REPORT OF EXPERT PANEL: UPDATE AND PERSPECTIVES

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CHAIR

THEREFORE, TO PROVIDE ADDED CONFIDENCE TO PATIENTS AND CLINICIANS THAT CAN READILY BE UNDERSTOOD, I RECOMMEND THAT ADDITIONAL POINT ESTIMATE BIOEQUIVALENCE CRITERIA BE ADDED FOR ALL DRUGS AS A SUPPLEMENT TO THE BIOEQUIVALENCE LIMIT CRITERIA.

INDIVIDUAL BIOEQUIVALENCE IS A PROMISING, CLINICALLY RELEVANT METHOD WHICH SHOULD THEORETICALLY PROVIDE FURTHER CONFIDENCE TO CLINICIANS AND PATIENTS THAT GENERIC DRUG PRODUCTS ARE INDEED EQUIVALENT IN AN INDIVIDUAL PATIENT.

HOWEVER, AS OF THIS TIME, LITTLE PROSPECTIVE DATA EXISTS WHICH MAY SERVE TO VALIDATE THE THEORETICAL APPROACH AND PROVIDE CONFIDENCE TO THE SCIENTIFIC COMMUNITY THAT THE METHODOLOGY REQUIRED AND THE EXPENSE ENTAILED ARE JUSTIFIED.

AT THIS TIME, INDIVIDUAL BIOEQUIVALENCE IS A THEORETICAL SOLUTION TO SOLVE A THEORETICAL CLINICAL PROBLEM. WE HAVE NO EVIDENCE THAT WE HAVE A CLINICAL PROBLEM, EITHER A SAFETY OR AN EFFICACY ISSUE, AND WE HAVE NO EVIDENCE THAT IF WE HAVE THE PROBLEM THAT INDIVIDUAL BIOEQUIVALENCE WILL SOLVE THE PROBLEM.

EXPERT PANEL MEMBERS VOTING (9/1/99)

BARR

BARRETT

BENET

BOLTON

BON

ENDRENYI

LALONDE

MIDHA

ZARIFFA

WHAT IS NEEDED IS THE GENERATION OF A LARGE DATA BASE WHICH WILL PROVIDE THE FDA AND COMPANY SCIENTISTS WITH THE NECESSARY INFORMATION TO MAKE A REASONED CONSENSUS JUDGMENT AS TO THE APPROPRIATE CRITERIA FOR INDIVIDUAL BIOEQUIVALENCE.

It is recommended that parameters, including relevant co-variates, from replicate-design studies which FDA analyzes for the determination of population and individual bioequivalence be placed on the Internet at regular intervals in order to make them available to the pharmaceutical scientific community.

MODIFIED RELEASE DRUG PRODUCTS

Recommendation: For a two year period, all modified release drug products should be approved based on fasted single dose 4-way replicate design studies powered and analyzed for average bioequivalence.

At least 40% of the analyzed subjects must be males/females if the drug product is intended for use in both genders. If the drug product is to be used predominantly in the elderly, at least 40% of the analyzed subjects must be 60 years or older.

Dissolution profiles in three media at pH 1.0, 4.5 and 6.8 must be submitted.

COMMENT:

Analysis method for approval:

Average bioequivalence	6
Scaled individual bioequivalence	3

Highly Variable IR Dosage Forms

(particularly Class II BCS products)

Drug sponsors are encouraged to conduct single-dose 4-way replicate design studies

Analysis Method for Approval

Scaled individual or average bioequivalence **5**

Average bioequivalence - not scaled **4**