

A considerable period of time will probably be required to complete the total revision of the individual compendia monographs and to expand them to include as many of the marketed drug products as possible. However, the FDA has the authority to modify the CGMP guidelines and should use it as rapidly as possible to establish more comprehensive standards for drugs and drug products. This could be accomplished by establishing a comprehensive list of appropriate tests for use

at three stages--raw material, intermediate, and finished product. The individual manufacturers could then be required to develop specific standards for their individual preparations, and a reasonable period of time should be allowed for the implementation of these standards."

Since different manufacturers use different equipment and processes for the manufacture of tablets and capsules and include different excipients in them, certain aspects of these specifications will have to be individualized. It will be necessary to develop specific deaggregation and/or dissolution tests for the products at intermediate steps of the manufacturing, process as well as certain other unique test procedures in order to insure that the quality and uniform bioavailability of the product can be maintained.

Finally, consideration should be given to the problem of determining how batches of fabricated tablets that do not meet specifications should be reprocessed. The availability of sufficiently detailed specifications for intermediate stages should allow evaluation of whether the reworked material possesses sufficiently similar specifications to qualify for continued processing.

We recommend that the CGMP guidelines be amended to require that every manufactured drug product have its own quality assurance plan, with attention in each plan given to each major step of the manufacturing process. Suitable testing procedures should be specified at each key stage of manufacturing to insure identification of any stage that is out of control. The design of such quality assurance plans should be regarded as an important component of the preformulation investigation of each product.

Quality assurance plans should be drawn up by the manufacturer and need not follow a standardized format. The plans should take into account special features associated with the plant, its personnel, and the drug product. The plans need not be static and should be modified by the manufacturer whenever appropriate. Thus, the CGMP would shift in emphasis from a concern for a clean and safe working environment to the control of all major design factors in the manufacturing process.

We also recommend more frequent inspection of manufacturing plants by the FDA to assess the degree of compliance with new compendia standards and

improved CGMP guidelines. As we recommend below on pages 46-48ff, the FDA should also be given the authority to request the submission of a company's records that demonstrate compliance with standards. To conduct the kind of inspection that we recommend, on a frequent basis, substantial increases will be required in both the number and capability of inspectors in the FDA.

The recommendations that we have made in this section all have the goal of making far more specific the requirements for the manufacture of each drug product, including coverage of all raw materials to be used, processes by which they are to be assembled, and tests to be applied at every stage to make certain that the requirements are being met.

The resulting set of new standards should not be considered to be a fixed ideal. Rather, it should be revised on a continuing basis as new information and advances in the state of the art are developed. On the other hand, we could caution against the capricous introduction of new requirements; changes should be made only when the benefit to be derived warrants the disruption of manufacture that they might impose. We believe that the kinds of changes in procedure that we have recommended will greatly increase the quality and uniform bioavailability of drug products and warrant the new designation of pharmaceutical equivalents.

7

ADDITIONAL RESEARCH AIMED AT IMPROVING THE ASSESSMENT AND PREDICTION OF BIOEQUIVALENCE IS NEEDED, THIS RESEARCH SHOULD INCLUDE EFFORTS TO DEVELOP IN VITRO TESTS OR ANIMAL MODELS THAT WILL BE VALID PREDICTORS OF BIOAVAILABILITY IN MAN,

An effective technological base is required for the provision of reasonable assurance that patients will experience adequate and predictable blood levels of orally administered drugs. Although much of the necessary methodology is already developed, additional research is needed to strengthen this technology in several areas.

REFINEMENT AND DEVELOPMENT OF ANALYTICAL METHODOLOGY

The ultimate proof of bioequivalence is achieved by demonstrating equivalent concentrations of drugs in plasma over an appropriate period of time after administration. Methods are now available for measuring the concentration of most drugs in blood and/or urine. Further, presently available analytical techniques could be applied to the analysis of some drugs for which methods are not now available. For some drugs, however, new analytical methods will have to be developed and present capabilities refined to permit reliable measurement of their concentration in plasma. For example, certain drugs used in cancer chemotherapy, some steroid drugs and reserpine cannot currently be measured adequately in studies of bioavailability. Whereas these analytical problems are potentially solvable through application of

existing technology, their solution is not likely to be easy. It will require substantial initial investment in the synthesis of drugs labeled with stable, and radioactive isotopes and development of appropriate antibodies for radioimmunoassay.

SPECIAL POPULATION GROUPS

At present, there is inadequate information regarding the prediction of bioequivalence in ill patients from bioavailability studies in normal adults. The uncertainty hinges on the importance of differences in absorption rates. It is possible that two drugs which are totally absorbed but have different absorption rates in the normal adult might differ significantly in the degree of their absorption in sick patients. Similarly, drugs that are absorped in the normal adult may be incompletely absorbed in infants since infants have immature digestive enzyme systems and differ from adults in other aspects of gastrointestinal function. Additional research is required to determine whether factors such as differences in absorption rate do, in fact, constitute a problem in the application of data derived from studies in normal adult subjects. Sensitive legal and ethical issues make research on drug absorption in young humans difficult, but we believe that, where possible, attempts should be made to obtain useful bioavailability information for populations other than healthy adults.

IN VITRO CORRELATIONS

It is not practical (or desirable) that all batches of drugs be tested in man to assure adequate and predictable bioavailability. Accordingly, in vitro methods that are predictive of bioavailability must be developed to confirm the bioequivalence of (1) different batches of the same drug product made by the same manufacturer, (2) drug products made by different manufacturers and (3) drug products held in storage for a relatively long time.

Several investigations have indicated that in vitro tests (for example, dissolution tests) may be correlated with bioavailability. However, such data are lacking for most drug products. In addition, research is needed on the development of animal models that can be used for predicting bioavailability in man.

The development of such predictive systems would greatly simplify the establishment and monitoring of standards insuring adequate and uniform levels of bioavailability.

RELATIONSHIP BETWEEN PLASMA LEVELS AND THERAPEUTIC EFFECTS

Decisions about which drugs do indeed require direct proof of bioequivalence in man will be based in part on knowledge regarding the relationship of plasma levels of the drug to its therapeutic effect. This type of pharmacologic information in man is not well developed for many drugs. Research on the relationships between plasma levels and efficacy and toxicity will facilitate rational regulatory decisions.

RESOURCES FOR ADDITIONAL RESEARCH

The foregoing discussion has described several kinds of research needed to strengthen the assurance that products will provide adequate bioavailability. The particular agency appropriate for sponsoring this research will depend upon the kind of research that is initiated. For example, research directed toward the improvement of analytical methodology for in vivo studies of drugs, or toward investigations of the relationships between plasma levels of drugs and' their therapeutic effect, is already included in the program objectives of several of the National Institutes of Health, particularly the National Institute of General Medical Sciences. These efforts should be encouraged and supported with clear recognition of their importance.

Research concerned with the improvement of methodology for in vitro tests related to the establishment of new compendial standards might be sponsored by the proposed new standard-setting organization, discussed on pages 53 ff., or the FDA. These organizations might also become increasingly involved in sponsoring research concerned with the application of existing technology to the formulation, production and quality assurance for new drug products.

In order for research to be sponsored by either the new organization or the FDA, substantial new resources will be required because support for such research is almost completely lacking at the present time.

The FDA has been only minimally involved in research activities of these kinds and, of course, the new standard-setting organization has yet to be developed. Irrespective of the agency sponsoring the research, the base of scientific staff will have to be expanded in order to design proposals and monitor research activities adequately.

8

CURRENT LAW REQUIRING MANUFACTURERS TO MAINTAIN RECORDS AND MAKE INFORMATION AVAILABLE TO THE FDA IS AMBIGUOUS OR INADEQUATE AND SHOULD BE CLARIFIED AND STRENGTHENED, IN PARTICULAR, MANUFACTURERS SHOULD BE REQUIRED TO SUBMIT ALL INFORMATION RELATING THE TESTS THEY CONDUCT TO THE BIOAVAILABILITY DATA THEY DEVELOP IN ORDER TO HELP PROVIDE INFORMATION ON THE FACTORS THAT MODIFY THE BIOAVAILABILITY OF DRUG PRODUCTS, THIS INFORMATION SHOULD BE AVAILABLE TO AID IN THE ESTABLISHMENT OF COMPENDIA STANDARDS,

Under the Food, Drug, and Cosmetic Act, authority is provided to the FDA to obtain proof of safety and efficacy (and, in some instances, bioavailability) of certain drug products. Section 505 of the Act authorizes the extensive collection of data on new drug products with respect to both the safety and efficacy of the products as labeled. There is continued surveillance by the FDA of new drug products after they enter the marketplace. Manufacturers with New Drug Applications are required to establish records and make reports concerning clinical experience and other information needed for regulation by the FDA.

However, current law is ambiguous with respect to providing the FDA with general authority to require drug manufacturers to maintain records and to make

reports demonstrating their compliance with compendia standards for drug products. Furthermore, it is not clear that the law provides authority to require manufacturers to submit information concerning quality control procedures and manufacturing processes.

It has been indicated in testimony presented before this Panel and elsewhere that manufacturers often perform tests of product quality in addition to those set forth in compendia standards. Although the FDA is informed of these tests, the frequency with which manufacturers set standards that are more stringent than official standards is unknown to us at this time, but it appears to vary among drug products and among manufacturers. Information is also lacking about the specific kinds of tests conducted beyond those required in the official standards.

In addition, there is currently no general legislative authority to require manufacturers to submit data, generated in their research and development activities, concerning formulation, bioavailability, or new procedures correlating bioavailability with in vitro tests. In its investigations of a new drug and the development of dosage forms, a pharmaceutical company may conduct studies of bioavailability on a series of formulations and carry out related in vitro tests. The FDA does not have access to the results obtained with these research formulations.

Certain kinds of information currently made available to the FDA by manufacturers are required under current law to be held confidential and cannot be used in establishing either new compendia standards or enforcement requirements. We believe this provision is too restrictive. The fact that such information may not be made public does not mean that relevant portions of it should not be used by appropriate experts to establish new standards or requirements or to revise existing ones. For example, if a company develops information that can be used to improve procedures or methods for testing drug products, relevant portions of this information should be made available to appropriate experts to aid them in establishing new or revised compendia standards or enforcement requirements. This objective can be achieved even though the confidentiality of the specific proprietary information is maintained.

We make the following recommendations:

- The ambiguity in current law regarding requirements for keeping records and reporting results of compendia tests should be removed; such requirements should be specifically mandated. Results of batch-to-batch testing or testing of single batches over time should be made available to the FDA as requested.

- The FDA should be given the authority to request (on a routine basis if it elects to do so) information describing the methodology, specifications and results of tests conducted on commercial products.

- A standardized and simple format that facilitates clear understanding should be designed for the presentation of the aforementioned data to the FDA.

- Manufacturers should, upon the request of the FDA, be required to submit any information in their files that relates manufacturing processes and in vivo and in vitro tests to the bioavailability of any drug product. This requirement should apply to technical information obtained during research related to the development of new drug products, even when such information bears only an indirect relationship to the final dosage form.

- When the FDA finds that particular in vitro or in vivo tests are useful and deserve wider application, it should be empowered *to* share the information with appropriate experts and to incorporate those tests into the compendia standards to be applied to all manufacturers of that drug product.

9

EXEMPTIONS PROVIDED IN CURRENT LAW FOR SOME DRUG PRODUCTS BASED ON THEIR YEAR OF INTRODUCTION IN RELATION TO AMENDMENTS IN THE FOOD, DRUG, AND COSMETIC ACT SO-CALLED GRANDFATHER CLAUSES) HAVE IMPEDED IMPROVEMENT IN THE QUALITY OF THESE PRODUCTS, SUCH EXEMPTIONS SHOULD BE ELIMINATED,

The Food, Drug, and Cosmetic Act provides authority to establish standards and to regulate drugs and drug products under the new drug provisions (Section 505) and under the drug adulteration and misbranding provisions (Section 501 and 502). However, drug products that were marketed prior to 1938 are not covered by the "new drug" provisions of the Act, but are subject to so-called grandfather provisions. Thus, unless the product or the labeling is changed, these products are exempt from regulations to insure their quality. Similarly, for a drug product marketed after 1938, but prior to 1962, regulatory authority is limited to a qualitative description of the product's composition in which a concentration range of the adjuvants, instead of an exact formulation, may be submitted.

We believe that these limitations have interfered with the process of establishing standards to insure the quality of drugs and drug products marketed before 1962, especially those marketed before 1938. Such exemptions provide an incentive for drug manufacturers to maintain the status quo for those drug products rather than to make improvements based on more recent research or advances in technology, since any change in formulation or labeling may open the door to reclassification of

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the product as a “new drug, ” subject to more rigorous regulatory standards.

Drug products available before 1962, and especially those available before 1938, were formulated under conditions of relatively limited technology compared with that of today. As a result, the older products, as indicated on pages 11-12, are more likely to be subject to bioavailability problems than products that became available after 1962 when the New Drug Application and Abbreviated New Drug Application requirements were implemented. The most important example of such a problem with an older drug product arose with the therapeutically important and highly potent drug, digoxin. As we discussed on page 13, the bioavailability of a batch of this drug was found to be greatly reduced, resulting in a potentially dangerous situation for patients using the drug. However, the only legal authority which the FDA was able to use in acting to correct the situation was a provision regarding labeling and formulation. Such ambiguous legal authority may be inadequate to prevent delays brought about by court actions at a time when immediate action is required to protect the American public.

We believe there should be a clear legal mandate to establish and apply regulatory standards uniformly to all drug products, irrespective of when they were introduced on the market. We strongly recommend that the legal authority be provided to establish standards for all drugs and drug products, introduced both before and after 1938, based on the best available technology in order to insure that the drug products made available to the American public are of the highest quality possible.

10

A SINGLE ORGANIZATION CAPABLE OF SETTING STANDARDS ADEQUATE TO INSURE THE QUALITY AND UNIFORM BIOAVAILABILITY OF DRUG PRODUCTS SHOULD BE ESTABLISHED TO REPLACE THE PRESENT USP AND NF AS THE OFFICIAL STANDARD-SETTING ORGANIZATION OF THE FEDERAL GOVERNMENT,

To carry out the task of establishing drug standards adequate to insure the quality and uniform bioavailability of drug products, we strongly recommend that a single organization be established to supersede the USP and NF as the official standard-setting organization of the Federal Government. We do not believe that continuation of the current organizations with an admonishment to "do better" would be adequate to insure the level of quality of drug products that the public deserves. We believe there are too many weaknesses in the structure of the present organizations for them to be able to do the job adequately.

The basic function of the new standard-setting organization should be to establish and revise drug and drug product standards continuously on the basis of the best available technology in order to insure that drug products meeting these standards would have the highest quality and uniformity.

The establishment of improved standards for drugs and drug products will require an expanded research program as discussed on page 43 ff. This research should be conducted through both grants and contracts with outside organizations as well as by

the scientific staff of the new standard-setting body. To conduct the research, the new organization must have an adequate staff of scientists actively engaged in research. This staff must be capable of evaluating research conducted by outside groups and developing proposals for additional research.

Although the new standard-setting organization should have a sizable scientific staff, we do not believe that it would be efficient to try to encompass within this staff all the expertise necessary for setting all drug standards. Instead, a series of expert panels should be assembled to establish standards for drugs and drug products in the various classes. Individuals who serve on these panels should have expertise in pharmaceutical and analytical chemistry, statistics and other disciplines that are related to analytical methodology, materials to be used in the manufacture of drug products, techniques of testing, etc. A single panel should not be expected to have the knowledge required to deal with all drugs and drug products; nor should a single group be expected to do the extensive amount of work required to establish standards for all drugs.

In addition to making decisions regarding the establishment of standards, the expert panels should also review the results of relevant research conducted by outside groups as well as by staff scientists and should recommend additional research to be conducted where necessary. As discussed on page 47, the panels should also have access to appropriate information from industry for use in establishing standards.

Members of these panels should be objective experts who are not in a position to derive economic or political benefit from the manufacture of drug products. They should be appropriately paid for their efforts; no longer should drug standards be set by those few individuals who can afford to volunteer significant amounts of their time to perform this service for the public.

Although scientists from the pharmaceutical industry should not be allowed to exert a controlling influence on the standard-setting organization, scientific input from industry must be encouraged. One possible form of participation of industrial scientists might be as members of technical advisory committees reporting to the panels of experts. Individuals from industry who participate on these technical advisory committees should be

selected for their technical capabilities rather than for the managerial positions they may hold.

Cooperation and coordination of the activities of the new standard-setting body with those of several other groups is essential to accomplish the objectives set forth in this report. The pharmaceutical industry will continue to conduct a major share of the research related to the development of new testing methods and technology. The industry will also be responsible for applying the new standards in their manufacturing processes. In addition, health professionals, scientists, and others responsible for prescribing and dispensing drugs or performing the research needed to meet the requirements for improved drug standards and for data on bioavailability of drugs will also be affected by implementation of our recommendations. The functions of the new standard-setting organization must be closely coordinated with those of the FDA in order to insure a meaningful and productive interchange of information between those who establish drug standards and those who monitor for compliance with those standards. It should be the responsibility of the new standard-setting Organization to insure coordination of its activities with those of the regulatory and enforcement groups.

We do not recommend a specific organizational location for the new standard-setting body, although we strongly recommend that it be organized and located in such manner as to allow reasonable freedom from inappropriate industrial or political influence. Drug standards should be concerned with assurance of the highest quality drug products for the American people rather than with economic or political considerations. We do not believe that the standard-setting organization and the compliance-monitoring organization should be the same; but there should be a healthy, cooperative relationship between these groups.

Several options are readily apparent for the location of the new organization: within the FDA but separate from the compliance-monitoring group, within HEW but separate from FDA, or outside of the Federal Government as an independent organization. The possibility that the USP and the NF could merge and make sufficient changes in their structures and functions to fulfill the criteria for an effective standard-setting organization is not precluded, but the changes necessary would be extensive.

Wherever the new organization is located administratively, it will require federal funding commensurate with its responsibilities for setting the standards that would be employed as a basis for federal regulation. If the organization is placed within the structure of HEW, direct federal funding will be straightforward. If it is established as an organization independent of the federal structure, it could still receive direct federal funding, or it could be funded through a grant or contract from HEW. In any case, we strongly recommend that sufficient federal funds be supplied to insure that the objectives are achieved.

1 1

A SYSTEM SHOULD BE ORGANIZED AS RAPIDLY AS POSSIBLE TO GENERATE AN OFFICIAL LIST OF INTERCHANGEABLE DRUG PRODUCTS, IN THE DEVELOPMENT OF THE LIST, DISTINCTIONS SHOULD BE MADE BETWEEN TWO CLASSES OF DRUGS AND DRUG PRODUCTS:

1. THOSE FOR WHICH EVIDENCE OF BIOEQUIVALENCE IS NOT CONSIDERED ESSENTIAL AND THAT COULD BE ADDED TO THE LIST AS SOON AS STANDARDS OF PHARMACEUTICAL EQUIVALENCE HAVE BEEN ESTABLISHED AND SATISFIED,

2, THOSE FOR WHICH EVIDENCE OF BIOEQUIVALENCE IS CRITICAL, SUCH PRODUCTS SHOULD BE LISTED ONLY AFTER THEY HAVE BEEN SHOWN TO BE BIOEQUIVALENT OR HAVE SATISFIED STANDARDS OF PHARMACEUTICAL EQUIVALENCE THAT HAVE BEEN SHOWN TO INSURE BIOEQUIVALENCEI

The question that led to the genesis of this study and report addressed the economics of drug purchase; and, although we have not given consideration to other possibly significant economic issues, our charge does relate to whether drug products are or can be made sufficiently interchangeable so that price can be a major factor in their selection.

It is clear from the conclusions we have already stated that we do not believe that all chemical equivalents are, at present, interchangeable. We do believe, however, that the goal of interchangeability is achievable within most, if not all, classes or oral drug products and that a system should be organized as rapidly as possible to establish the conditions that will permit a listing of interchangeable products.

Establishment of such a listing should begin with a series of judgments regarding classes of drugs and individual drug entities that will yield a division of drugs into two groups: those for which evidence of bioequivalence is considered essential and those for which such evidence will not be required. The general criteria for such decisions have been set forth on pages 21 ff.

Upon classification of a drug as one requiring evidence of bioequivalence, products of that drug should be included on the list of interchangeable drug products only after data supporting their bioequivalence have been provided and approved. Furthermore, beyond the question of bioequivalence among interchangeable drug products in this category, methods to insure pharmaceutical equivalence between batches of the same drug product deserve special attention.

It is apparent that many drug products are therapeutically equivalent even though they may vary somewhat in bioavailability. Included in this category, for example, are many groups of drugs that are customarily given in doses that insure concentrations in the blood well in excess of the minimum effective concentration. These drugs have a wide margin of safety between effective and toxic concentrations. Moderate variation within this wide margin can be considered to have little or no therapeutic significance.

It is our opinion, however, that even within these groups of drug products, for which evidence of bioequivalence can be waived, there is room for considerable improvement of standards for the control of manufacturing processes and the testing of products. Such-improvements as we have recommended will have the effect of minimizing many important sources of variability among chemically equivalent products. When improved standards of pharmaceutical equivalence have been established, drug products meeting the standards and falling into categories for which evidence of equivalent bioavailability is not essential can be

considered to be interchangeable and listed as such for the guidance of purchasers, prescribing physicians and dispensing pharmacists.

The official list of interchangeable drug products need not be permanently limited to those for which studies of bioavailability are now available or considered unnecessary. As compendia standards are developed specifying in vitro tests whose results correlate with bioavailability, it should be possible, in most instances, to use the in vitro tests as a basis for providing ongoing evidence of bioavailability. Products meeting these conditions can and should then be added to the list of interchangeable drug products. The ultimate goal should be that virtually all marketed drug products should fulfill the criteria necessary for inclusion in this list.

It should be recognized, however, that there may remain a few drugs--those that have low therapeutic indices and, possibly, unfavorable physical properties, but that are critically important in the treatment of serious illnesses--whose products should be considered noninterchangeable even though they meet these conditions, at least until experience has shown that improved in vitro testing or testing in animal model systems can be relied upon for the precise prediction of their bioavailability.

Many decisions requiring well-informed judgments will be necessary in establishing a list of interchangeable drug products and in the continuing operation of the system. The essential judgments should be based upon the highest level of expertise in many specific areas of medicine, clinical pharmacology and associated scientific disciplines. The wide range of the necessary fields of specialization and the extensive experience and depth of knowledge that will be required are not to be found within the staff of any single organization. Further, we do not believe that it would be efficient for the FDA to try to encompass all the necessary expertise within its own ranks. Rather, it will be essential to call upon the most knowledgeable individuals in each field, wherever they may be found, to provide the advice needed to arrive at appropriate decisions.

To accomplish this goal, a series of groups advisory to the FDA should be established, each to deal with specific areas in which decisions must be made. It is not to be expected that a single advisory group would be able to deal effectively with the full range

of responsibilities involved. For example, those who are best equipped to deal with drugs affecting the cardiovascular system are not likely to be the same individuals best able to offer the most useful advice about anti-infective agents. It is our belief that an appropriate range of advisory groups will not only make certain that decisions are reached on the basis of the best informed judgments but that the acceptance of these decisions by all interested parties will also be immeasurably enhanced.

The major expertise required to establish a list of interchangeable drug products will be provided by advisory groups rather than staff personnel. However, capable scientific staff will be essential to support the work of the advisory groups. Current staffing and funding levels are not adequate for the FDA to meet the significant new responsibilities proposed in this recommendation. Consequently, additional financial and staffing support will be required to develop and maintain the list of interchangeable drug products and to coordinate these efforts with the agencies involved in setting standards and supporting research. Such resources should be made available as rapidly as possible.

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Health Protection Branch, Department of National Health and Welfare, Canada

Lederle Laboratories Division, American Cyanamid Company

National Association of Pharmaceutical Manufacturers

National Formulary Board

Pfizer, inc.

Pharmaceutical Manufacturers Association

Softcon Products Division, Warner-Lambert Laboratories

Upjohn Company

U.S. Department of Defense

United States Pharmacopeial Convention, Inc.

appendix

PROCEEDINGS OF THE PANEL

To enable the Office of Technology Assessment (OTA) to provide the Subcommittee on Health (U.S. Senate Committee on Labor and Public Welfare) with recommendations regarding drug product equivalence and variation, it was necessary to select a group of representative experts who could review all pertinent technical information and report their conclusions within three months.

OTA initiated discussions with several organizations that might be able to furnish staff support and carry out other responsibilities to assist the expert panel in its deliberations. A proposal from Family Health Care, Inc., Washington, D.C., and ensuing negotiations resulted in the award of a contract to that firm to provide staff assistance to the panel. With the guidance and approval of OTA, Dr. Robert Berliner, Dean of the Yale University School of Medicine was selected as Chairman of the panel.

Under Dr. Berliner's direction and with OTA approval, eight additional members and one ex-officio member (from the OTA Advisory Council) were selected. A press release on April 11, 1974, formally announced the study and the formation of the Drug Bioequivalence Study Panel. The following is a review of the activities and proceedings of the Panel.

The first of four planned meetings of the Panel was convened in Washington, D.C., on April 12. At this meeting, the Panel discussed the scope of the study and developed wording to state its interpretation of the charge it had been given. It was agreed that information regarding bioequivalence should be obtained from a number of organizations

and institutions in order to give the fullest possible consideration to all points of view. Every possible effort was made to obtain the information needed from all appropriate groups within the time available.

A press release on April 23 announced the charge to the Panel and the Panel's desire that all relevant technical information be submitted by May 20, 1974. This announcement was released through a variety of news resources and subsequently printed in the Congressional Record.

Between the first and second meetings of the Panel, the staff was directed to initiate contact and, if appropriate, to hold meetings with selected groups to inform them of the study and its purposes and to determine what information these groups would be able to provide. Contact was made with the following organizations:

American Medical Association (AMA) Department of Drugs

American Pharmaceutical Association (APhA) , including the Academy of Pharmaceutical Sciences (APS) and the National Formulary (NF)

Health Protection Branch, Department of National Health and Welfare, Canada

Ministry of Health, Ontario, Canada, PARCOST Program

National Association of Pharmaceutical Manufacturers (NAPM)

National Pharmaceutical Council (NPC)

Pharmaceutical Manufacturers Association (PMA)

U.S. Department of Health, Education, and Welfare, Food and Drug Administration (FDA)

United States Pharmacopeial Convention (USP)

Several of these organizations were asked to present statements at the second meeting of the Panel on May 1-2. Representatives from the PMA, USP, NF, FDA, NAPM and the PARCOST Program presented prepared statements and responded to questions. Because of possible legal and proprietary constraints, this information was received in confidence, with the Panel meeting privately with representatives of

each group. These groups were also asked to submit additional documentation by May 20.

Since many professional and scientific organizations, government agencies, manufacturers and academic institutions were willing and anxious to present information and to provide assistance, the April 23 news release was used as a public announcement inviting interested groups and individuals to submit statements for consideration. It was made clear that their submissions would be given full consideration although time constraints made their direct testimony impossible. Many statements containing information related to the issues of the study were received, including letters from individuals and organizations and reports from pharmaceutical manufacturers.

After the May 1-2 meeting, the staff was directed to continue its collection of relevant data. Information from two programs in Canada--the PARCOST Program in Ontario and the Federal QUAD Program in the Health Protection Branch, Canadian Department of National Health and Welfare--was of particular interest since the experiences of these two programs were especially relevant to the issues under examination.

In preparation for the third panel meeting on May 21-22, members accepted individual assignments to review and report on the data that had been submitted. Most documentation, however, was submitted on or close to the May 20 deadline, leaving little time for review before the third meeting of the Panel. On May 21, published studies of bioequivalence and the additional documentation that had been received were reviewed and summarized.

Using this information and discussions based upon it as well as the knowledge and experience of its members, the Panel proceeded to formulate a series of conclusions and recommendations about present and future technological capability for assuring uniform bioavailability and quality of drug products.

By the conclusion of the third meeting, a tentative set of conclusions and recommendations had been agreed upon. Members of the group were assigned the task of writing supporting information and providing data that would go into the final report to be submitted to OTA.

The written recommendations were submitted to the Chairman for review prior to the final meeting on

June 13-14; during this meeting, the Panel members worked as individuals, in small groups, and as a whole, to prepare a draft of the final report and recommendations. During this process, Mr. Jack Cooper served as consultant to the Panel.

The draft was then edited and revised by the *Chairman* and the staff and sent to all *members* of the Panel for review prior to publication.

glossary*

- Abbreviated New Drug Application (ANDA) Shortened application for obtaining approval from the Food and Drug Administration to market a drug. The ANDA may require information on characteristics of the drug such as method of use, method of manufacture, adverse reactions, physical and chemical stability, packaging, extent of use.

- Active ingredient That portion of a drug product intended to produce a therapeutic effect.

- Bioavailability The extent and rate of absorption from a dosage form as reflected by the time-concentration curve of the administered drug in the systemic circulation.

- Bioequivalents Chemical equivalents 'which, when administered to the same individuals in the same dosage regimen, will result in comparable bioavailability.

- Chemical equivalents Drug products that contain the same amounts of the same therapeutically active ingredients in the same dosage forms and that meet present compendia standards.

- Crossover study An experimental plan for comparing two treatments which reduces the influence of the variation in individual responses.

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* The meanings of some of the terms used in this report are subject to various interpretations. The definitions given here are those used by the Panel.

Each individual is tested on both treatments at different times. Initially half of the individuals receive each drug product; each is then "crossed over" to the other drug product at a later time.

- Deaggreagation The breaking up of granules or aggregates into fine particles in aqueous fluid.

- Disintegration The breaking up of a tablet or capsule into granules or aggregates in aqueous fluid.

- Dissolution The breaking down of fine particles into molecules or ions homogeneously dispersed in aqueous fluid.

- Dosage form The form of the completed drug product (such as tablet, syrup, or suppository).

- Drug Any chemical administered to produce a pharmacologic effect.

- Drug product A dosage form containing one or more active therapeutic ingredients along with other substances included during the manufacturing process.

- Efficacy The ability to produce the purported therapeutic effect.

- Endogenous compounds Products of the chemical processes that occur in the organism.

- Excipient An inert substance used to give a preparation a suitable form or consistency.

- Formulation A complex mixture containing a selected chemical derivative of the drug compound, in proper physical form, together with excipients, diluents, stabilizers, preservatives, or a variety of other components.

- In vitro tests Tests carried out in laboratory apparatus.

- In vivo tests Tests carried out within living organisms by administering drug products to man *or* experimental animals.

- Investigational New Drug Application (IND) Application to begin clinical studies of the safety and efficacy of a new drug.

- Interchangeable drug products Pharmaceutical equivalents or bioequivalents that are accepted as therapeutic equivalents.

- Kinetic model An analysis of some process as a function of time,

- Margin of safety of drug The difference between a minimally effective and a toxic dose of a drug. The therapeutic index (q.v.) is frequently used as an indicator of the margin of safety.

- New compendial standards Standards to be established for active ingredients, excipients and drug products, including tests reflecting the best available technology to be performed before, during and after formulation.

- New Drug Application (NDA) Application for approval from the Food and Drug Administration to market a drug based on extensive documentation of safety and efficacy.

- Pharmaceutical equivalents Drug products that contain the same amounts of the same therapeutically active ingredients *in* the *same* dosage form and that meet standards to be established on the basis of the best available technology.

- Pharmacokinetics The discipline that treats the rates of absorption, distribution, metabolism and excretion of drugs.

- Present compendia standards The official standards for drugs, excipients, and drug products listed in the latest revision of the United States Pharmacopoeia (USP) and the National Formulary (NF).

- Radioactive labeling The introduction of a radioactive atom into a molecule to allow detection of the molecule by measurement of its radioactivity.

- Therapeutic index The ratio of the toxic dose to the minimally effective dose of a drug.

- Therapeutic equivalents Chemical equivalents which, when administered to the same individuals in the same dosage regimen, will provide essentially the same efficacy and/or toxicity.

- Tolerance The state in which the quantity of drug required to produce a specific biological effect in a particular individual has increased.

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