

# Generics substitution in primary care: summary of the Dutch community pharmacies guidelines

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Marketed medicines that have passed bioequivalence testing should in general be substitutable. However, for a variety of reasons, caution may be warranted, particularly with regard to narrow therapeutic index drugs and the indiscriminate use of biosimilars. The Royal Dutch Pharmacists Association (KNMP) has published professional guidelines for community pharmacies concerning generic substitution. The guidelines are based on scientific principles and provide a strong impetus for maintaining uniform professional standards. Here we present the main features of these guidelines [1].

**Keywords:** Biologicals, biosimilars, Dutch guidelines, generics substitution, interchangeability, narrow therapeutic index

## Background

The latest version of the guidelines was prompted by a renewed interest in generics substitution. The first edition of the guidelines was published following the introduction, in 1988, of a financial rule for pharmacists that offered them a fee of one-third of the price difference between a generic and a brand-name drug per substitution. This rule changed many times thereafter, but in year 2000 the interest in substitution rose again, partly for financial reasons and partly because 'prescribing on generics name' had been introduced. An updated version of the guidelines was deemed important for pharmacists as an instrument to weigh out the risks and benefits of substitution based on patient safety.

## Definition of substitution

Generics substitution is defined as the mutual substitution of medicinal products having the same active ingredient, the same strength, and the same dosage form. Substitution of medicinal products with different dosage forms and therapeutic substitution is excluded from the scope of the Dutch guidelines.

## Legislation

Every drug given marketing approval has been rigorously evaluated by licensing authorities and can be safely dispensed by any pharmacist. Legally, however, the pharmacist has to dispense only the prescribed product, and substitution requires the physician's consent. This is especially relevant to branded products. In practice, in a local healthcare setting, this usually means that physicians and pharmacists reach agreements about substitution. When a drug is prescribed using a generic name, the pharmacist will dispense the most cost-effective formulation.

## Bioequivalence

The decision on whether to substitute or not is determined by the degree of similarity of the products in question. For the market approval of generic drugs, pharmacokinetic bioequivalence studies are required. The European Medicines Agency (EMA) regards products as bioequivalent if the AUC ratio and Cmax results of comparative bioavailability studies produce a 90% confidence interval within 80.00–125.00% of the reference product. For narrow therapeutic index drugs the AUC limits

are 90.00–111.11%, and similar Cmax is only required in specific situations [2].

However, for drug substitution, other factors may be involved besides pharmacokinetic bioequivalence, as explained in the guidelines.

## Guidelines for generic medicine substitution in community pharmacies

When dispensing a licensed generic drug alternative for the first time, it is assumed to be as safe and efficacious for the patient as the innovator product.

However, when repeat dispensing is required for chronic use there may be situations—described in detail below—when caution is indicated before substitution:

- Prescription of narrow therapeutic index drugs (NTI). The Dutch guidelines contain a list of NTI drugs, including digoxin, lithium, and transplantation drugs like ciclosporin and tacrolimus.
- Prescription of drugs for which pharmacokinetic bioequivalence studies are not a good measure of interchangeability, such as oral drugs that have a local effect in the gastrointestinal tract, or inhalation medications with local effects in the lungs. Examples include: orally administered mesalazine, and inhalation of corticosteroids such as fluticasone.
- Prescription of biologicals. Unlike synthetic small molecule drugs, biosimilars—generic versions of biological drugs—do not match the innovator product in composition, and their characteristics cannot be fully determined using laboratory analytical techniques. Classical bioequivalence studies have limited value in indicating equivalent efficacy and safety compared to the reference product. Product efficacy, safety and traceability are therefore additional, important issues for biologicals. The Dutch guidelines cover these issues with reference, for example, to filgrastim, epoetin and somatropin.
- The recommendations for substitution of biologicals are as follows:
  - Based on scientific data substitution is not expected to cause problems if the route of administration and indication are

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the same as for the innovator product, on the basis that clinical tests have demonstrated comparable efficacy and safety between biosimilars and the innovator product. However, substitution is not recommended if it means a switch to a different route of administration for example, from subcutaneous to intravenous, for which the biosimilar has not been approved. This is because the immunogenicity of the biosimilar may vary from one route of administration to another. EMA does not formally recognise the safety of a biosimilar if its use involves a non-approved route of administration.

- Substitution is not recommended for unapproved indications. While EMA leaves open the possibility that similarity between a biosimilar and the innovator product may also apply to other indications, these are omitted from the biosimilar's drug approval dossier. The reasons are often unclear but may be found in the European public evaluation report (EPAR).
  - Random substitution without careful recording is not recommended owing to the risk of an immunogenic reaction. This can occur after a protracted period of time, and if it follows a substitution, it may not be clear which product has caused the adverse drug effect—the one used before or after substitution. Random substitution will compromise the reliable reporting of adverse drug effects.
- In the case of patient-related factors, random substitution can affect adherence or the ratio of benefit to risk of the medicine:
- Patient confidence in the medication can be undermined if the medicinal product looks different by, for example, its colour, or list of adverse reactions on the package insert. This is particularly relevant in disorders such as depression or psychosis, in which patients are sometimes distrustful of medication. A change in the external appearance of medicinal products or any change (real or imagined) in their action or adverse effects can damage patient adherence to treatment.
  - Random substitution can also affect the risk/benefit ratio in disorders for which the balance (dose versus efficacy and adverse reactions) of the therapy is critical, such as Parkinson's disease or in transplantation patients.
  - When a patient has an intolerance for a certain excipient, substitution with a drug containing that excipient should be avoided, for example, the excipients wheat starch and parabens must be avoided in patients with celiac disease, and paraben allergies, respectively.
  - The medicinal product pack or an associated device can significantly affect its ease of use or compliance. Examples are inhalation medications, contraceptive pills or packs tailored to specific patient groups, such as Ledertrexate tablets for rheumatoid arthritis patients.

### Additional considerations

When substitution is unavoidable, for example, when the innovator product is out of stock, the pharmacist should inform the patient properly, indicating the differences and similarities between the drugs in question. The patient should be warned not to take both drugs simultaneously and asked to monitor their drug responses in terms of efficacy and adverse reactions.

Generic products are tested for bioequivalence with the brand product as a reference. This means that the difference between two generic products can exceed the limit that is accepted for bioequivalence between a generic product and the reference product. If product A is bioequivalent with the reference product in the upper boundary of the AUC and product B in the lower boundary, these two generics versions are considerably different. Proper product information is mandatory in such a situation. The difference between two generics can be greater than the difference between a generic and a single reference product.

Although there may appear to be bioequivalence in a given small volunteer population, in practice, some patients experience problems following generics substitution. In most cases there is no satisfactory scientific explanation, but the patient's responses to substitution should always be taken seriously.

### In summary

Marketed medicines that have been tested for bioequivalence should in general be substitutable. However, caution in substitution is warranted in certain situations. To provide support to the pharmacy community, KNMP has issued a set of guidelines to promote a responsible substitution process in community pharmacies. This should help to maintain professional standards which in turn should help protect patients against harm caused by the effects of product substitution.

### Editor's note

The English version of the published *Guideline for generic substitution* is available for download on the KNMP website as well as GaBI Online ([www.gabionline.net](http://www.gabionline.net)).

A brief article detailing the process followed when drafting the guidelines is published on GaBI Online, available from: [www.gabionline.net/Guidelines/Guidelines-for-substitution-of-generics-in-The-Netherlands](http://www.gabionline.net/Guidelines/Guidelines-for-substitution-of-generics-in-The-Netherlands)

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