

General Policy Topics

Bioavailability and bioequivalence: moves towards consensus

The economic and political attractions of an open market in pharmaceuticals are incontestable. The competitive pricing that results from the marketing of generic versions of off-patent products significantly reduces drug costs to governments and other purchasers. Manufacture of these products within local industrial facilities can save valuable foreign currency. However, the philosophy is dangerously flawed if the safety and efficacy of these products cannot be adequately assured or if, in creating a more open market, the door is opened to counterfeit and spurious products that escape every modality of control.

Over the past five years WHO has directed much effort into assisting small and less affluent countries to meet this challenge. It has issued Guiding Principles for Small National Drug Regulatory Authorities which emphasize the need to ensure enforcement as well as promulgation of standards. It has revised the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce in a way that is intended to ensure that the true provenance of an imported product remains on record throughout its peregrinations within international distribution channels. It has updated its Good Practices in the Manufacture and Quality Control of Drugs to embrace recent advancements in pharmaceutical technology and modern concepts of quality assurance. At a more practical level, it has proposed a series of basic chemical tests for verifying the identity of active pharmaceutical substances both in bulk consignments and in finished dosage forms, and it has developed a computer software package to support a simple system of drug registration.

In one particular, however, it has been slow to offer didactic advice. It has not yet issued definitive guidelines on the technical basis for assuring the clinical interchangeability of different versions of a given multisource product. Proof that a product conforms to an agreed pharmacopoeial specification can be inadequate in this regard. Particularly for solid oral dosage forms, it may additionally be necessary to demonstrate bioequivalence *in vivo*.

This entails a comparative assessment, using an agreed reference product, of the rate and extent of absorption of the active principle from the dosage form under examination into the systemic circulation. This is a cumbersome and costly procedure that involves, for every product that is examined, collection of serial blood samples under standardized conditions from sizeable groups of volunteer subjects or patients.

Debate within regulatory circles about precisely how these tests should be conducted and in what circumstances they are required has now extended over two decades. Only recently has an initiative been taken to search for an international consensus (1). The resulting statement, which represents the view of an *ad hoc* group of scientists drawn from regulatory authorities and pharmaceutical companies in highly-industrialized countries, is rigorous in its demand for impeccable standards of experimental design to be applied to these studies. It is also commendably precise in defining those situations in which bioequivalence testing should be regarded as mandatory and those in which it has little relevance. The statement provides a welcome basis for advancing discussion on ways and means of assuring interchangeability of potent medicines. However, it does not touch upon some of the problematic issues that compromise a truly international approach to such testing and that create a measure of uncertainty over the criteria that should be applied to international trade in generic products.

Bioequivalence is assessed in terms of the performance of an accredited reference product. "For the present", the consensus statement proposes, "this will usually be a 'clinically proven' market leader product ... in the country or group of countries to which the [marketing] application is made". Missing from the discussion is any consideration of the need or practicability of establishing and maintaining internationally recognized reference standards. Nor is there any examination of ways to detect and rectify potential drift in bioavailability between successive batches of a reference product.

Similarly, the implications that genetically and environmentally determined community variation in drug absorption and metabolism may hold for the

interpretation of bioequivalence studies — or even for their validity within a global context — are acknowledged but not explored.

At a more fundamental level, discussion is not engaged in the working group's report on impaired bioavailability of readily-absorbed compounds resulting from inappropriate formulation of solid dosage forms. Basic errors in formulation are most likely to occur where technological resources and administrative controls are most severely constrained. Formal bioavailability studies are neither practicable in this context nor, it seems, are they necessary. Although *in vitro* dissolution tests are

unreliable when used in a comparative sense to establish bioequivalence between different products, they do have potential for screening out poor formulations. They are being introduced in leading pharmacopoeias for this purpose, and their application should be rated high on the list of regulatory priorities in both developed and developing countries.

Reference

1. Drug Information Association Working Group. International Harmonization and consensus DIA meeting on bioavailability and bioequivalence testing requirements and standards. *Drug Information Journal*, 25: 471-482 (1991).