

Generics: what is the role of registration authorities

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ABSTRACT

Substitution of branded medicines by cheaper generic medicines has been and is subject for debate in the Netherlands. One of the tasks of the Dutch Medicines Evaluation Board (CBG) is the evaluation of generic medicines. The way the CBG approves generics, as outlined in this paper, is based on assessment of the quality of the medicine and bioequivalence testing according to strict European guidelines. Registration of generic medicines in the Netherlands will only take place when bioequivalence has been demonstrated. Once bioequivalence has been demonstrated, the CBG is convinced that the generic has the same efficacy and safety as the branded medicine. Consequently, the CBG is of the opinion that the branded medicine can be safely exchanged with the generic medicine. However, for the acceptance of generics in daily practice adequate communication to the patient by prescriber, pharmacist, health insurance company and patient organisations is essential.

KEYWORDS

Branded medicines, generic medicines

INTRODUCTION

To constrain public health costs, the policy of the Dutch government and the health insurance companies is to substitute the more expensive innovator (brand-name) medicines by cheaper generic medicines. For many years, this generic substitution has been the subject of debate in the scientific literature.¹⁻¹¹ The Dutch Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen, CBG) is not directly involved in the actual substitution strategy in

the Netherlands, but the registration of generic medicines in the Netherlands will only take place when the CBG is convinced that the generic has the same efficacy and safety as the innovator medicine. As our contribution to the discussion on generic substitution, we felt it would be useful to elaborate on how the CBG approves generics based on assessment of the quality of the medicine and bioequivalence testing. The CBG has started to publish public assessment reports for generics on its website (<http://www.cbg-meb.nl/nl/gnsmiddl/index.htm>).

A generic is a medicinal product which has the same qualitative and quantitative composition of active substances and the same pharmaceutical form as the branded product. In other words, the generic is a pharmaceutical equivalent to the branded medicine. A company may seek marketing authorisation for a generic in the Netherlands ten years after a marketing authorisation has been issued for the innovator medicine in one of the EU States. The original preclinical and clinical data are then no longer legally protected and the generic company may refer to the file of the innovator medicine for those data.

REGISTRATION OF GENERIC MEDICINES BY THE CBG

The application for a generic medicine is based on a complete chemical-pharmaceutical file, similar to that used when applying for registration of the branded medicine, thus ensuring a good quality medicine as well on adequate bioequivalence testing. As the active substance's efficacy and safety have been well established for the innovator medicine, it is generally not required to provide results of preclinical tests in animals and of clinical trials with a generic application. Instead, a study is necessary to establish

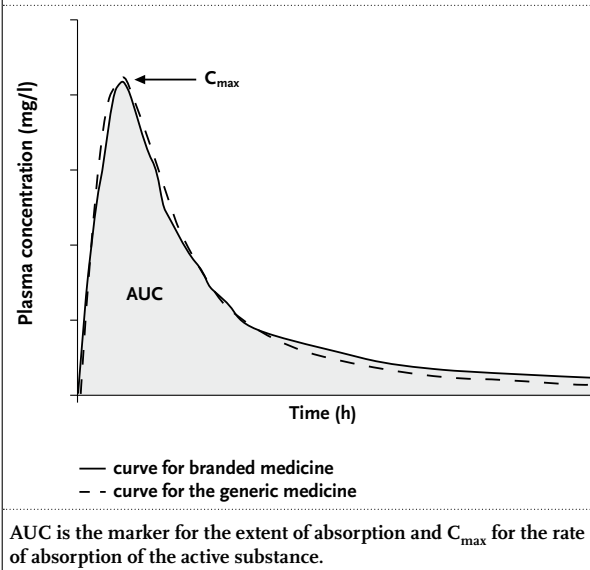
equivalence between the generic and brand-name medicine to prove that differences in excipients and/or the manufacturing process do not affect the absorption characteristics of the active substance. This is known as a bioequivalence study. The requirements for demonstrating bioequivalence are outlined in European Guidelines.¹²⁻¹⁵ The European guideline 'NfG on the investigation of bioavailability and bioequivalence (CHMP/EWP/QWP/1401/98)' forms the basis for the assessment of generics with a systemically acting active substance.¹² This guideline typically deals with medicinal oral formulations with immediate-release characteristics.

Bioequivalence is generally determined by comparing the time course of the plasma concentration of the active substance after a single administration of the generic and the innovator medicine in a two-way cross-over study in healthy volunteers. The design of bioequivalence studies is standardised in order to minimise the variability of all the factors involved, so that the effect of the formulation on plasma exposure can be distinguished from other effects. The number of subjects required, usually 24 to 36 subjects, depends on the variability of the pharmacokinetics of the active substance.

Bioequivalence studies are conducted according to the principles of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP). These requirements are the same worldwide, whether in Western countries or in 'low cost' countries. The same criteria that apply for GCP and GLP in the European study centres also apply for these low-cost study centres, and these centres are also subjected to inspection by the various European States.

Bioequivalence is aimed at demonstrating identical plasma exposure over time. Critical parameters used to demonstrate this are the extent of absorption of the active substance (as measured by the area under the concentration time curve (AUC)) and the rate of absorption (as measured by the maximal plasma concentration (C_{max})) (figure 1). The individual test/reference ratio (generic/innovator) is calculated for the (log-transformed) AUC and C_{max} values. Subsequently a 90% confidence interval for the mean ratio is calculated for both AUC and C_{max} . When the 90% confidence interval of the test/reference ratio is within the 0.80 to 1.25 interval for both AUC and C_{max} , it is concluded that the generic and branded product are bioequivalent with respect to the rate and extent of absorption of the active substance. After a long international discussion it was decided that a 0.80 to 1.25 90% confidence interval ensures that possible differences in formulation due to excipients and/or the manufacturing process between the generic and branded product do not affect the systemic exposure of the active substance to a clinically relevant extent. The same 90% confidence interval is used when innovator companies decide to change their formulation during development or marketing

Figure 1. Illustration of plasma concentration-time curves from a bioequivalence study



of their products. Consequently, if bioequivalence is demonstrated within the 90% confidence interval, the positive benefit risk established in clinical studies for the branded medicine also applies for the generic.

SPECIAL FORMULATIONS

When a generic concerns a product with controlled or delayed-release characteristics (e.g. long-acting or slow-release medicines), additional studies are required as is outlined in a European guideline on modified release products.¹⁴ For such formulations, bioequivalence should generally be demonstrated both after single dose and after multiple dose administration. In that case, it is not only the rate and extent of absorption that are critical parameters, but also the trough concentration (C_{min}) and peak-trough fluctuations need to be taken into account for concluding bioequivalence. Furthermore, for oral formulations with regulated release characteristics, bioequivalence should not only be demonstrated under fasting conditions but also under fed conditions in order to examine a known food effect or to exclude dose dumping and/or instability of the product.

For dermal patches, which can be considered a regulated-release product, the generic should not only demonstrate bioequivalence as indicated for oral formulations, but also the same or less adhesiveness to the skin, sensitisation and local irritation compared with the branded product. The precise type and number of studies to be performed for generic products with controlled-release characteristics is defined on a case by case basis taking into consideration the intrinsic properties of the active substance, the route of administration, the type of delivery system and the intended therapeutic indication(s).

SPECIAL CIRCUMSTANCES

Low absolute bioavailability

In some cases the systemic absorption of the active substance is so low that plasma levels cannot be measured reliably. This has been reported for e.g. alendronate (Fosamax). Due to its low absolute bioavailability of only 0.6%, the plasma concentrations hardly exceed the detection limit. Since alendronate is almost exclusively excreted unchanged in the urine, the amount excreted in the urine is directly related to the plasma AUC. Thus, the amount excreted in the urine can be used as a measure for the extent of absorption, instead of the plasma AUC value.^{12,13} Analogously, the rate of absorption can be determined using the rate of excretion. It is acknowledged that this rate of excretion can be determined somewhat less accurately in urine than in plasma because of the less frequent sampling of urine. Therefore, to ensure that the rate of absorption does not differ essentially, additional comparable *in vitro* dissolution under various conditions is required for these alendronate applications. With recent improvements in the sensitivity of alendronate analytical assays, the generic application for the 70 mg, high-dosage form of alendronate can be based on the urine measurement for the amount absorbed, combined with the plasma C_{max} as an accurate measure for the rate of absorption. With this procedure efficacious and safe generic products for alendronate can be registered.^{12,13}

Locally acting drugs

For locally applied medicines, which exert their effect at the site of application, the common systemic bioavailability approach cannot be applied because the plasma concentration in such a case is not representative for its efficacy. Examples are certain dermatological products and inhalation products. Registration of these generic products based on bioequivalence testing is in principle not possible and therapeutic equivalence needs to be demonstrated using pharmacodynamic endpoints or clinical studies.¹⁵ Although efficacy of these products is dependent on local exposure, often a small fraction of the dose reaches the systemic circulation which may thus exert undesired effects. For this reason a comparative bioavailability study can be supportive for the safety of the generic product. One exceptional case of a locally acting drug is mesalazine, which is indicated for ulcerative colitis and Crohn's disease. Despite the local action in the intestinal tract, a generic has been registered in the Netherlands supported by systemic bioequivalence studies. The reason for this is that on the basis of the plasma concentration time course of mesalazine and its metabolite, the site of absorption of mesalazine can be assessed. This means that indirectly the local availability of mesalazine in the relevant parts of the intestine is known and can be compared.^{16,17}

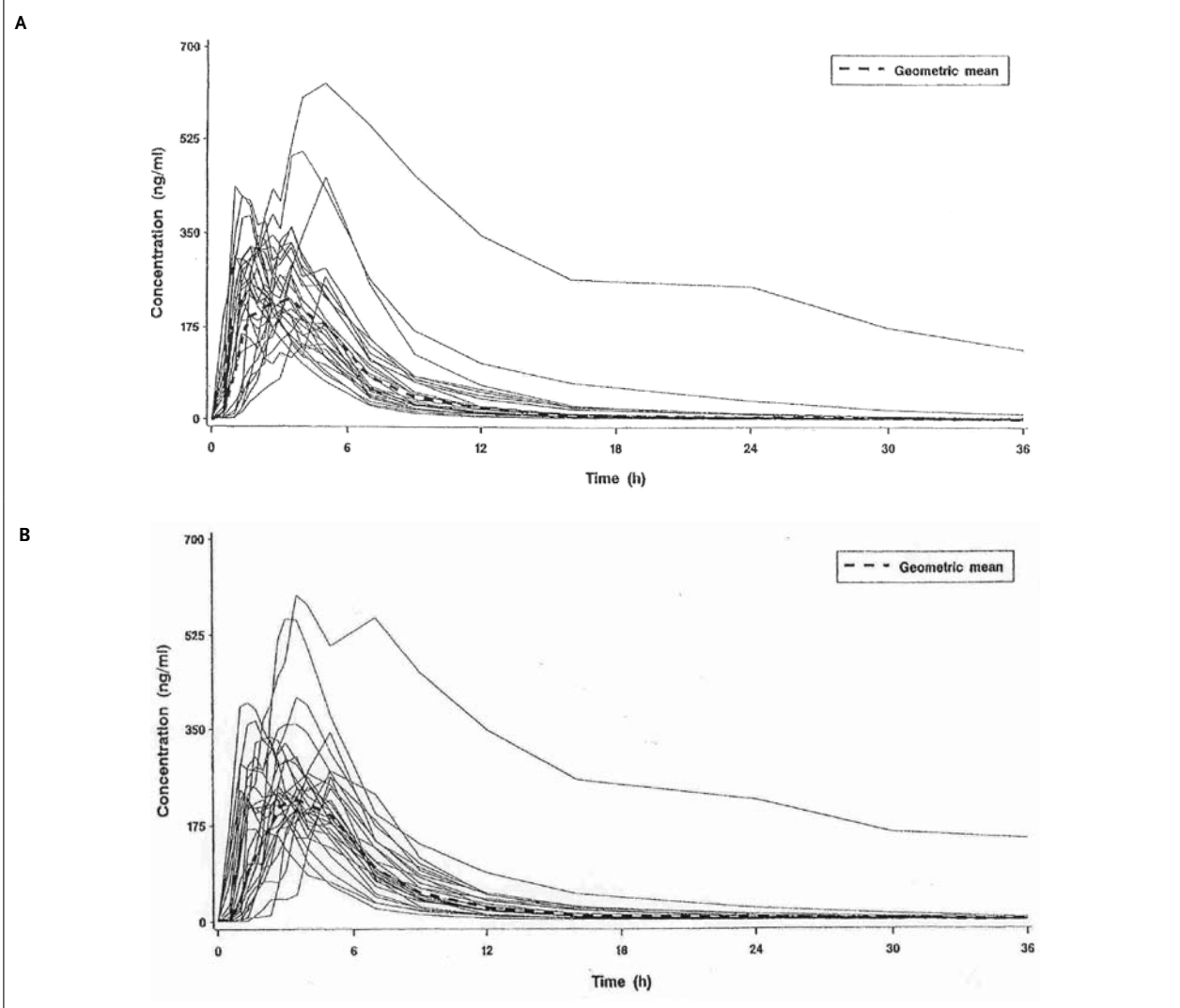
CONCERNS ABOUT GENERICS IN DAILY PRACTICE

Some concerns about the use of generics in daily practice are frequently expressed in the literature^{1,3,6,7,16} and received by the CBG. The CBG is aware of additional circumstances which may unfortunately affect overall acceptance of generic substitution. Some questions that are posed frequently are dealt here.

Why is it sufficient for a systemically acting generic product to demonstrate bioequivalence with the branded medicine in healthy volunteers instead of demonstrating therapeutic equivalence in patients? The rationale for this is that there is always a relationship between the concentration profile of the active substance in plasma or blood over time and the efficacy and safety of the substance, although this relationship may be indirect. Consequently, if the active substance has a similar plasma concentration time course this will result in the same concentration at the site of action and is thus expected to result in an essentially similar efficacy and safety.

Does the outcome of a bioequivalence study in healthy volunteers also apply for the target patient population? Yes, with the bioequivalence study similar absorption into the systemic circulation of the active substance is demonstrated for the branded and generic products. This absorption from the intestine into the systemic circulation is the critical part, in which a difference in e.g. excipients between the branded and generic medicine may become apparent, and may thus have clinical consequences. After absorption, only the active substance, which is identical in the branded and generic medicine, will be present in the systemic circulation. Due to the active substance being identical and being present at the same levels, other intrinsic factors caused by illness e.g. local intestinal factors, renal or hepatic impairment, will have the same effect on the branded and generic medicine. That this principle works can be demonstrated by the effect of poor metabolisers in the bioequivalence study population. *Figure 2* is a typical example of such an event. From this figure it is clear that subject X has a much higher systemic exposure compared with the mean values of the study population. This high exposure was caused by the poor metabolising phenotype of this subject, leading to reduced metabolism and elimination, and thus to persistent high plasma levels of the active substance. It is, however, crucial to acknowledge that the higher exposure in this subject occurred for both the generic and the branded medicine (compare upper and lower figures 2A and B). From a clinical perspective it is clear that this poor metaboliser phenotype may well require a lower dose in order to avoid adverse events, but it is important to realise that this adjusted dose will be the same for the branded and the generic medicine. Therefore, although the absolute plasma levels deviate markedly and significantly

Figure 2. Example of individual plasma concentration time course curves for the generic and branded medicine in a cross-over bioequivalence study



from the mean exposure in the whole population, the AUC and C_{max} generic/innovator ratios for this subject do not differ from the mean ratio of the population and hence the conclusion of bioequivalence is not affected. The same will happen for e.g., renally or hepatically impaired patients, or with any physiological differences between healthy volunteers and patients: the consequences will be the same for the generic and branded medicine. Bearing this principle in mind, in a crossover study design the subject is its own control and this means that formulation effects (generic vs branded medicine) can be evaluated without interference from such intrinsic factors affecting the bioavailability of the active substance. Therefore, the results obtained in healthy volunteer bioequivalence studies will be fully valid for the real-life patient population.

Are cheaper generics of lower quality? Cheaper medicines are sometimes interpreted as being of lower quality. However,

this is not the case, the quality of the generic should meet exactly the same requirements as for the branded medicine. Moreover, pharmaceutical quality characteristics have sometimes improved considerably since the launching of the branded product. Pricing differences are possibly caused by the fact that at the time of registration of a generic, the efficacy and safety of the active substance are considered well established and there is no need for repeating the expensive (pre)clinical programme which was conducted for the branded medicine.

What about the name, colour and form? An issue which is relevant for acceptance of generic substitution by the public is the name, colour and form of the medicine.^{18,19} As recognition by colour and form is an important visual check for the intake of medicines, such a difference for generic compared with branded products is a point of concern for an uncomplicated branded-generic substitution, especially

when many different products have to be taken daily. Moreover, the branded product has a 'fantasy' name, while the generic product is named after the active substance. The colour and form of the medicinal product as such is not part of the assessment of generics. As long as bioequivalence has been demonstrated, form and colour may be different from the branded product. The importance of colour and form for the public acceptance of a product can be illustrated with Losec (omeprazole): shortly after the introduction of the new branded tablets, Losec MUPS, as replacement for the original branded Losec capsules, many complaints on differences in efficacy were received at LAREB, the Pharmacovigilance Centre of the Netherlands.²⁰ Both branded products are from the same company and Losec MUPS was registered after bioequivalence and pharmacodynamic studies demonstrated equivalence with Losec capsules. This example indeed shows that the form and shape may be critical in the perception of being different. In order to deal with this issue, both prescriber and pharmacist can be of assistance by explicitly explaining that differences in name, colour and form of generic medicines do not affect the efficacy and safety of the medicine, as compared with the branded medicine.

What about generic vs therapeutic substitution? Another issue complicating acceptance of generic substitution in practice is that generic and therapeutic substitution are often confused and considered to be the same.¹¹ It is important to realise the difference between generic and therapeutic substitution: generic substitution means replacing the branded medicine by a bioequivalent generic containing the identical active substance, whereas therapeutic substitution means replacement by another registered product with another active substance from the same therapeutic class, for example substitution of omeprazole by pantoprazole. Since the pharmacokinetics and pharmacodynamics, and thus the benefit-risk ratio, of these different active substances may be different in a certain individual, there is no guarantee that therapeutic substitution will be harmless.

CONCLUSION

The CBG evaluates an application for registration of a generic medicine according to strict European Guidelines.¹²⁻¹⁵ The CBG is of the opinion that when equal quality as well as equal exposure, by means of appropriate bioequivalence studies, has been demonstrated, the positive benefit-risk balance of the branded medicine also applies for the generic medicine. Consequently, the branded medicine can be safely exchanged with the generic product. If in an exceptional case an exchange between the generic medicine and the branded product is not possible, this is explicitly mentioned

in the product's summary of product characteristics (SPC). Nevertheless, for an uncomplicated branded-generic substitution the above-mentioned concerns about the acceptance of generics in daily practice should be taken into account. It is clear that adequate communication to the patient, by prescriber, pharmacist and patient organisations, is essential for optimal generic substitution.

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