International Pharmaceutical Federation

FIP STATEMENT OF POLICY
Pharmacist's authority in pharmaceutical product selection: therapeutic interchange and substitution

Purpose:
The purpose of this document is to provide a set of recommendations on therapeutic interchange and substitution of pharmaceutical products, including with biosimilars.

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Background:
In 1992, FIP issued a statement calling on all countries to ensure the adequate quality of pharmaceutical products. Since then, countries have developed systems that guarantee that all pharmaceutical products, both manufactured locally and imported, meet regulatory standards of quality, safety and efficacy, including bioavailability and bioequivalence. As recommended by FIP at the time, governments apply the same principles for quality, safety and efficacy standards to branded and generic products.

Until recently, the marketing of some pharmaceutical products was based on the premise that the brand-name product is different from its competitors in scientifically and clinically important ways. However, it is now clear, that with appropriate exercise of medical and pharmaceutical judgement, pharmaceutical products may be interchanged according to defined criteria and the needs of the patient without compromising patient outcomes.

The WHO-FIP Joint Guidelines on Good Pharmacy Practice (2011)[1] outline the key roles of the pharmacist. Among other points, the two organisation jointly urge action by all governments, in collaboration with national pharmaceutical associations, to make full use of the expertise of the pharmacist at all levels of the healthcare system. The guidelines also recommend generic substitution where possible as part of the pharmacist's role.

In addition, the emergence and use of biosimilar medicines in clinical practice in developed countries has become more widespread over the past decade. To date, no major safety issues with the use of biosimilars as alternatives to the

[1] WHO-FIP Joint Guidelines on Good Pharmacy Practice (2011) Available from: https://bit.ly/2uqSjck

original biological medicine have been reported. Thus, this policy statement on therapeutic interchange and substitution now includes biosimilars.

Taking into account this introduction and the definitions below, FIP has the following policies:

Policy on substitution

Where substitution is allowed by legislation and regulation, or the prescriber indicates that a generic or biosimilar alternative is acceptable, the responsibility for selection of the generic or biosimilar pharmaceutical product — unless specified otherwise — will be that of the pharmacist. It should be made within the criteria defined below, having regard to efficiency or following the country specific lists of products that meet the criteria.

Policy on therapeutic interchange

Therapeutic interchange is a collaborative action between the prescriber and the pharmacist designed to achieve maximum therapeutic benefit for the patient and to ensure the safest, most effective and economic use of pharmaceutical products. It is in accordance with a protocol previously established and agreed between the prescriber and the pharmacist, or after individual prior consultation with the prescriber. Therapeutic interchange may be within or outside a formulary system.

The concept of therapeutic interchange, as defined above, using the relevant expertise of the pharmacist and the prescriber, should be promoted, when this provides the best outcome for the patient. Such circumstances may occur during medicine shortages.

Points for consideration when performing substitution or therapeutic interchange

To ensure safe substitution or therapeutic interchange by the pharmacist, information about excipients should also be taken into account. In October 2017, the European Medicines Agency published an updated annex[2] with a list of all excipients known to have a recognised action or effect[3] that needs to be displayed on the label of any medicine authorised in the European Union. The regulatory authorities should provide all necessary information about excipients to pharmacists to ensure the most suitable product for the patient is selected.

[2] European Medicines Agency. Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use.' EMA/CHMP/302620/2017 Available from: https://bit.ly/2JbRehc

[3] Excipients may only show an effect above a certain amount/threshold. For any amount above this threshold, it is necessary to state the quantification information about excipients present in the pharmaceutical product.

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The packaging and labelling of a pharmaceutical product should also be taken into account in pharmaceutical product selection, in order to minimise confusion and ensure adherence.

When a “multiple tablet regimen” is formulated into a “single tablet regimen”, the quality and safety of the active pharmaceutical ingredients (APIs) in the single tablet formulation will be equivalent to that of the multiple tablet regimen. Combined pharmaceutical products in a single tablet formulation and the combination of pharmaceutical products as a multiple tablet regimen may be bioequivalent, but due to differences in adherence, therapeutic outcomes may differ.

Use of the international nonproprietary names (INN)
For non-biological medicines, prescribers should be recommended to use the international nonproprietary name (INN) to reduce errors in prescribing/dispensing, for professional communication and to ensure patient’s safety/benefits.

Countries have different approaches on the need for distinguishable INN names in biological medicines.

Access to information on pharmaceutical products
The decision that a product is substitutable should be informed by the regulatory or other bodies in charge and through publicly accessible resources, and based on scientific literature including bioequivalence and/or clinical studies, information from the manufacturer and professional societies, medicine recalls, manufacturer reputation and other pertinent factors including legislation.

The composition of pharmaceutical products should be described accurately in package leaflets, product information and packaging and include information about the active substances and excipients and their quantities.

Pharmacists and other healthcare professionals should be well informed by their governments about the approval process for biosimilars, particularly about the principles of determining biosimilarity, to avoid misalignment of expectations, beliefs and the available data; and to address issues concerning attitudes towards biosimilars and doubts on the economic need for biosimilars. Effective information dissemination channels should be used and include economic considerations.

Pharmacovigilance
Adequate pharmacovigilance that will ensure correct identification of a biological medicine if any product-specific safety (or immunogenicity) concerns arise, needs to be included in the regulatory framework. Post-marketing safety studies

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should be performed by the companies marketing generic medicines or biosimilars, and periodic safety update reports should be submitted to regulators and made publicly accessible.

Along with the Good Pharmacy Practice principles, it is recommended that pharmacists record the trade name, batch number and expiry date in the patient's healthcare information. Countries have different approaches on the period of data keeping.

Real-world evidence may be used in post-marketing studies or by pharmacists to help evaluate the safety, efficacy and cost-effectiveness of generic medicines and biosimilars.

Clinical practice guidelines
The use and availability of clinical practice guidelines should be encouraged. These guidelines should inform the rational use of old and new medicines, including biosimilars, and inform their place in therapy, leading to the appropriate and cost-effective use of originator reference and biosimilar products.

Education
All national associations representing pharmacists, prescribers, pharmaceutical manufacturers and consumers should be urged to collaborate by working on quality improvement programmes and by providing continuing education to ensure safe and effective practice of substitution and therapeutic interchange, and to enable practitioners to offer sound advice to professional colleagues and patients.

Furthermore, healthcare professionals' curricula should include principles of economic evaluations that inform medicine prescribing and supply.

Economic sustainability
Local legislations/regulatory authorities should provide enabling environments for the cost-effectiveness and economic sustainability of substitution practice for pharmacists.

Dialogue with partners
Dialogue with the World Health Organization (WHO), international organisations representing the medical and pharmacy professions, other prescribers, pharmaceutical manufacturers, consumers and funders regarding the role of the pharmacist in product selection should continue and this should be encouraged at national level.

Definitions

The following terms are defined as indicated:

Active pharmaceutical ingredient (API) The active ingredient that alone or in combination with one or more other active ingredients is considered to fulfil the intended activity of a pharmaceutical.[4]

International nonproprietary name (INN) The unique naming of a pharmaceutical substance or active pharmaceutical ingredient that is globally recognised and is public property. In many countries, it will be the same as the name of the active pharmaceutical ingredient.

Originator medicine The first version of a medicine that has been developed and is patented by a pharmaceutical company. This company will have exclusive rights to market the pharmaceutical product for the life of the patent. An originator medicine has a unique trade (or brand) name for marketing purposes. It may also be called "first-in-class product" or "innovator product".[5] Once the patent(s) and marketing exclusivity (if relevant) have/has expired, and other products containing the same active pharmaceutical ingredient(s) are entering the market, the originator brand serves as the reference pharmaceutical product.

Generic medicines These are pharmaceutical products containing the same amount of the same active pharmaceutical ingredients, formulated for administration by the same route and the same dosage form, meeting the required regulatory and pharmacopoeial standards and the same satisfactory standards of quality, safety and efficacy.[6] Generic medicines are bioequivalent to an originator medicine.[6] Generic medicines can only be marketed after the originator's patent(s) protection and marketing exclusivity (if relevant) have/has expired.

Biological medicine A medicine whose active ingredient is, wholly or in part, produced by or extracted from a biological source and requiring a combination of physical-chemical-biological testing together with the production process and its control in order to characterise the medicine and determine its quality. It may also be called the "biotherapeutic product", "biologic medicine" or "biopharmaceutical".[5]

[4] PHIS glossary
[5] Adapted from European Medicines Agency (EMA). Guideline on similar biological medicinal products (2014) CHMP/437/04 Rev 1 Available from: http://bit.ly/2ckWrzf
[6] Adapted from 2018 U.S. Food and Drug Administration. Generic Drugs Facts [website]. Available from: www.FDA.gov/GenericDrugs

Biosimilar product A biological product that is highly similar in terms of quality, safety and efficacy to an already licensed reference biological product in quality, non-clinical and clinical evaluation. A biosimilar product and its reference biological product are expected to have similar safety and efficacy profile and once approved are used to treat the same indications.[5] A biosimilar is also highly similar to the reference biological medicine in terms of immunogenicity profile, which is the intrinsic ability of proteins and other biological medicines to cause an immune response.[7] Due to their nature, biosimilars are not automatically bioequivalent to their reference biological medicine and are not automatically regarded as a generic of a biological medicine.[3] However, they are expected to produce the same clinical result as their reference biologic product and if a regulatory body in a country deems products to be interchangeable, this is the guidance a pharmacist should seek to support physicians and patients to navigate options to select the product best for the patient and the healthcare system.

Equivalence Two pharmaceutical products are said to be pharmaceutically equivalent if they have the same amount of the same active substance(s), are in the same dosage form, to be administered by the same route of administration and meet the same or comparable standards.[8]

Bioequivalence Two pharmaceutical products are said to be bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their efficacy and safety profiles can be expected to be essentially the same.[8] Regulators set parameters for bioequivalence designation. Regulator-approved bioequivalence to an original reference product is a necessary criterion for a pharmaceutical product to be classified as a generic brand in the regulator's country.[8,9] While generics are by definition bioequivalent, biosimilars are not.

Interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This term most often refers to the replacement of a reference pharmaceutical product with a biosimilar (or vice versa) or replacing one biosimilar with another.[10] Regulators of countries may differ in their position regarding interchangeability of biological medicines.

[7] European Medicines Agency. Biosimilar medicines [website]. Available from: https://bit.ly/2sQBhUF
[8] Birkett DJ (2003). "Generics - equal or not?" (PDF). Aust Prescr. 26: 85–7. doi:10.18773/austprescr.2003.063
[9] Center for Drug Evaluation and Research. Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations (PDF). (2003). United States Food and Drug Administration. Available from: https://bit.ly/2psJlJd and Committee for Medicinal Products for Human Use. Guideline on the Investigation of Bioequivalence (pdf). European Medicines Agency. 2010. Available from: https://bit.ly/1OLUxYt
[10] European Medicines Agency (EMA). Biosimilars in the EU. Information guide for healthcare professionals (2017) Available from: https://bit.ly/2qXnNpI

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Substitution The act of dispensing a generic equivalent or a biosimilar as a replacement for the prescribed pharmaceutical product for the same treatment period.

Therapeutic interchange The act of dispensing a pharmaceutical product containing different active ingredient(s) which are of the same pharmacological class, and which have similar therapeutic effects as the prescribed pharmaceutical product.

Switching The decision by the treating physician to exchange one pharmaceutical product for another pharmaceutical product with the same therapeutic intent.[10]

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