Measuring Switchability and Prescribability: When Is Average Bioequivalence Sufficient?

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Recent work, beginning with that of Anderson and Hauck in 1990, has led to a general acceptance of the need to ensure switchability in bioequivalence testing for approval of generic drugs. In other applications of bioequivalence testing, prescribability may be sufficient. However, there is less acceptance of the need to change statistical procedures and study designs from those currently used to assess the current criterion of average bioequivalence. We propose easily interpreted measures of switchability and prescribability. These measures provide bases for assessing conditions under which average bioequivalence is not sufficient to ensure switchability and prescribability, and hence for which a procedure for individual or population bioequivalence is required. The required conditions are sufficiently tight that they cannot be presumed to hold. Thus, there are reasonable conditions for which current practice is not sufficient. An outcome of this development is a connection between two current approaches for assessing individual bioequivalence.

\textbf{KEY WORDS:} individual bioequivalence; population bioequivalence; prescribability; switchability.

INTRODUCTION

There has been a long-standing concern regarding interchangeability of bioequivalent drug products. An early discussion is the letter of Hwang \textit{et al.} (1). More recently, Anderson and Hauck (2) brought the issue back to the forefront of discussion. One of Anderson and Hauck's contributions was identifying two situations, what they termed "prescribability" and "switchability," and two corresponding types of bioequivalence, what they

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called "population" and "individual." Prescribability refers to the choice between two products for a drug-naive patient. Anderson and Hauck noted that population equivalence is sufficient for prescribability. Population bioequivalence means that the population distributions of bioavailability of the two products are sufficiently similar, generalizing the current practice of average bioequivalence, which ensures similar average bioavailabilities but does not control variabilities. Population bioequivalence is sufficient for prescribability, because there is no information or experience of that patient on that drug.

For a patient who has been taking a product, and possibly been titrated, and is to be switched to another formulation, switchability is required. Anderson and Hauck identified individual bioequivalence as a criterion where a large proportion of individuals will be sufficiently similar on the two formulations and noted that individual bioequivalence is needed for switchability. There has been widespread acknowledgment of the importance of ensuring switchability for approval of generic drugs. In other contexts, prescribability may be sufficient. For further discussion of the issues regarding types of bioequivalence, readers are referred to Anderson and Hauck (2) and Hauck and Anderson (3).

Simultaneous with the acceptance of the need to ensure switchability, there is widespread questioning whether additional statistical methods and different trial designs are required. The question being asked is: Is not the current practice, average bioequivalence, sufficient to ensure switchability? There is an understandable reluctance to replace a known set of procedures and regulations in the absence of well-demonstrated problems. This is particularly understandable given the simultaneous concern that procedures to demonstrate individual or population bioequivalence may require more subjects and/or longer studies.

The purpose of this paper is to develop an analytic basis for addressing the question of when average bioequivalence is and is not sufficient to ensure switchability and prescribability. The approach is to develop measures of switchability and prescribability and then to identify the situations where average bioequivalence holds but that still cause a substantial loss of switchability and prescribability. We are interested in whether such situations are plausible. As a by-product, we are also able to make a connection between two current statistical approaches to individual bioequivalence, namely, the probability-based approach (2,4,5) and the moment-based approach (6–10).

THE MEASURE OF SWITCHABILITY

We begin with a basic concept of switchability, namely that the two formulations, the Test (T) and Reference (R), should be likely to give similar