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Ministry of Health

Generic Medication Substitution

Purpose

Provide standard procedure and guidance for the Brand-Generic, Generic-Brand and Generic-Generic substitution for formulary drugs and drug dosage forms.

Definitions

- **Bioequivalence:** Indicates that a drug in a similar dosage form to the reference drug (brand) reaches the general circulation at the same relative rate and extent; i.e., the plasma level profiles of the drug obtained using the two dosage forms are similar.
- **Bioavailability:** A term that indicates measurement of both the rate and total extent of drug absorption that reaches the general circulation from an administered dosage form.
- **Pharmaceutical equivalence:** Refers to two drug products with the same active ingredient(s), same route of administration, same dosage form, same strength and same conditions of use, but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.
- **Therapeutic equivalence:** Drug products meeting the following criteria are therapeutically equivalent and can be substituted with the full expectation that the substituted product shall produce the same therapeutic effect as the prescribed product. Drug products that meet the following general criteria are classified as therapeutically equivalent. (US-FDA definition)
  - They are approved as safe and effective
  - They are pharmaceutically equivalent
  - They are bioequivalent
  - They are adequately labeled
  - They are manufactured in compliance with Current Good Manufacturing Practice Standards
- **Generic product:** A pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a license from the innovator company and marketed after expiry of patent or other exclusivity rights.
- **Generic substitution:** The substitution of drug products that contain the same active ingredient(s) and are chemically identical in strength, concentration, dosage form, and route of administration to the drug product prescribed (i.e., these are "pharmaceutical equivalents" as defined in the FDA Orange Book). These products can also be termed "generic equivalents."
- **Narrow therapeutic index drugs:** Any drug for which a 20% or smaller change in dosage, with bioavailability remaining constant, produces clinically significant and undesirable pharmacodynamics alteration, that is, increased adverse effects, decreased therapeutic efficacy, or excessive therapeutic effects.

Equipment/Materials

- International Centers for Conducting Bioequivalence Studies: Appendix A
- Product Evaluation Request Form: Appendix B
- Scientific evidence provided by the manufacturer
- Generic Medication Substitution Checklist: Appendix C
- Generic Medication Substitution Workflow: Appendix D

References

- Executive Board of the Health Ministers' Council for GCC States Guidelines for Drug Bioequivalence Nov 2003
- Regulation for Registration of Pharmaceutical Companies & their Products, Ministerial resolution NO.1214/20 dated 17/6/1409H
- SFDA/MOH recommendation on Narrow therapeutic index, biosimilars, and inhaled medications. 2024631-1439. 27/10/1439.
- SFDA approved medications list website. https://www.sfda.gov.sa/en/drug/search/Pages/default.aspx.

Policy

1. A generic or brand drug product may substitute the formulary alternative available in the Ministry of Health (MOH) Formulary only upon the approval of Supply chain, through a review by the Pharmacy and Therapeutic (PTC) coordinator and in collaboration with Pharmaceutical Care Department.
2. Narrow therapeutic index, biosimilars, and inhaled medications are required to go through the PTC coordinator as per the regulations of MOH and SFDA.
3. The generic switch for medications that exist in several strengths and forms should cover all strengths and/or forms available in the MOH Formulary.
4. Supply chain and pharmaceutical care department shall evaluate and approve alternative generic or brand products which may include multiple approved generics for the same brand in a sequence of preference based on pharmaceutical equivalency, registration status, bioequivalence, quality, manufacturer reputation, post-marketing surveillance reports, product availability, cost, patient acceptance, and safety.
5. Generic or brand substitution of narrow therapeutic index (NTI) drugs, medication sensitive to manufacturing techniques and variability, or difficult to manufacture is not allowed unless absolutely necessary, as judged by PTC coordinator in collaboration with involved medical department.

Procedure

Procedures	Explanation
1. Forward a request for brand or generic substitution	1.1. The Supply Chain Management will forward the request of brand or generic substitution request pharmaceutical care department and copy PTC coordinator. A sample of the requested generic substitute should accompany the request for evaluation when applicable (especially if it is not a familiar company or if the item is in non-English labeling). (see 6.1) 1.2. The request should clearly justify the switching from the Formulary item to new generic (ex. Cost savings, discontinuation, recall, shortage in supply, etc.). 1.3. Submit the request on standard format (Appendix-B) and Generic Medication Substitution Checklist: Appendix-C
2. Assess Pharmaceutical equivalence and evaluate if the bioequivalence requirements have been met through the Orange Book.	2.1. The generic or brand product substitute must be pharmaceutically equivalent to the formulary item. 2.2. Generic or brand product that is not pharmaceutically equivalent is not acceptable. 2.3. The official SFDA website will serve as reference to determine if the generic product has passed the bioequivalence requirements and registration.

Procedures	Explanation
3. Check the approval/registration status of the generic product that will be evaluated.	3.1. Generic product must be registered in Saudi Arabia. In case no product is registered by SFDA, then it has to be registered in one of the four reference countries/regulatory bodies (USA, UK, Canada, EMA) 3.2. For generic products manufactured outside the US, Canada, UK, or EMA, the product must be already in use in at least one of the main hospitals in the Saudi Arabia prior to its admission to MOH.
4. Assess the therapeutic class of the drug requiring generic or brand substitution by pharmaceutical care department	4.1. Generic or brand substitution of narrow therapeutic index (NTI) drugs, medication sensitive to manufacturing techniques and variability, medications that are difficult to manufacture, biosimilars, or inhaled medications is not allowed unless absolutely necessary as judged by PTC committee. 4.2. Switching formulary product of the above medications in 4.1 to other generic/brands alternative shall take place only after PTC notification to the prescribers, accompanied by appropriate monitoring of patients to identify and prevent any unexpected or untoward patient response due to variation in drug bioavailability/effect. 4.3. NTI drugs include; but not limited to; digoxin, phenytoin, carbamazepine, warfarin, cyclosporine, tacrolimus, sirolimus, etc. 4.4. Medications sensitive to manufacturing technique, or are difficult to manufacture include; but not limited to levothyroxine, metered dose inhalers, patches, vaccines, etc.
5. If evaluation in 2 does not yield a result on bioequivalence, retrieve and evaluate information regarding the bioequivalence based on bioequivalence studies and product literature.	5.1. Bioequivalence studies must be approved by respective regulatory body. 5.2. Review product literature provided by the drug company including bioequivalence studies when needed.
6. Retrieve and request the information regarding the quality of generic or brand substitute.	6.1. Evaluate pharmaceutical elegance of products e.g., broken tablets, powder in bottles…etc. 6.2. Notify Generic Substitutions to hospitals, physicians, pharmacists and patients. 6.3. Obtain feedback from Supply Chain Management/NUPCO about the reputation of the manufacturer in terms of its ability to adhere to good manufacturing practices (GMP) standards is considered. Establishment Inspection Reports and recall reports are available from FDA through Freedom of Information (FOI) request or reports from SFDA for local products shall be retrieved if available.
7. Assess for continuous product supply.	7.1. Assess availability of local agent for the manufacturer. 7.2. Assess company commitment to the education of practitioners when needed, e.g. method of administration for new dosage form, stability information, etc. 7.3. Drug company manufacturer/local vendor should guarantee the consistency of the supply for 2-3 years according to NUPCO bidding contracts requirement. 7.4. Assess that the same company will supply all requested/required strengths of their generic/brand product. 7.5. Assure acceptable duration between product receipt and expiration (at least two third of the shelf life). 7.6. MOH shall not entertain a switch among generic or brand within one year or unless clearly necessary.

Procedures	Explanation
8. Evaluate factors that involve patient compliance and ease of administration.	8.1. MOH shall take into account the patient's need when selecting from multi-source drug products. Such as availability of suitable dosage form for patient age
9. Evaluate medication safety issues.	9.1. Look-alike, sound-alike products are not acceptable unless absolutely necessary. 9.2. The package insert and the outer package should be bi-lingual (English and Arabic) or English only. Any other languages are not acceptable. In cases where absolutely no alternative MOH will evaluate that product individually. 9.3. For all non-bulk products, the containers must be child resistant, if possible. 9.4. Clear information on stability and storage conditions must be available.
10. Evaluate the cost of the generic or brand product compared to Formulary item.	10.1. Cost of the product should be considered in selecting among candidate generic or brand as judged by supply chain/NUPCO
11. Finalize the decision for generic or brand substitution.	11.1. Obtain input from end-users only if deemed necessary. 11.2. Pharmaceutical Care department will inform Supply Chain Management about acceptance or rejection of product within two weeks. (it needs more involvement from supply chain team) 11.3. If the product is accepted, Pharmaceutical Care department will communicate with supply chain if this will be on permanent or temporary basis. 11.4. A list of approved generics for each brand will be sent to supply chain e.g. approved generic number 1, approved generic number 2, etc. 11.5. If product is accepted as temporary, original formulary product shall be reinstated once available. In case of rejection, the decision will be considered final for one year unless new data are provided or become available.
12. Review the temporary products on periodical basis	12.1. Review the temporary products on periodical basis and assure that original formulary product is restocked.
13. Keep copy of the product evaluation and related documents.	13.1. Copy of the product evaluation and related documents will be kept in the Pharmaceutical Care department and Supply Chain Management.

Appendix- A

International Centers for Conducting Bioequivalence Studies Gulf Countries

International Centers for Conducting Bioequivalence Studies Gulf Countries	
Gulf Countries	1. Faculty of pharmacy, King Saud University 2. King Faisal Specialist Hospital and Research Center, Riyadh
Arab Countries	1. International Pharmaceutical Research Center (IPRC), Jordan 2. Acdima Center for Bioequivalence and Pharmaceutical Studies, Jordan

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Appendix- B

Product Evaluation Request Form

Product Evaluation Request

To:	Date:
	Reference #:
Thru:	From: NUPCO/ Supply Chain

We are requesting your immediate assistance to please check; whether the following alternative is acceptable as substitute / replacement for item code:

Item Description		
Manufacturer		
Price		

☐ Sample Enclosed ☐ Documents

Department Reply

The Department has evaluated the alternative product and finds it:

☐ Acceptable ☐ Not Acceptable

If **Acceptable**, the item will serve as:

☐ A permanent replacement for current brand ☐ A temporary replacement once present brand is not available

If **not acceptable**, please state the reason:

Approved by: _____ Date: _____

Prepared by:

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Appendix- C

Generic Medication Substitution Checklist

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Generic Medication Substitution Checklist

Brand Name (Current):			**Dosage Form Description (Current):**					
Proposed Generic Name (Alternative Generic):			**Dosage Form Description (Alternative Generic):**					
Registration status (mark all that apply)			☐ SFDA	☐ US-FDA	☐ HC	☐ EMA	☐ Not Registered	
1. Drug Evaluation Form accompany (Package insert, picture of item, and quotation)	☐ Yes	☐ No	1. Narrow Therapeutic Index / Biosimilar Medication				☐ Yes	☐ No
2. Cost of current item per unit			2. Pharmaceutical equivalence acceptable?				☐ Yes	☐ No
3. Cost of suggested item per unit			3. If SFDA registered, skip # 5 and 6 below				☐ Yes	☐ No
4. Potential cost -savings value			4. Bioavailability for US product (Orange book codes) *If item is not USA registered move to point 5*				☐ Yes	☐ No
5. Potential cost inflation value			5. Bioequivalence acceptable through clinical review?				☐ Yes	☐ No
6. Product availability (Drug company should guarantee the consistency for 3 years through written documentation	☐ Yes	☐ No	6. Quality acceptable? (shape/container/coating/color) ☐ Sample not available				☐ Yes	☐ No
7. Acceptable Purchasing History of agent	☐ Yes	☐ No	7. History of Manufacturer/Drug recall				☐ Yes	☐ No
8. Manufacturer's reputation is acceptable as per MOH policy	☐ Yes	☐ No	8. Language of the product (outer & inside the package)				☐ English ☐ Arabic	☐ Other, _____
9. Used in other reputable hospital?	☐ Yes	☐ No	Pharmacy Comments: ☐ Recommend approval ☐ Require PTC Approval ☐ Recommend rejection					
10. Lead time								
11. Relevant documents have been submitted to Pharmacy?	☐ Yes	☐ No						

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Appendix D

Generic Medication Substitution Workflow