So what’s wrong with generics anyway?

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In the context of our current economic climate, more and more pressure is being put on us to use generics, as a means of cost containment. One can, of course debate at length who benefits from this cost containment. Nevertheless, in the interests of being the advocates for our patients it behoves us to explore generics as an option.

Generic and therapeutic substitution
In generic substitution, a generic drug is substituted for a brand-name drug. However, both drugs have the same active chemical ingredient, same dosage strength and same dosage form.

Therapeutic substitution occurs when a pharmacist substitutes a chemically different drug for the drug that the physician prescribed. The drug substituted by the pharmacist belongs to the same pharmacologic class and/or to the same therapeutic class. However, since the two drugs have different chemical structures, adverse outcomes for the patient can occur.

Some history
The US Pure Food and Drug Act of 1906 mandated that drugs be manufactured under sanitary conditions and made free of impurities; the law also outlawed misbranding.

The Food, Drug and Cosmetic Act in 1938 mandated that a manufacturer demonstrate a drug's safety before bringing it to the marketplace.

In the 1950s as many as 40 states had strict anti-substitution laws, prohibiting pharmacists from substituting generic equivalents for branded drugs prescribed by physicians. The pharmaceutical industry supported these laws and helped get the legislation passed.

In the 1970s the American Pharmacists Association aligned with third-party payers and consumer advocacy organisations to repeal anti-substitution laws in order to give patients access to less expensive drugs. In 1976 the Federal Trade Commission (FTC) conducted a study of generic drug substitutions and concluded that forcing consumers to use branded medications resulted in higher out-of-pocket costs. It also concluded that allowing pharmacists to make drug substitutions encouraged price competition.

At that time generic medications underwent the same drug approval process as their branded counterparts, requiring clinical studies that demonstrated safety and efficacy and only a handful of generic medications were granted FDA approval.

In the 1980s, with the passage of the Hatch-Waxman Act the approval process for generic medications became abridged and generic manufacturers have been allowed to submit an Abbreviated New Drug Application which does not require animal or clinical studies. Bioequivalence testing was still required.

The Hatch-Waxman Act also allowed manufacturers of branded drugs to seek patent extensions and it both paved the way for generic drug makers to manufacture less expensive formulations and allowed branded drug makers to obtain longer patent lives.

Since the repeal of the 1950's anti-substitution laws, many states have allowed pharmacists to substitute brand-name drugs with less expensive, therapeutically equivalent alternatives without consulting the prescriber, unless the prescription specifically prohibits such substitution. In cases in which the prescriber writes "brand medically necessary" or "brand necessary" on the prescription, the pharmacist must dispense that branded formulation.

Some states have a "positive formulary" which identifies generic products that can be interchanged with their branded counterparts, while others have a "negative formulary" that specifies which drugs cannot be interchanged with other drugs.

In the RSA the pharmacist is obliged to supply the less expensive preparation unless the prescriber specifies that there is to be no substitution.

Some definitions
Pharmaceutical equivalents are drug products containing the same active ingredient(s), same strength, dosage form, route of administration and identical strength or concentration. They may or may not have different shapes, colouring, packaging or inactive ingredients.

Therapeutic equivalents are products that are pharmaceutical equivalents and that produce the same clinical effect and have the same safety profile. They must be manufactured under Good Manufacturing Practice and be labelled properly.

Pharmaceutical alternatives contain the same active therapeutic ingredient, but are formulated with a different salt, ester or complex. They may come in different dosage forms or strengths.

Bioavailability is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

Bioequivalent drug products are pharmaceutical equivalents or pharmaceutical alternatives that show comparable bioavailability under similar experimental conditions.

Testing equivalence
Bioequivalence can be determined through one of four paths: pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials or in vitro studies. Pharmacokinetic studies test bioequivalence by measuring plasma levels to determine the rate and extent of absorption. The area under the concentration-time curve (AUC) is obtained to determine the extent of absorption. In addition, peak drug concentrations (Cmax) are used to determine the rate of absorption. These studies are conducted with a 2-treatment crossover design in 24–36 volunteers and single doses of test and standard drugs are administered. Plasma samples are collected and evaluated at
various time intervals. If two drug products containing the same active chemical entity can reach the site of absorption in similar times and be absorbed to the same extent, bioequivalence can be established. Confidence intervals of the measured pharmacokinetic parameters are expected to fall between 80% and 125%.

**Drugs with a narrow therapeutic index**

Drugs that are classified as having a narrow therapeutic index (NTI) generate the greatest controversy in regard to generic substitution. According to FDA regulations, drugs are defined as having a NTI if:

- They have less than a 2-fold difference in median lethal dose and median effective dose values.
- They have less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood.
- Safe and effective use of the drug products requires careful titration and patient monitoring.

**Non-substitutable drugs in the RSA**

The Medicines Control Council recommends that substitution should not occur when prescribing and dispensing "generic" medicines that:

- have a narrow therapeutic range.
- have been shown to show erratic intra- and inter-patient pharmacokinetics.
- are contained in dosage forms that are likely to give rise to clinically significant bio-availability problems, e.g. extended or delayed release preparations, as well as those known to be super bioavailable or
- are intended for the critically ill and/or geriatric and paediatric patient.

SASA has endorsed this statement, as many patients having anaesthetics fall into one or more of these categories.

**The World Medical Association Recommendations (Santiago, 2005)** state the following:

**Introduction**

1. The prescription of a drug represents the culmination of a careful deliberative process between physician and patient aimed at the prevention, amelioration or cure of a disease or problem. This deliberative process requires that the physician evaluate a variety of scientific and other data including costs and make an individualised choice of therapy for the patient. Sometimes, however, a pharmacist is required to substitute a different drug for the one prescribed by the physician. The World Medical Association has serious concerns about this practice.

2. Drug substitution can take two forms: generic substitution and therapeutic substitution.

3. In generic substitution, a generic drug is substituted for a brand-name drug. However, both drugs have the same active chemical ingredient, same dosage strength and same dosage form.

4. Therapeutic substitution occurs when a pharmacist substitutes a chemically different drug for the drug that the physician prescribed. The drug substituted by the pharmacist belongs to the same pharmacologic class and/or to the same therapeutic class. However since the two drugs have different chemical structures, adverse outcomes for the patient can occur.

5. The respective roles of physicians and pharmacists in serving the patient's need for optimal drug therapy are outlined in the WMA Statement on the Working Relationship between Physicians and Pharmacists in Medicinal Therapy.

6. The physician should be assured by national regulatory authorities of the bioequivalence and the chemical and therapeutic equivalence of prescription drug products from both multiple and single sources. Quality assurance procedures should be in place to ensure their lot-to-lot bioequivalence and their chemical and therapeutic equivalence.

7. Many considerations should be addressed before prescribing the drug of choice for a particular indication in any given patient. Drug therapy should be individualised based on a complete clinical patient history, current physical findings, all relevant laboratory data and psychosocial factors. Once these primary considerations are met, the physician should then consider comparative costs of similar drug products available to best serve the patient's needs. The physician should select the type and quantity of drug product that he or she considers to be in the best medical and financial interest of the patient.

8. Once the patient gives his or her consent to the drug selected, that drug should not be changed without the consent of the patient and his or her physician. Failure to follow this principle can result in harm to patients. On behalf of patients and physicians alike, National Medical Associations should do everything possible to ensure the implementation of the following recommendations.

**Recommendations (WMA)**

1. Physicians should become familiar with specific laws and/or regulations governing drug substitution where they practise.

2. Pharmacists should be required to dispense the exact chemical, dose and dosage form prescribed by the physician. Once medication has been prescribed and begun, no drug substitution should be made without the prescribing physician's permission.

3. If substitution of a drug product occurs, the physician should carefully monitor and adjust the dose to ensure therapeutic equivalence of the drug products.

4. If drug substitution leads to serious adverse drug reaction or therapeutic failure, the physician should document this finding and report it to appropriate drug regulatory authorities.

5. National Medical Associations should regularly monitor drug substitution issues and keep their members advised on developments that have special relevance for patient care.

6. Appropriate drug regulatory bodies should evaluate and ensure the bioequivalence and the chemical and therapeutic equivalence of all similar drug products, whether generic or brand-name, in order to ensure safe and effective treatment.

7. National Medical Associations should oppose any action to restrict the freedom and the responsibility of the physician to prescribe in the best medical and financial interest of the patient.

8. National Medical Associations should urge national regulatory authorities to declare therapeutic substitution illegal, unless such substitution has the immediate prior consent of the prescribing physician.

**Generic drug substitution in the RSA – is its cost justified?**

Each and every anaesthesiologist needs to decide for him- or herself on the risk-benefit of generics for every patient, and whether the costs are justified.

Scott and Reekie in the South African Medical Journal stated the following:

The causes of the recent rapid increases in health care costs in the RSA are briefly studied. Drug costs have increased largely through the use of new innovations, greater usage and price factors, but price increases have been below the rate of inflation. The savings in drug costs to be expected from the introduction of generic substitution have been calculated to be low in relation to overall health care costs, although of significance in relation to the survival of individual drug manufacturing businesses. The thrust towards generic substitution is possibly misplaced in that the potential savings in hospitalisation costs from the discovery of new drugs are so large that they justify the encouragement of the innovative drug manufacturers.