

BIOEQUIVALENCE CRITERIA

RESEARCH PROGRAM

DRAFT 2

November 1, 2001

I. INTRODUCTION

On September 23, 1999, the Advisory Committee for Pharmaceutical Science met to discuss the use of different criteria to allow comparison of bioavailability (BA) measures in bioequivalence (BE) studies. These criteria and their use in specified BE studies have been described in two draft FDA guidances entitled, respectively, *Average, Population, and Individual Approaches to Establishing Bioequivalence (Criterion Guidance)* and *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products (General Guidance)*. The Committee's deliberations focused on six discussion topics. The last of these discussion topics and the Committee's recommendations were:

Discussion Topic:

The Advisory Committee is asked to comment on plans for further research programs and projects associated with the use of average and individual criteria to allow comparison of bioavailability measures.

Committee Response:

The Committee endorsed plans proposed by FDA for better mechanistic understanding, clinical pharmacology studies (proof of concept and goalpost studies) and other approaches as well. The Committee recommended that outliers should be studied as a means of identifying important causes for a subject-by-formulation interaction. The Committee endorsed creation of a research document to guide the interim study period and to request a review of this document by the Expert Panel.

This draft research program has been prepared by the Population and Individual Bioequivalence Working Group/Replicate Design Technical Committee of the Biopharmaceutics Coordinating Committee in accordance with the requests of the Advisory Committee.

II. Program Overview

- C This document describes a research program with the following three projects: A) Criteria for BE Comparisons; B) Data Analyses and Statistical Methodology; and C) Mechanistic Understanding of Mean/Variance Test/Reference Differences.
- C The intent of the research program is to provide general information to allow a final regulatory decision regarding the use of criteria to compare BA measures in BE studies.
- C The proposed BCS guidance allows waiver of *in vivo* studies for Class I drugs that are rapidly dissolving. Depending on a better mechanistic understanding of the origin of differences in means and variances, a further intent of the research program is to extend the BCS approach to other categories, e.g., Class III/rapidly dissolving.
- C Each of the three projects is designed as a separate investigation or group of investigations that will follow a standard research protocol. Reporting of each project will cover objectives, methods, results, discussion and conclusions.
- C A major source of data for the research program will be drawn from replicate and non-replicate BE studies conducted by drug sponsors. The *General Guidance* recommended that *in vivo* BE studies for 1) modified release dosage forms, and 2) highly variable drug products be conducted using replicate designs.
- C The descriptions of the projects in this document are brief, with the understanding that a more formal and elaborate protocol might be developed to guide a project.

III. PROJECTS

A. Criteria for BE Comparisons

Primary Objectives

- C Determine the most appropriate criterion (average, population, individual) for use in BE studies for IND, NDA, ANDA, and post-approval supplement filings.
- C Identify clinically important differences between test and reference within- and total-subject variances.
- C Identify clinically important subject-by-formulation interactions and establish, as feasible, their origin (outlier, subgroup). Determine whether subject-by-formulation interactions

occur more often than by chance.

- C Observe and assess the importance of mean/variance trade-offs. Consider cases where a product would pass the aggregate criterion but not the average BE criterion due to the mean/variance trade-off. Assess in terms of potential clinical impact.
- C Consider outcomes based on use of selected disaggregate criteria and compare with proposed aggregate criteria.
- C Develop mechanisms to resolve the discontinuity aspect of the population and individual criteria.

Secondary Objectives

- C Evaluate regulatory standards for narrow and non-narrow therapeutic range drugs, if possible, from the range of data submitted.

B. Data Analyses and Statistical Methodology

The objectives of this research project are to assess the performance of proposed criteria (individual, population, average, other).

Primary Objectives

- C Assess methods for estimation of means and variances in the presence of missing data.
- C Assess the impact of apparent outlier data on the properties of the aggregate criterion.

Secondary Objectives

- C Where needed, consider proposed methods (e.g., Hyslop and Wang's methods) to calculate confidence intervals for the criteria.
- C Monitor and assess carryover effects using analyses of data sets with replicate designs.
- C Identify the types (e.g., age, gender, ethnic factors) and numbers (e.g., 12, 24, other) of subjects for inclusion in BE studies. Expansion of the study population to other subpopulations may be explored.

C. Mechanistic Understanding of Mean/Variance T/R Differences

The objectives of this research project are to develop mechanistic understanding for:

- C Important mean differences.
- C Important differences in within-subject variance for test and reference products.
- C Important subject-by-formulation interactions.
- C Bases for differences in within-subject variability between highly variable, moderately variable, and minimally variable drug products.