

Interchangeability of generics

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Zagreb, 14 June 2011

Definition of a generic product

- According Art 10.1 of Dir 2001/83/EC a medicinal product is a generic product if it has
- the same qualitative and quantitative composition in active substance
- the same pharmaceutical form
- and whose bioequivalence has been demonstrated by appropriate bioavailability studies

Against the reference medicinal product

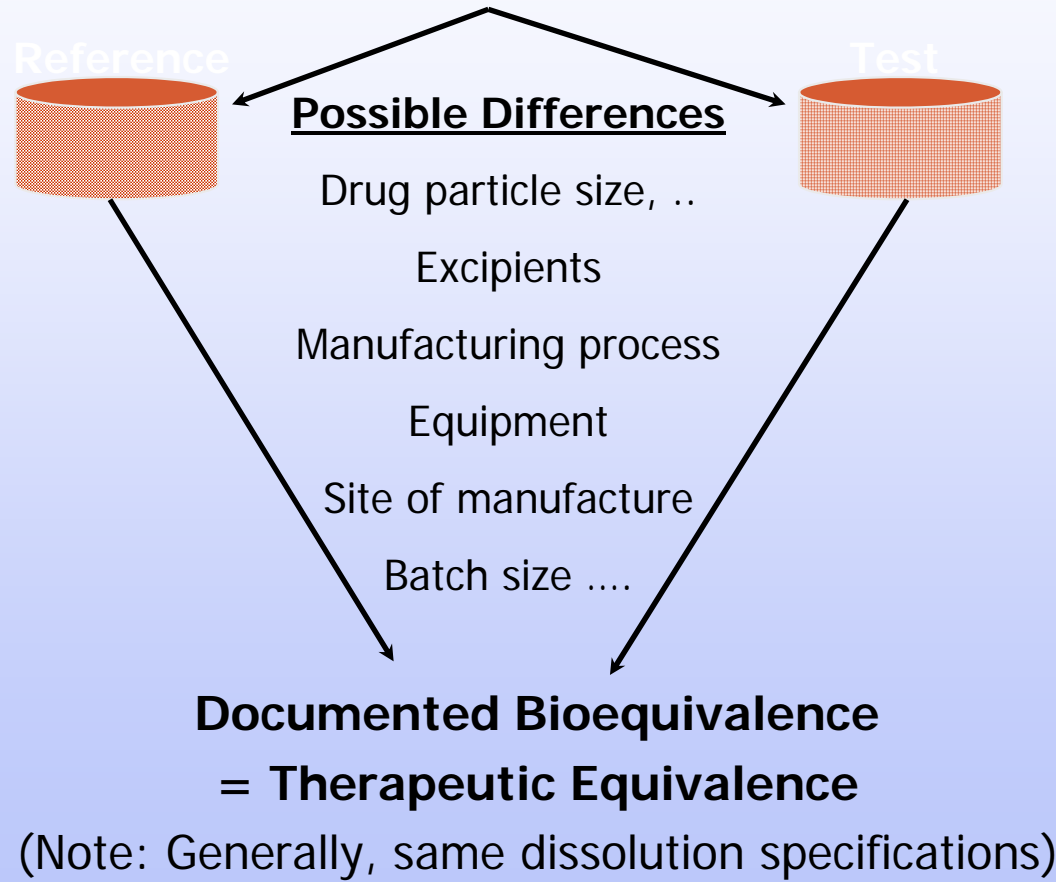
Substitution

- When data exclusivity has expired it is possible to apply for a generic version of that medicine
- Patients are no longer treated with the original branded medicine (innovator) but the generic product: generic substitution
- Generic substitution \neq therapeutic substitution (medicine replaced by another from same therapeutic class)

Bioequivalence

- If a generic manufacturer can demonstrate that plasma exposure in time of generic can be considered equal to that of branded medicine the generic is considered to be therapeutic equivalent and efficacy and safety are considered to be the same
- Requirements for pharmaceutical quality of the product are the same as branded products
- Generics don't need to be **identical** as reference product; differences can exist for excipients, size,color,scoring etc
- SmPC and PL can be different because of different outcome in procedures (DCP and MRP)

Pharmaceutical Equivalent Products



Are all generics interchangeable?

- Concept of substitution is based on experience with immediate release formulations
- It has worked well in the past and can still be applied

However:

- More complex formulations such as liposomal packaging of doxorubicine come to the market
- Products with different mechanism for modified release formulations are on the market
- Biosimilar products are on the market
- Locally applied products (inhalers, nasal sprays)
- Not all products with same active substance are generics (hybrid applications, well established use applications)

Legal framework

- Different application types are possible for submission of dossiers:
- Art 10.1 Dir 2001/83/EC
- Art 10.3 Dir 2001/83/EC
- Art 10.a Well established use
- Art 10.4 Biosimilars

- The reference product can be the European reference product , not always similar to the national reference product
- However, health professionals are not aware about differences in dossiers and consequences for interchangeability

The concept of interchangeability

- Bioequivalence = therapeutic equivalence
- Experience based on immediate release oral formulations
- Guidelines for substitution often developed by other organisations and influenced by pricing
- Interchangeability more and more a case by case decision, depending on type of product, more information for health professionals needed on complex molecules
- Approaches can be different for patients starting with the therapy , or changes during the course of treatment f.e recommendations for anti-epileptic medicines (in some MSs) are not to change a MP (independent whether this is a generic or Brand leader) during treatment

Substitution and Clinical practice

- When generics/hybrids/biosimilar products have received a marketing authorisation the CHMP/NCA has considered that the benefit/risk balance is positive under normal conditions of use
- Dossiers are assessed on their own and in accordance with their legal basis
- ‘Substitution’ is not part of EU discussion and decision, but can create problems at national level
- Health professionals (prescribers, pharmacists) need guidance how to use generic medicines safely
- This should be done at national level and in accordance with national policies

Example Biosimilars (MEB website)

- A biosimilar product is a medicinal product that is equivalent to a biological medicinal product that has previously received a marketing authorisation.
- As biosimilar products are similar, but not identical every biosimilar is assessed separately
- If a patient switches from one biological product to another this must be carefully monitored by the treating physician. This is true for both innovator products and interchangeable medicinal products

Example Biosimilars (MEB website)

- The safety of all medicinal products, including biosimilar medicinal products, is continuously monitored after approval. Each company must introduce a system to control the safety of marketed products. The Inspectorate can also inspect this system.
- It is known that biological medicinal products can be immunogenic (i.e. causing an immune response) and that this can have an impact on the product's efficacy and safety. However, it is difficult – if not impossible – to predict the potential immunogenicity based on non-clinical studies. Moreover, these relatively rare, but severe, adverse events can only be detected in a larger patient population and after long-term use.

Are biosimilar medicinal products interchangeable?

Biosimilar medicinal products are equivalent, but not necessarily identical. This must be kept in mind if a switch from one biological medicinal product to another biological medicinal product is being considered, or if the pharmacy delivers a biosimilar rather than the reference medicinal product. The treating physician must be involved in the decision to switch from one biological medicinal product to another. Because biological medicinal products are not necessarily identical, it is vitally important to carefully record which product a patient has been given, especially if a causal link with an undesirable effects is suspected.

The Medicines Evaluation Board (MEB) is of the opinion that:

New patients can be treated with a biosimilar.

Patients must be kept on a biological medicinal product as much as possible if they respond well to it clinically with respect to efficacy and adverse events.

Uncontrolled – that is, without adequate clinical monitoring – exchange between biologicals (regardless of whether it involves innovator products or biosimilar medicinal products) must be avoided.

If this exchange nevertheless takes place, detailed product and batch information must be recorded in the patient file to guarantee the traceability of the product in the event of problems.

Substitution policies

- Some countries have a list with products that can be substituted, e.g MPA
- Other countries have lists of generic products (Legal basis Art 10.1 of Dir 2001/83/EC) that are reimbursed
- ‘Automatic substitution, the pharmacist has to provide the generic that is reimbursed; INN prescribing , e.g Netherlands

Example MPA

<http://www.lakemedelsverket.se/english/product/Medicinal-products/Substitution>

- MPA has written instructions to pharmacists with regard to the list over substitutable medicinal products (MP)
- The MP must have the same packaging (e.g jar, bottle, cartridge, combination pack, etc)
- Substitution may occur if pack of same size exists. Personnel may choose another pack of nearly the same size
- Packages that are especially designed for e.g rheumatic patients and calender pack may not be substituted without consent of patient
- If half a dose has been prescribed, no substitution is permitted
- Parallel-distributed products may be substituted for the normally distributed products

Complex formulations

Doxorubicine

- **Doxorubicine 2 mg/ml**, solution for injection

SmPC: Aqueous solution

- **Doxorubicine (Caelyx)**, concentrate for solution for infusion 2 mg/ml

SmPC: 1 ml of Caelyx contains 2 mg doxorubicine in a pegylated liposomal solution

- These products are not interchangeable
- Potential risk for medication errors if only INN name is used in prescription
- *More attention needed for name of generic products, to express different composition, to avoid confusion in medical practice*

Retard versus immediate release formulations

Tacrolimus

- Tacrolimus, capsules 1.5, 1.0, and 5 mg
Posology: 2 gifts per day
(reference product Prograf)
- Tacrolimus, prolonged release formulations 0.5, 3, and 5 mg
Once a day schedule
(reference product Advagraf)
- These products are not interchangeable
- Potential risk for medication errors if only INN name is used in prescription

The patient's perspective

- Substitution can influence patient compliance
- Minor differences in color, formulation, appearance, excipients can worry patients
- Different information in PL can confuse patients
- Information to patients and Health care professionals about the assessment of medicines is important
- Transparency and communication is important:
 - Public assessment reports
 - Communication on website agencies
 - Communication on interchangeability to health professionals about specific products may be needed

Recommendations (1)

- The concept of interchangeability is a good concept for immediate release generic medicinal products; it should be maintained
- Generic medicinal products are assessed on their own, and the public should understand that these product have the same quality as branded products
- Interchangeability of complex formulations, biosimilars and products with a different reference product than the national one should be carefully assessed on a case by case basis
- The health professionals should have a better understanding about different requirements for generics (Art 10.1 of Dir 2001/83/Ec) and products approved in accordance with other legal bases (10.3, well established use, biosimilars) and agencies should better communicate these differences
- It should be clearly communicated if products are interchangeable under certain conditions such as biosimilars

Recommendations (2)

- Communication about interchangeability should be done at national level because clinical practice differs in Member States
- More attention should be paid to possible consequences for patients with substitution (e.g special packaging, scoring lines)
- More attention should be paid to the labelling and name of complex formulations and modified release products to avoid confusion in clinical practice and medication errors

Thank you

Questions?

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