CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

Center for Drugs and Biologics
Food and Drug Administration
Department of Health and Human Services

GUIDELINE FOR THE FORMAT AND CONTENT OF THE HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION OF AN APPLICATION

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I. INTRODUCTION

Biopharmaceutic studies are required by Part 320, Title 21, and by the Waxman-Hatch Amendments to the Federal Food, Drug and Cosmetic Act (the act). These amendments define bioequivalence and require generic drugs to show bioequivalence to the previously approved dosage form. The regulations define important biopharmaceutic terms and establish acceptable procedures for determining the bioavailability of drug products. The new drug application (NDA) rewrite regulations require a separate biopharmaceutic review section in the NDA (21 CFR 314). This guideline is intended to assist applicants to prepare the biopharmaceutics section of the NDA.

The guideline is issued under 21 CFR 10.90. An applicant may, but is not required to, rely upon the guideline in preparing the biopharmaceutics section of an application. When a different approach is chosen, the applicant is encouraged to discuss the

matter in advance with FDA to prevent the expenditure of money and effort on preparing a submission that may later be determined to be unacceptable.

II. TYPES OF STUDIES

The particular studies required for a specific drug will depend on many factors. If there is any question concerning the requirements, the Division of Biopharmaceutics should be consulted for NDAs and the Division of Bioequivalence should be consulted for abbreviated new drug applications (ANDAs).

The studies included in the Biopharmaceutics Section are of five general types:

A. Pilot or Background Studies

Pilot studies are carried out in small numbers of subjects/patients to provide a preliminary assessment of the absorption, distribution, metabolism and/or elimination (ADME) of a drug as a guide to the design of early clinical trials and definitive kinetic studies. As analytical methodology for measuring blood levels of the drug and its metabolites is often incomplete at the time such studies are carried out, radioisotope techniques may be used.

B. Bioavailability/Bioequivalence Studies

Bioavailability studies are intended to measure the rate and extent to which an active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action. Several types of studies fall under the classification of bioavailability studies including:

1. Bioavailability studies to define the rate and extent of absorption relative to a reference dosage form (e.g., an intravenous injection, true solution, or suspension).

2. Bioequivalence studies comparing pharmaceutical equivalents/alternatives for the purpose of establishing equivalent extents and (where necessary) equivalent rates of absorption.

3. Dosage strength equivalence studies which show that equivalent doses of different dosage forms deliver the same amount of drug (e.g., 3 X 100 mg vs. 1 X 300 mg tablets).

C. Pharmacokinetic Studies

Pharmacokinetic studies are intended to define the time course of drug and, where appropriate, major metabolite concentrations

in blood and other body compartments. In the studies provided to support an NDA, usually the most critical information is that showing (by measurement of plasma drug levels) the rate of drug absorption and delivery to the systemic circulation, and the rate of elimination by metabolic or excretory processes. Of particular interest are changes in kinetic parameters with dose (i.e., dose-dependent kinetics) within the recommended clinical dosing range. When appropriate, other information may include influences of demographic characteristics (age, sex, race), influences of certain disease states, influences of external factors, such as meals or other drugs (drug-drug pharmacokinetic interaction), drug binding to biological constituents (e.g., plasma protein, red blood cell), studies performed in special patient populations and studies performed under conditions of therapeutic use.

D. Other In Vivo Studies

These are bioavailability studies employing pharmacological or clinical measurements/endpoints in humans or animals. In addition, chemical analysis of body fluids in animals may be used, when appropriate.

E. In Vitro Studies

In vitro dissolution studies are intended to define the release rate of a drug substance from the dosage form. They are conducted to characterize a dosage form and assure consistent batch-to-batch behavior. Other in vitro studies may be conducted to characterize further the drug moiety (e.g., protein binding).

III. FORMAT AND CONTENT OF THE BIOPHARMACEUTICS SECTION OF AN APPLICATION

The following format should be used to present biopharmaceutic data submitted in all types of NDAs. The submissions should be legible and should use only standard abbreviations. The tables and graphs should be well constructed, clearly identified, and captioned. Studies should be identified as interim or final reports, reports of published literature, etc., and the sponsor's contact person(s) should be identified.

Format for Biopharmaceutic Submission for an NDA, Paper NDA and ANDA

A. Summary of Studies

An overall tabulated summary of all in vivo biopharmaceutic studies carried out on the drug grouped by type, in the format shown in attachment A, "Biopharmaceutics Study Summary," should

be provided. Each type of study (pharmacokinetic, bioavailability, etc.) should be listed in descending order of importance.

B. Summary of Data and Overall Conclusions

There should be a summary of all the bioavailability/pharmacokinetic data and overall conclusions. The summary should include a table with the following information: pharmacokinetic parameters giving the values, as appropriate, for the major parameters (mean and %CV) such as the peak concentration (C max), area under the curve (AUC), time to reach peak concentration (t max), the elimination constant (Kel), distribution volume (Vd), plasma and renal clearance, urinary excretion, etc., derived from each in vivo study (Attachment B). Overall conclusions to be derived from the data should be discussed, and any unresolved problems should be identified.

C. Drug Formulation

A list of all formulations used in clinical trials and in vivo bioavailability/pharmacokinetic studies should be provided. The studies in which each formulation was used should also be identified. For those batches employed in the

bioavailability/pharmacokinetic studies, significant manufacturing and formulation changes for the drug product over the course of its evaluation should be identified clearly (Attachment C).

D. Analytical Methods

A summary of the analytical method employed in each in vivo biopharmaceutic study should be provided in the format shown in Attachment D (In Vivo Analytical Methods Summary). Detailed information should be provided with the individual study. (See paragraph F below.)

E. Dissolution

Dissolution data on each strength and dosage form for which approval is sought should be provided, including a comparison dissolution study with the lot undergoing an in vivo biopharmaceutic study.

1. A summary of the product's dissolution performance should be included (See Attachment E).

2. A summary of the dissolution method and specification proposed for the candidate product for approval should be provided. (See Attachment F).

F. Individual Study Reports Format and Other Considerations

Each study report should contain the following information: objective, dosage form(s) studied, principal investigator, clinical facilities, facilities where collected samples were assayed, all individual data needed for conclusions, including demographic information, concomitant medication, if any, blood/urine levels, abnormal laboratory test values, and adverse reactions, all presented in coherent tables, with an analysis of the data and conclusions. In addition, documentation should be provided of the sensitivity, linearity, specificity, and reproducibility of the analytical method, including sample chromatographs, recovery studies, etc.

The data analyses should include appropriate statistical analyses usually involving Analysis of Variance, calculations of power analysis, 95% confidence intervals, and ratio analysis

(75/75-125 Rule). The details of pharmacokinetic parameter calculations, including pharmacokinetic models and equations utilized, should be adequately described and referenced.

A brief paragraph summarizing the pertinent conclusions of the study should be provided.

Firm_____

Drug_____

NDA/ANDA_____

ATTACHMENT A

BIOPHARMACEUTICS STUDY SUMMARY

Study Number	Route	Dosage Form(s) Study Designs	Dose	Batch No. Plant/Date Manufactured	No. of Subjects	Related IND or NDA Numbers	Submission Date	Applicant Conclusion	Previous Agency Responses on Study or Protocol with Date of Correspondence

Firm_____

Drug_____

NDA/ANDA_____

ATTACHMENT B

IN VIVO STUDY DATA SUMMARY

Study Number	Route of Administration Dosage Form	Dose	Parameters Cmax	Tmax	Vd	AUC	T1/2	Urinary Excretion	CLp	CLr	Comments

Firm_____

Drug_____

NDA/ANDA_____

ATTACHMENT C

DRUG FORMULATION DEVELOPMENT SUMMARY

Study Number	Lot No.	Dosage Form and Strength	Batch Size	Formulation or significant Manufacturing Change (if any) and reason for change	Effect of Change

Firm_____

Drug_____

NDA/ANDA_____

ATTACHMENT D

IN VIVO ANALYTICAL METHODS SUMMARY

Study Number	Submission Date	Type of Biol. Fluid	Method	Sensitivity of Method/Range	Specificity (parent/metabolites)

Firm_____

Drug_____

NDA/ANDA_____

ATTACHMENT E

DRUG PRODUCT DISSOLUTION TESTING

Date of Test	Dosage Form and Strength	Lot Number	Dissolution Apparatus	Media/ Temperature	Speed of Rotation/Flow	Collection Times	Units Tested/ Range/Mean % Dissolved/% C.V.

Firm_____

Drug_____

NDA/ANDA_____

ATTACHMENT F

PROPOSED PRODUCT DISSOLUTION METHOD

AND SPECIFICATION

(1) Dosage Form:

(2) Strength(s):

(3) Apparatus Type:

(4) Media:

(5) Volume:

(6) Speed of Rotation: (Rate of Flow for Flow-through Apparatus)

(7) Sampling Time(s):

(8) Brief Description of Dissolution Analytical Method:

(9) Recommended Dissolution Specification:

For further information regarding the guidelines please contact:

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