CHMP Question: If the SmPC of a reference product allows for the possibility to administer a tablet crushed or disintegrated (and mixed with food), would a specific bioequivalence study with administration of crushed/disintegrated tablets (Test and Reference) always be required for a generic application?

PKWP response

The bioavailability of an active substance(s) may be altered if products are crushed/disintegrated to assist swallowing and also if a crushed/disintegrated tablet is mixed with food. This change in bioavailability may be formulation/product-specific as well as drug-dependent. Therefore, a test product that is shown to be bioequivalent when administered as a whole tablet in a fasted state, may exhibit significantly different bioavailability compared to the reference product, when both are administered crushed/disintegrated (and dispersed in food). Consequently, if the SmPC of the reference product allows for the possibility to administer the tablet crushed/disintegrated (and dispersed in food), bioequivalence should also be demonstrated, in principle, for a test product with this additional mode of administration. It is proposed, however, to define conditions which would avoid such an additional bioequivalence study for generic products as follows:

a) the drug substance is highly soluble and stable in the pH-range of the gastrointestinal tract according to BCS-based biowaiver criteria and

b) surface active excipients do not differ qualitatively nor quantitatively, and have no specific formulation characteristics or specific technologies - e.g. an amorphous solid dispersion (ASD) in order to stabilize a polymorphic form and

c) disintegration time is comparable between test and reference and

d) dissolution profiles are similar between test and reference product at pH 1.2, 4.5 and 6.8 at 50 rpm in the paddle apparatus, or 100 rpm in the basket apparatus, and in the QC method if a different medium is used for this.

The following data are, therefore, required to waive additional in-vivo investigations and to allow for the administration of the crushed product:

- Successful bioequivalence with uncrushed products;
- BCS classification of the drug substance as class 1 or 3;
- Comparative evaluation of excipients, particularly regarding potentially surface active excipients;
- Comparative multimedia in-vitro dissolution;
- Comparative disintegration testing.