



EGA *fact sheet*

on generic medicines

Bioequivalence is the Key to Ensuring Safe and Effective Generic Medicines

Generic medicines producers perform “bioequivalence studies” to demonstrate that a generic medicine is equivalent to its originator reference product.

Generic medicinal products contain well-known safe and effective active pharmaceutical ingredients that have been on the market, normally for minimum of 10 years. Because of this, producers of generic medicines are not required to repeat pre-clinical tests and clinical trials on animals and patients. Instead, they must perform “bioequivalence studies” to demonstrate that the generic medicine is equivalent to the originator reference product.

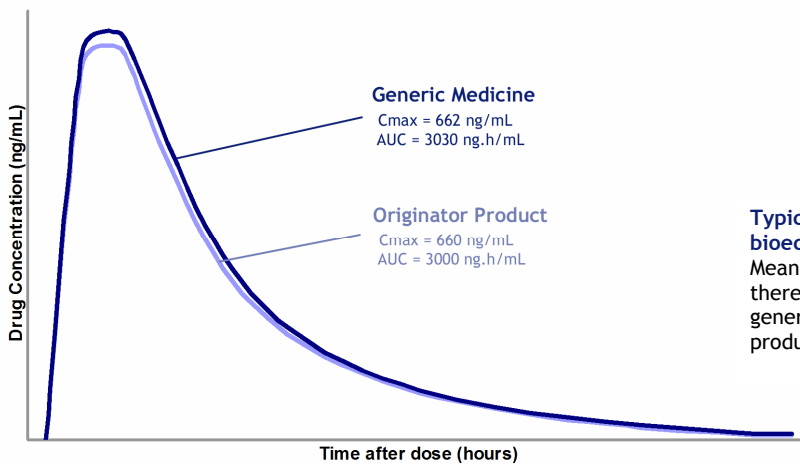
Bioequivalence studies demonstrate equivalence between the test product and the reference product. The generic medicine and the reference product are considered to be bioequivalent (and therefore interchangeable) when the bioequivalence study demonstrates that the two formulations have no significant differences in the rate and extent of absorption in the human body (see figure below).

The test involves comparing the same dose under the same conditions. The very strict criteria for bioavailability studies include nine components.

Bioequivalence Testing Includes:

- A detailed design of the study (protocol);
- Submission of the protocol to and approval by an ethics committee;
- Sufficient number of volunteers to ensure the study is capable of showing significant differences;
- Thorough medical examinations of the volunteers before, during and after the study;

- Usually a cross-over design of the study, meaning all volunteers receive both the reference and test product with a “washout period”¹ in between;
- Volunteers are randomised to receive either the reference product or the test product first;
- Compliance with Good Clinical Practice (GCP)² and the analysis to Good Laboratory Practice (GLP)³;
- Standardised study conditions (eg, composition and timing of meals); and
- Sufficient “washout” periods between tests.



Typical results from a hypothetical bioequivalence study⁴

Mean concentration-time curves showing that there are no significant differences between a generic medicine and the originator reference product after single oral doses.

- ¹ The “washout period” is the time necessary (usually several days) after the first tablet or capsule has been taken for the drug to be eliminated from the body before the second tablet/capsule is taken by the same volunteer in a cross-over study.
- ² Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. For further information on Good Clinical Practice (GCP) see: Clinical Trial Directive (Directive 2001/20/EC) (Official Journal L 121, 1/5/2001 p 34-44) and GCP Directive (Directive 2005/28/EC) (Official Journal L91, 9/4/2005 p 13-19) For further information and a list of all relevant EU legislation, see page 22 of the draft “User Guide for Micro, Small and Medium-sized Enterprises (SMEs) on the administrative and procedural aspects of the provisions, laid down in Regulation (EC) No 726/2004, that are of particular relevance to SMEs”, December 2006. Available at: <http://emea.europa.eu>.
- ³ The principles of Good Laboratory Practice (GLP) define a set of rules and criteria for a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, reported and archived. For further information on Good Laboratory Practice (GLP), see: Directive 2004/9/EC (Official Journal L50, 11/2/2004 p 28-43) and Directive 2004/10/EC (Official Journal L50, 20/2/2004 p 44-59).
- ⁴ As seen in the graph above, the peak plasma concentration (C_{max}) and the extent of absorption (the area under the concentration curve, AUC) of the original product and the generic product are compared in the bioequivalence study. The method for testing pharmacokinetic bioequivalence is based on the determination of the 90% confidence interval around the ratio of log-transformed mean values. Studies are carried out in line with the European Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98) where it is stated that the 90% confidence limits of the ratio of C_{max} and AUC should lie between 80 and 125%. These limits may be wider or narrower in certain justified circumstances. This guidance and test procedure does not apply only to generic medicines. It is also used when originator companies wish to develop new formulations of their original product. It is, for example, becoming commonplace for originators to develop a new tablet formulation which dissolves in the mouth, and they will use the same scientific procedure to apply for a line extension – ie, comparing the original tablet against the dissolving tablet and obtaining approval through cross-reference to the original clinical data. This preset range for demonstrating bioequivalence is sometimes incorrectly interpreted to mean the rate of absorption and the maximum concentration of the reference and test formulations differ by 20 to 25%, which is both incorrect and misleading. In fact Regulatory Authorities, based on large numbers of applications, have concluded from using this standard that the difference between the original product and the generic product is less than 5%.

Formed in 1993, the EGA is the official representative body of the European generic pharmaceutical industry, which is at the forefront of providing high-quality affordable medicines to millions of Europeans and stimulating competitiveness and innovation in the global pharmaceutical sector.

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