Forum

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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?

Anne-Marie Keuk
General practitioner
France

During the last revision of the European legislative framework governing medicinal products, the notions of generics and bioequivalence were under intense debate, most likely because of the massive financial stakes involved. European Directive 2004/27, amending Directive 2001/83 and published on 30 April 2004, must be enacted into national law no later than 30 October 2005 (1,2). Some articles of Directive 2004/27 have already been enacted in France: for example, the French law dated 13 August 2004 pertaining to health insurance includes an article that addresses the definition of generic drugs, in line with European Directive 2004/27.

A new definition of "generic drugs". At the present time, a "generic drug" is defined as follows in the EU: "*'Generic medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant* [Editor's note: for marketing authorisation]. *The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.*" (1)

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.

Authorised and properly controlled generics: no major adverse effects. For more than 10 years there have been no major changes in regulatory requirements concerning the bioequivalence of generics or originator drugs. Thus far, our literature search for problems linked to the replacement of an originator drug by a generic has identified no reports of serious clinical consequences occurring as a result of substitution of properly approved and controlled generics. Current bioequivalence requirements therefore appear adequate.

The main problem with generic substitution is the use of counterfeit or unapproved products in countries where drug distribution and supply are poorly controlled. Another problem is the risk of overdose due to concomitant use of several medications with different trade names corresponding to the same, poorly known INN (5).

1- "Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use" *Official Journal of the European Union* 30 April 2004: L136/34 - L136/57.
2- Prescrire Editorial Staff "Medicines in Europe: the most important changes in the new legislation'' see http://www.prescrire.org/aLaUne/dossierEuropeSynthese2En.php.
3- "Analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products" *Officiel Journal of the European Union* 27 June 2003: L 159/49 - L 159/94.
4- The European Agency for the Evaluation of Medicinal Products - Committee for proprietary medicinal products "Note for guidance on the investigation of bioavailability and bioequivalence" 26 July 2001: 18 pages.
5- Prescrire Rédaction ''Générique et surdosage. Vingtièmes journées françaises de pharmacovigilance - les faits marquants'' *Rev Prescrire* 1999; **19** (197): 519-521.