Date: 10th March 2022.

THE DIFFERENCE BETWEEN A COMBINATION MEDICAL DEVICE AND A REGISTERED MEDICINE

ARE THEY SUBSTITUTABLE?

The purpose of this review is to help differentiate important aspects that define a registered medicine and a combination medical device. Medical Device regulation and registration in South Africa and in fact Southern Africa is in its infancy and product registration policies are still being developed by the Regulators in these regions.

This summary of regulatory requirements and conditions of regulatory authorisation is a motivation prepared in defense of routine therapeutic substitution of a registered medicine with a combination medical device. We argue that a registered medicine, with reference to its therapeutic indication, cannot routinely be substituted with a combination medical device, without considering the regulatory differences.

The Medicines and Related Substance Act 101/1965 (Section 22F) requires that a pharmacist *"shall"* promote the benefits of substitution for a branded medicine of an interchangeable multi-source medicine. However, Section 22F (4) reads that a pharmacist **shall not sell an interchangeable multi-source medicine**— if the person prescribing the medicine has written in his or her own hand on the prescription the words 'no substitution' next to the item prescribed.

"Interchangeable multi-source medicine" is the term used in Act 101/1965 for a generic medicine. Generic medicines undergo robust SAHPRA regulatory and scientific evaluation before they are registered as medicines. Generic medicines contain the same active substances which are identical in strength or concentration, dosage form and route of administration (to the innovator) and "*meet the **same or comparable standards, which comply with the requirements for therapeutic equivalence as prescribed."***

Considering all aspects of the registration and regulatory requirements and frameworks for registered medicines and medical devices, the question of whether the routine substitution of a medicine with a medical device – when the substitution is intended for the same therapeutic outcome – must be questioned.

In addition, is the question of whether a pharmacist is permitted, in his/her scope of practice, to routinely and with confidence substitute a prescribed registered medicine with a (non-registered) medical device – when intended for the same or comparable therapeutic outcome.

Below is a summary of the regulatory framework and environment that defines and distinguished between registered medicines and medical devices, that I hope offers clarity on some of these ethical questions.

REGISTERED MEDICINE	MEDICAL DEVICE
Definitions: Act 101/1965	
"(a) means: any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in- *(i) the diagnosis, **treatment,** mitigation, modification, or **prevention of disease,** abnormal physical or mental state or the symptoms thereof in humans; or* *(ii) restoring, correcting or modifying any somatic or psychic or organic function in humans;"*	*"means any instrument, apparatus, implement, machine, appliance, **implant,** reagent for in vitro use, software, material or other similar or related article, .[...]* *(b) which does not achieve its primary intended action by pharmacological, immunological, or metabolic means, in or on the human or animal body, but which may be assisted in its intended function by such means;" ...* The intention of medical devices is for one or more of the following: (i) diagnosis, prevention, monitoring, treatment, or alleviation of disease. (ii) diagnosis, monitoring, treatment, alleviation of or compensation for an injury. (iii) investigation, replacement, modification, or support of the anatomy or of a physiological process. (iv) supporting or sustaining life. (v) control of conception. (vi) disinfection of medical devices; or (vii) providing information for medical or diagnostic purposes by means of in vitro examination of specimens derived from the human body. which **does not achieve** its primary intended action by **pharmacological, immunological or metabolic** means, in or on the human or animal body, but which may be assisted in its intended function by such means. Combination products constitute a specific group of products consisting of both medicine (active pharmaceutical ingredient) and medical device. In such a case, both constituents (medicine and medical device) are supplied together and intended to be used together for a single medical purpose. The regulatory approach to such products is based on determining the leading product/constituent i.e. the one that is responsible for a primary mode of action. This determination impacts the regulatory classification and registration procedure to be followed.

REGISTERED MEDICINE	MEDICAL DEVICE
	For instance, if a combination product achieves its primary goal through the effect caused by a medicine, while the functionality of a medical device is limited to a merely ancillary action, the product will be considered a registerable medicine.
	The Acid Test of whether a product is a medicine or Medical Device [1] [2]
	"The acid test of whether something is or is not a medical device or an /VD is: what is it used for and how does it work? *The "how" is important because for something to be a medical device, it cannot achieve its primary intended action by pharmacological, immunological, or metabolic means (so a medical device is not a drug or vaccine, for instance). These processes could support the intended functioning of a medical device but would not be the main activity.* *This narrows down. the possibilities somewhat, but the potential range is still extremely wide.* *If the function of an instrument, apparatus, implement, machine, implant, software and the like is intended by the manufacturer to diagnose, prevent, monitor, treat or alleviate disease, then it is a medical device.* *If it is intended to diagnose, monitor, treat, alleviate, or compensate for an injury, it is a medical device.* *The same applies if it is intended to control conception, disinfect medical devices, or support or sustain life.* *It is also a medical device if it is meant to investigate, replace, modify, or support the anatomy or a physiological process.* *All in all, the definition of a medical device is so wide that it has some industry watchers wondering whether it includes*

[1] Bowmans. South Africa: Regulation of Medical Devices is Set to Become a Reality in SA, Julie Oppenheim, dd 30 September 2020.

[2] MCC (SAHPRA) Guideline 2.45 on Borderline Products, dcl March 2017

REGISTERED MEDICINE	MEDICAL DEVICE
	devices such as fitness trackers, which measure the wearer's persona/fitness by monitoring various factors such as heart rate, steps walked and calories consumed. *Chances are that such items are not medical devices as long as they only provide data for the edification of the wearer.* *If used for any form of diagnostics or treatment, however, then it arguably crosses the line into medical device or /VD territory. An iter;n? that almost certainly is a medical device is a blood-glucose monitor that people with diabetes might use to inform them when to take their medication. Another example is an app that sends an emergency signal in the event of a stroke, heart attack or other health crisis.* [3]
Registration as a Medicine	**Classification of Combination Medical Devices**
Medicines in South Africa are subject to a system of scheduling based on the active pharmaceutical ingredients that they contain. The primary consideration in scheduling a substance is its safety profile, in relation to the therapeutic indications for its use e.g., antibiotics such as Gentamicin are listed in the medicine schedules as a S4 medicinal substance. Medicines are required to be fully registered with SAHPRA (South African Health Products Authority) before they are authorized for sale in South Africa. The SAHPRA registration process includes a scientific review of all aspects of quality, safety and efficacy for the product and marketing authorization is conditional on the Applicant meeting the strict SAHPRA licencing standards for all partners in the supply chain, including Licenced Distributors/ Wholesalers. The conditions of registration also include stringent product quality management control, such as pharmacovigilance, post-importation quality analysis, validation of transportation, on-going stability testing, the provision of product quality review reports etc.	Currently, this is based upon a **self-assessment** by the licensed Applicant based upon a set of classification rules supplied by the Regulatory Authority [4], based on:- • the manufacturers or distributor's intended use of the device or IVD; • level of risk to patients, users and other persons (the probability of occurrence of harm and the severity of that harm); • degree of invasiveness in the human body; and • duration of use and exposure. However, the Regulatory Authority has the responsibility and authority to determine the final classification. According to SAHPRA Guidelines medical devices are classified into the following four risk classes, determined according to published classification rules [5] • Class A - Low Risk • Class B - Low-Moderate Risk • Class C - Moderate-high Risk • Class D - High Risk

[3] Bowmans. South Africa: Regulation of Medical Devices is Set to Become a Reality in SA, Julie Oppenheim, dd 30 September 2020.
[4] SAHPRA Guideline 8.05 Classification of Medical Devices and IVDs Aug21v5
[5] SAHPRA Guideline 8.05 Classification of Medical Devices and IVDs

REGISTERED MEDICINE	MEDICAL DEVICE
In addition, the pharmacokinetic profile of the medicine, which supports the main indication of e.g. preventing infection, has been established by means of clinical trials which have been reviewed by the South African Health Products Regulatory Authority (SAHPRA / ex MCC). This falls part of the registered professional leaflet; "Pharmacokinetics".	Where risk relates to the patient, user or to public health [6] The highest risk devices are those that are implantable or invasive and are used in the long term. At this moment, there is no registration procedure for medical devices. A registration call-up program expected to "roll-out" in around 2025. The "call-up" procedure is anticipated to be risk based - which means that Class D Medical Devices will be called up first. As an example, Collagen implants with gentamicin, being a Class D Medical Device, will be amongst the initial registration phase.
Generic / Substitutable Medicines	
What is a Generic Medicine? Interchangeable multi-source medicine (generic medicine) — is defined in terms of the Medicines Act as medicines that contains the same active substances which are identical in strength or concentration, dosage form and route of administration and **meet the same or comparable** standards, which comply with the requirements for therapeutic equivalence as prescribed.	No definition is given for a generic / Interchangeable multi-source medical device.
Generic substitution (Section 22F7; Act 101/1965)	
Section 22F of the Medicines Act states that: (1) A pharmacist shall— (a) inform all members of the public who visit his or her pharmacy with a prescription for dispensing, of the benefits of the substitution for a branded medicine of an interchangeable multi-source medicine; and (b) dispense an interchangeable multi-source medicine instead of the medicine prescribed by a medical practitioner, dentist, practitioner, nurse or other person	There is no provision in law that provides for the routine substitution of, and between, medical devices or that declares medical devices as interchangeable multi-source products. There is no provision in law that allows a pharmacist to routinely substitute therapeutic equivalents – this can only be done by the Healthcare Professional.

[6] Regulations Relating to Medical Devices and In-vitro diagnostic Medical Devices (IVDs) Government Gazette 9 December 2016 No 40480. Regulation 11(1)

REGISTERED MEDICINE	MEDICAL DEVICE
registered under the Health Professions Act, 1974, unless expressly forbidden by the patient to do so. (2) If a pharmacist is forbidden as contemplated in subsection (1)(b), that fact shall be noted by the pharmacist on the prescription. (**3) When an interchangeable multi-source medicine is dispensed by a pharmacist, he or she shall note the brand name or where no such brand name exists, the name of the manufacturer of that interchangeable multi-source medicine in the prescription book.** (4) A pharmacist shall not sell an interchangeable multi-source medicine— (a) if the person prescribing the medicine has written in his or her own hand on the prescription the words 'no substitution' next to the item prescribed. (b) if the retail price of the interchangeable multi-source medicine is higher than that of the prescribed medicine; or (c) **where the product has been declared not substitutable by the Medicines Control Council**.	There is no provision in law that provides for the routine substitution of, and between, medicines and medical devices.
THERAPEUTIC EQUIVALENCE [7]	
2. (1) A medicine is considered therapeutically equivalent to another medicine if both medicines:- (a) Are:- (i) Pharmaceutically equivalent, in that they contain the same amount of active substances in the same dosage form, meet the same or comparable standards and are intended to be administered by the same route; or (ii) Pharmaceutical alternatives, in that they contain the same active moiety but differ either in chemical form of the moiety or in the dosage form or strength; and (b) after adminitration in the same molar dose, their	Therapeutic equivalence as defined in the Regulations only relates to a registered medicine. There is no provision in law that describes a therapeutically equivalent medical device.

[7] Medicines and Related Substance Act, 1965. General Regulations. Government Gazette No 41064, Notice 859. dd 25 August 2017.

REGISTERED MEDICINE	MEDICAL DEVICE
effects with respect to both efficacy and safety are essentially the same. (2) Therapeutic equivalence is determined from comparative bioavailability, pharmacodynamic, clinical or in vitro studues which meet the requirements and accepted criteria for bioequivalence as determined by the Authority.	
REGISTRATION OF MEDICINES IS PRESCRIBED IN TERMS SECTION 14 OF ACT 101/1965	**REGISTRATION CALL-UP PLAN FOR MEDICAL DEVICES[8]**
"14. Prohibition on the sale of medicines, medical devices or IVDs which are subject to registration and are not registered.— *(1) Save as provided in this section or sections 21 and 22A, no person shall sell any medicine, medical device or IVD which is subject to registration by virtue of a declaration published in terms of subsection (2) unless it is registered.* *(2) (a) The Authority may from time to time determine that a medicine, medical device or IVD, or class or category of medicine, medical device or IVD or part of any class or category of medicine, medical devices or IVDs mentioned in the declaration, shall be subject to registration in terms of this Act.* *(b) Any such declaration may also relate only to medicines, medical devices or IVDs which were available for sale in the Republic immediately prior to the date on which it comes into Operation in terms of paragraph (c) or only to medicines, medical devices or IVDs which were not then so available.*	*Although, the Medicines Act and General Regulations provides for the above, SAHPRA's registration process is currently in development. To ensure its mandate that medical devices are safe, effective and of good quality, when SAHPRA registers medical devices, it must "call-up" specific products or product classes for registration by publishing a call-up notice in the Government Gazette.* *A draft call-up plan outlines the steps involved in this process. It explains that SAHPRA will use a risk-based approach in calling up medical devices for registration, prioritising the registration of more risky products and products of public health importance. Product call-ups will cover medical devices that are already on the market in South Africa as well as new medical devices that are being introduced. In the absence of medical device registration, SAHPRA has established several "quasi-registration" requirements as part of its medical device establishment licensing processes to enable oversight and control of medical devices used in South Africa. [9]*

[8] Medical Devices and Consumer Health Products 2021; Fasken Law Practice, dd August 31, 2021
[9] Medical Devices and Consumer Health Products 2021; Fasken Law Practice, dd August 31, 2021

Borderline Products (Ref SAHPRA Guideline 2.45)
[10]

"Health products which cannot be classified as either a pharmaceutical, medical device, cosmetic, food supplement, or biocidal product because they are indistinguishable from one another are referred to as "borderline" products until SAHPRA determines their categorisation status and assigns them to a specific regulatory pathway.

SAHPRA issued a [Borderline] guideline in 2017 to provide applicants with recommendations regarding the registration of borderline and combination products. However, the guideline, which proposes the framework discussed below, has not yet been finalised." [11]

Determination of whether a product is a Medicine or Medical Device will consider the following: *-*

- *The primary mode of action (PMOA} means "the single mode of action of a borderline product that provides the most important therapeutic action of the borderline product."*
- *The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effect(s) of the borderline product.*
- *The claimed effect or purpose must be achieved by the most important therapeutic action.*

Where the primary intended mode of action is achieved by pharmacological, immunological or metabolic means, in or on the human or animal body, the borderline product is designated to be a medicine;
where

- *Immunological - is understood as an action in or on the body by stimulation and/or mobilisation of cells and/or products involved in a specific immune reaction;*
- *Metabolic - is understood as an action which involves an alteration of the normal chemical processes participating in, and available for, normal body function. The fact that a product is itself metabolized does not imply that it achieves its principal intended action by metabolic means; and*
- ***Pharmacological - is understood as an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent and, for the purposes of this policy, includes anti-infective activity.***

Where the primary intended mode of action is achieved by pharmacological, immunological or metabolic means, and the action occurs in vitro, without reintroducing a modified cellular substance to the patient, the product will be designated to be a medical device.

Where the primary intended mode of action by which the claimed effect or purpose is not achieved by pharmacological, immunological, or metabolic means, but may be assisted in that effect or purpose by pharmacological, immunological, or metabolic means, the borderline product (including a combination product) will be designated to be a medical device.

[10] SAHPRA publication; ITG Meeting update, November 2021. Status of Guideline 2.45 (Borderline Products) - Comments under review.
[11] Medical Devices and Consumer Health Products 2021; Fasken Law Practice, dd August 31, 2021

A borderline product may be classified as a medicine or a medical device, even when no explicit therapeutic claim is made. A therapeutic claim may also be implicit. Both types of claims are considered when a product is classified. Explicit claims are stated with no ambiguity with regard to their meaning or intent. In contrast, implicit claims made in the representation of a product indirectly suggest a therapeutic benefit. Product representation includes the appearance, labelling, and advertising of a product.

In the absence of either an explicit or implicit claim, a product may be classified (e.g. as a medicine or a medical device) if the intrinsic properties of the product are such that there is no other possible use. For example, acetaminophen(paracetamol) has no other use but as a medicine, so the absence of a claim will not change its classification as a medicine.

In addition to the primary mode of action - the composition and form of the product and the therapeutic effect of the product may be considered to assist in the designation of the product.

The composition and form of a product may help to distinguish a medicine from a medical device. A medical device exhibits structure in its final therapeutic form, that is, the structure of the product when it is achieving its effect. With a medical device, its structure contributes directly to its effect. In contrast, the physical structure of a medicine (that is, in its dosage form, such as a tablet or an ointment, not its chemical structure) does not usually contribute directly to its therapeutic effect.

Consideration is also given to the therapeutic effect of a product and how this effect is achieved. In Act 101, as amended, the definition of a medicine and medical device differ respectively in whether a product is used to restore, correct or modify any somatic or psychic or organic function (as with a medicine) OR treat or alleviate a disease; treat, alleviate or compensate for an injury, or modify or support of the anatomy or of a physiological process (as with a medical device).

Bonusing and Sampling

This relates to Sections 18A and 188 of Act 101/1965.

18A. Bonusing: Prohibits the supply any medicine, medical device or IVD according to a bonus system, rebate system or any other incentive scheme. **18B. Sampling**: Prohibits sampling of any medicine, medical devices or IVD. *"For the purposes of this section 'sample' means the free supply of products, medical devices or IVDs by a device or IVD establishment, manufacturer or wholesaler or its agent to a pharmacist, medical practitioner, dentist, veterinarian, practitioner, nurse, or other person registered under the Health Professions Act, 1974".* **This includes consignment stock**.	Although Medical Devices are referred to in Sections 18A and 18B of Act 101/1965, Medical Devices currently have a temporary exemption from these sections in the Act, by means of a three-year Section 36 exemption notice

SEP (Single Exit Pricing)	
The Medicines Act provides for a transparent pricing system which incorporates a single exit price (SEP) for medicines and scheduled substances. The SEP is the price at which manufacturers (including importers) are required to sell medicines and scheduled substances to anyone other than the government. A pharmacy, wholesaler, distributor, or any person licensed under the Medicines Act is prohibited from selling a medicine for more than the prescribed SEP, refer Section 22C of the Medicines Act.	
The pricing breakdown of medicines is transparent and is regulated. These prices are published on the Department of Health website. Annual increases are pre-set and pre-determined and published annually in the Government Gazette. Only one SEP increase is permitted annually.	Currently and temporarily not applicable to Medical Devices - temporary exemption granted. There are no regulatory restrictions on the pricing of Medical Devices. Medical Device prices may be fluctuated and changed according to market needs.
Advertising Restrictions	
S4 may only be advertised to the Profession	Class C and D may only be advertised to the Profession. Medical devices are required to be listed in the South African Medical Device Register.
The CPA predominantly sets out the requirements for advertising and marketing of products and services (general, medical or otherwise). The CPA requires that the advertising and marketing of goods is to be done in a manner that is not reasonably likely to imply a false or misleading representation concerning those goods and is not misleading, fraudulent or deceptive in any way. With respect to claims, suppliers are warned in the CPA that strict liability will be imputed onto producers, importers, distributors or retailers of any goods on which inadequate instructions or warnings are provided to the consumer relating to any hazard arising from or associated with the use of the goods.[12]	
General Legislation of Application: Consumer Protection Act (No 68 of2008): A Measure of Risk [13]	
In South Africa, product safety in general is governed by the Consumer Protection Act (No 68 of 2008) (the CPA). The CPA provides for the promotion of a fair, accessible and sustainable marketplace for consumer products and services and for that purpose, establishes national norms and standards relating to consumer protection, provides for improved standards of consumer information, prohibits certain unfair marketing and business practices, promotes responsible consumer behavior, and promotes a consistent legislative and enforcement framework relating to consumer transactions and agreements. This consequently creates an obligation on suppliers of products (from the beginning to the end of a supply chain) to provide healthcare products and medical devices free of defects.[14] *The CPA imposes strict liability on producers or importers, distributors or retailers for any harm caused by a product (which would include medical devices) caused wholly or partly as a consequence of:* • *supplying unsafe goods.*	

[12] Medical Devices and Consumer Health Products 2021; Fasken Law Practice, dd August 31, 2021
[13] Medical Devices and Consumer Health Products 2021; Fasken Law Practice, dd August 31, 2021
[14] Medical Devices and Consumer Health Products 2021; Fasken Law Practice, dd August 31, 2021

- *a product failure, defect, or hazard in any goods; or*
- *inadequate instructions or warnings provided to the consumer pertaining to any hazard arising from or associated with the use of any goods, irrespective of whether the harm resulted from any negligence on the part of the producer, importer, distributor or retailer, as the case may be.*

In summary, and in terms of current regulations:

1. Medical Device establishments are required to be SAHPRA Licensed.
2. The SAHPRA website references a list of locally licenced Companies. This list is open for regulatory transparency and reference.
3. There is currently no formal SAHPRA registration procedure for medical devices yet.
4. A Borderline Medical Device containing active chemical substances: -
    a. Does not achieve its primary intended action by pharmacological means / action.
    b. The pharmacological action of active ingredients in borderline medical devices is secondary and auxiliary to the primary indication of hemostasis.
5. Registered medicines: -
    a. achieve their primary indication by means of pharmacological action i.e. the proven clinical action of e.g. gentamicin;
    b. are supported by vast clinical studies, experience and knowledge that has regulatory review and approval in terms of its registration status.
6. The quality and efficacy of Medicines throughout the distribution chain is assured by means of comprehensive Quality Management systems that are SAHPRA audited. These systems require validation throughout manufacturing, stability, transportation, post-importation quality analysis, Release procedures, distribution, marketing/sales and pharmacovigilance.

Conclusion: -

The routine therapeutic substitution of a registered medicine with a combination medical device is not provided for in either the Pharmacy Act or the Medicines Act and requires careful consideration by the prescribing Healthcare Professional.

The substitution of an innovator medicine with a generic medicine is common-cause and falls within the scope of practice of a pharmacist. This substitution is made easy because the generic is registered by SAHPRA as a generic to the innovator – after careful regulatory scrutiny and registration of the generic medicines' registration application.

The practice of medicine substitution with a medical device, is however, somewhat different and does not fall within the same substitution mandate of a pharmacist as there is no clear (regulatory) certainty and guarantee that the pharmacologic, pharmacodynamic and pharmacokinetic profile and spectrum, and quality of the active ingredient in the medicine can be substituted with the same / or similar active ingredient claimed to be present in the medical device for the purpose of the same clinical outcome.

I argue that a registered therapeutic medicine can only be substituted with another therapeutically registered generic/interchangeable multisource medicine – for the purposes of the same pharmacologic purpose and clinical outcome.

References (available upon request): -

1. Bowmans. South Africa: Regulation of Medical Devices is Set to Become a Reality in SA, Julie Oppenheim, dd 30 September 2020.
2. MCC (SAHPRA) Guideline 2.45 on Borderline Products, dd March 2017.
3. SAHPRA Guideline 8.05 Classification of Medical Devices and IVDs Aug21v5
4. Regulations Relating to Medical Devices and In-vitro diagnostic Medical Devices (IVDs)
5. Government Gazette 9 December 2016 No 40480. Regulation 11(1)
6. Medical Devices and Consumer Health Products 2021; Fasken Law Practice, dd August 31, 2021;
7. SAHPRA publication; ITG Meeting update, November 2021. Status of Guideline 2.45 (Borderline Products) - Comments under review.