MEDICAL UNIVERSITY OF VIENNA

Wiener Biometrische Sektion
der Internationalen Biometrischen Gesellschaft
Region Österreich – Schweiz

Please join the virtual Biometric Colloquium

HELMUT SCHÜTZ

BEBAC, Vienna, Austria

BIOEQUIVALENCE: AN OLD AREA WITH SOME UNCHARTED TERRITORIES

December 15th, 2021 at 9:00 am

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HOSTS: Martin Wolfsegger

ABSTRACT

Comparative bioavailability (BA) studies are required in the regulatory approval process of generic products, supporting formulation changes, developing line extensions to approved products, and for testing of food effects or drug-drug interactions. Such studies have to be designed based on an in-depth knowledge of the drug of interest. We will give a brief history of Pharmacokinetics (PK) and its underlying concepts, namely LADME (Liberation, Absorption, Distribution, Metabolism, and Excretion). We will outline the different 'types' of BA (absolute, relative, comparative) and their application in related areas (e.g., assessment of linear PK, controlled vs immediate release formulations, etc).

Bioequivalence is a regulatory concept and concentrates on the rate and extent of absorption by comparing certain metrics of interest. Since the late 1980s BE (mainly in healthy volunteers) is the globally accepted surrogate for therapeutic equivalence (studies in patients). However, it is based on several assumptions which must not be forgotten. Selection of one of the standard designs (2×2×2 crossover, higher-order crossover, replicate, parallel) depends on the nature of the drug (half life, healthy volunteers vs. patients), number of treatments and their regimina (single vs. multiple dose), access to reliable information about the variance (fixed-sample vs. adaptive designs), and applicable regulatory goalposts. The latter might be different for highly variable drugs / drug products and narrow therapeutic index drugs.

Alas, the recommended statistical methods vary between agencies. Whereas for decades Average Bioequivalence (ABE) was the only established method, recent approaches allow for reference-scaling (i.e., based on the variability of the reference product to modify the traditional acceptance range of 80–125%) or adaptive two-stage designs with sample size re-estimation. As usual, it is of utmost importance to control the type I error. We will concentrate on problems of the currently implemented approaches and discuss potential solutions.