Generics: the limits of bioequivalence

We were rather puzzled when, during a continuing education session on pharmacovigilance, we were told that generics must not only meet safety and efficacy requirements, but also be biologically equivalent to the originator drug, to within 25%. Is this true, and if so, what are the practical implications for an antiarrhythmic or an anticoagulant, for example?

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The new definition may seem broader in scope than the previous one, as it includes the different salts and other derivatives of a given substance. Unfortunately, it is also likely to lead to disputes, given that it does not specify who decides (and how they decide) whether a drug “differs significantly in properties with regards to safety and/or efficacy”.

No changes concerning bioequivalence. Annex I of the Directive, which deals with the standards and protocols to be respected during the analytical, pharmacotoxicological and clinical evaluation of a drug prior to marketing approval, was not modified in 2004 (3). The most recent changes were made in 2003.

In respect to bioequivalence studies, annex I of the Directive refers to the last revision of the European Medicines Evaluation Agency’s Note for Guidance on the investigation of bioavailability and bioequivalence, dated July 2001 and in effect since January 2002 (4). According to these guidelines, “in vivo bioequivalence studies are needed when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence”. The guidelines indicate that the bioavailability of the tested drug can be accepted if the 90% confidence interval for “maximal plasma concentration” (Cmax) and the “area under the curve” (AUC) is between 0.80 and 1.25 of that of the originator drug.

These figures correspond to the requirement for bioequivalence ‘within 25%’, which Anne-Marie Keuk raised as a concern for medications such as antiarrhythmics and anticoagulants. In addressing this issue, the EMEA guidelines state that: “In specific cases of narrow therapeutic margins, the accepted interval may need to be reduced. In certain cases a wider interval may be acceptable. The interval must be prospectively defined, e.g. 0.75–1.33 and justified addressing in particular any safety or efficacy concerns for patients switched between formulations”.

The guidelines do not set a numerical limit for drugs with narrow therapeutic margins, leaving it to drug regulatory agencies and their experts to decide these limits case by case, according to the substance concerned and the target population.

Recommendations in other industrialised countries are compatible with these European guidelines, due to international harmonisation of drug assessment requirements.