Topical treatments:
Pharmaceutical, medical device or cosmetic?

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Abstract
Products for topical use include formulation types such as creams (emulsions), ointments, liquids and gels. Products may look the same, have similar indications and be placed next to each other on the shelf in pharmacies or drug stores, but their regulatory classification may be different. The classification of a pharmaceutical (medicinal) product, medical device or a cosmetic product depends on its intended use, mode of action, composition, physiological properties and the risk which its use may entail. The level of evidence regarding efficacy and safety differs between the product categories. To facilitate informed product choices, a transparent system is required that enables both consumers and professionals to evaluate the scientific evidence regarding the claimed effect on the skin, as well as of the safety assessment and potential adverse effects.

In the EU, products for dry skin and eczema may be classified as pharmaceuticals (ie, medicinal products), medical devices or cosmetics. Products for lice infestation are available as either topical pharmaceuticals or medical devices. Sunscreens are regulated as cosmetics, but similar formulations can be found as medical devices. One of the first internationally acknowledged products for the improvement of fine lines and hyperpigmentation is regulated as a pharmaceutical, whereas topical anti-wrinkle products in general are classified as cosmetics. However, fillers to smooth the skin by injection, such as hyaluronic acid, are classified as medical devices.

Pharmaceuticals are the most stringently regulated product category (see Table 1). As a consequence of the differences in the regulatory burden, an increasing interest in non-pharmaceutical product categories can be seen. In this article, some of the differences between the product categories are discussed, with some aspects from the new European cosmetic regulation highlighted (EC No 1223/209).[1]

Classification and approval

The three classifications of topical products are shown in Figure 1.[2] In cases of doubt, the national competent authorities and national courts assess which regulatory framework applies for a particular formulation on a case-by-case basis.

A pharmaceutical product is defined either by virtue of its "presentation" or its "function". Thus, any substance or combination of substances presented for treating, alleviating or preventing disease in human beings is considered a pharmaceutical if the action is generally achieved by pharmacological action, immunological action or by metabolic action. Furthermore, products which are used in or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action are also covered by the Medicinal Products Directive, 2001/83/EC (ie, definition by virtue of function).

If the function of the product is achieved by physical means (including for example mechanical action and a physical barrier) the product can be classified as a medical device. Medical devices are further divided into different classes which are determined on the intended use and mode of action of the device and also on indications for use (outlined in Annex IX of Council Directive 93/42/EEC). The classification depends on rules that involve the medical device's duration of body contact and its invasive character, which determine the risks connected with the device.

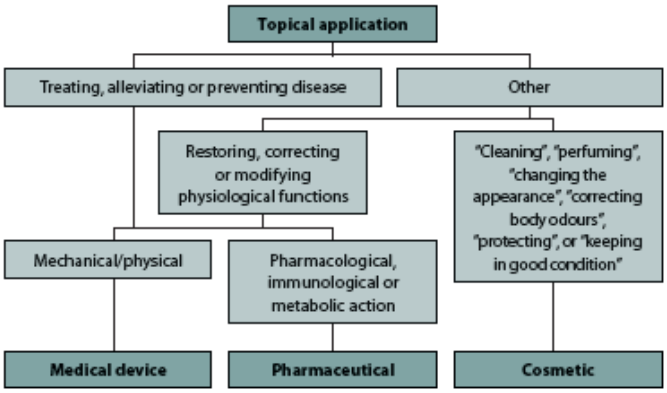
Non-invasive medical devices, which come into contact with skin, are in Class I (low risk) if they are intended to be used as a mechanical barrier, for compression or for absorption of exudates (eg, simple wound dressings). Products for treatment of lice infestation are also Class I if their mode of action is mechanical suffocation and dehydration of lice. Products belong to Class IIb (moderate–high risk) if they are intended to be used principally with wounds which have breached the dermis and can only heal by secondary intervention (eg, chronic ulcerated wounds, dressings for severe burns). Other non-invasive devices are Class IIa (low–moderate risk), including devices principally intended to manage the micro-environment of a wound. Medical devices which contain a substance which can be used separately as a drug (as defined in Article 1 of Directive 2001/83/EC) belong to Class III. Hence, for example, corn plasters containing salicylic acid will be considered as a Class III medical device due to the analgesic properties of salicylic acid, whereas those containing other acids (eg, trichoroacetic acid, nitric acid – defined as chemicals) for the treatment of corns are considered as Class IIa devices.

The principal purpose of a cosmetic product is "cleaning", "perfuming", "changing the appearance", "correcting body odours", "protecting", or "keeping in good condition".[1] However, "keeping in good condition" does not cover prevention of disease. For example, marketing of cosmetics for the treatment of dry skin to prevent relapse of eczema in connection with skin diseases such as atopic dermatitis is not allowed, whereas treatment

Table 1: Overview of differences and similarities in regulatory requirements for topical products.

Parameter	Pharmaceuticals	Medical device (Class I, non-sterile & non-measuring and Class IIa)	Cosmetics
Common formulation types	Emulsions, ointments, liquids, gels	Emulsions, ointments, liquids, gels	Emulsions, ointments, liquids, gels
Pre-market authorisation of product by competent authority	Yes	No	No
Authorisation of good manufacturing practice (GMP) by competent authority	Yes	No. Quality system according to the Medical Device Directive	No. ISO 22716
Mode of action	Changes of physiological functions via pharmacological, immunological and/or metabolic action	Mainly via physical effects, may include changes of physiological functions	Mainly physical, no significant modification of physiological functions via pharmacological, immunological and/or metabolic action
Targeted body regions	Skin, hair, teeth, inner and outer genitalia/vulva, nasal cavity, ear canal	Skin, hair, teeth, inner and outer genitalia/vulva, nasal cavity, ear canal	Skin, hair, teeth and outer genitalia and mucosa in the mouth
Marketing, presentation	Treatment and/or prevention of diseases	Treatment and/or prevention of diseases	No reference to diseases
Proof of efficacy/effectiveness	Assessed and approved by competent authority	Self-certification. No external approvals for Class I. Other classes approved by notified body	No external approvals, but consumers can request certain product-related information in order to make informed product choices
Safety assessment	Assessed and approved by competent authority	No external approvals for Class I. Other classes approved by notified body	No external approvals
Shelf life/expiry date	'EXP' (for expiry date) 'Do not use after the expiry date'	Expiry date or the symbol: 	"Best used before the end of" or any of the symbols with information: 
Consumer information on possible side effects	In Package Leaflet (PIL).	In Instruction for Use (IFU).	May be labelled, but is available on demand by the consumer.

Figure 1: Determining the classification of a topical product (medical device, pharmaceutical or cosmetic) dependent on its presentation and mode of action.



of dryness in connection with cold and arid weather may be allowed as long as no reference to disease is made by the company. Sunscreens for the prevention of sunburn are regulated as cosmetics, but sunscreens for the prevention of skin cancer are also available as medical devices.

Pharmaceuticals need to be approved by the competent authority before being placed on the market. In contrast, cosmetics need only to be 'notified'. The authorisation of medical devices is guaranteed by a Declaration of Conformity made by the company. The manufacturer alone takes full responsibility for the assessment of the conformity of a Class I device (except sterile devices and those used to measure a function) and to certify its product. A notified body must be involved for Class IIa devices, whereas devices with a high risk potential, Classes IIb and III, also require inspection by a notified body with regard to both the design and manufacture of the devices.

Presentation and warnings

Medical devices can easily be distinguished from medicines and cosmetics by their CE marking. It may be more complicated to identify and distinguish between pharmaceuticals and cosmetics from the labels on the outer packaging. Pharmaceutical products typically reference the active ingredient (often with the dose) on the principal display panel and should have an authorisation number somewhere on the packaging.

Pharmaceuticals are also required to carry the warning: 'Do not use after the expiry date'. Cosmetics, too, are required to carry this warning if they have a shelf life of 30 months or less. The new Cosmetics Regulation allows cosmetic products to carry the same type of symbol as used on medical devices to denote an expiry date. If the cosmetic product has a shelf life longer than 30 months, it can carry an open jar symbol together with a figure denoting a 'period after opening' during which the product can be used (the 'PAO symbol'). Of the three classifications, only a cosmetic product can carry the PAO symbol (see Table 1).

The nomenclature for ingredient labelling is not harmonised for the three regulatory categories of topical products, although there is some overlap. This can make it complicated for consumers to avoid products with substances for which they have known contact allergies, such as preservatives.[3] The three different categories may carry differing precautions and warnings on their products. For example, commonly used ingredients such as emulsifiers, fatty ingredients and preservatives are highlighted as potential causes for irritation and other adverse skin reactions on the package leaflets (PILs) of pharmaceuticals.[4] These same ingredients used in a cosmetic or medical device would not typically require any special warnings. On the other hand, take the case of Benzalkonium Chloride. Its use is allowed in cosmetics as a preservative but a warning is required on the label to 'avoid contact with the eyes'.[1] In contrast, it is commonly used as a preservative for eye products which are classified as medical devices or pharmaceuticals, and no warning is required in these instances. Furthermore, fragrance ingredients known to sometimes cause contact allergy need to be labelled on cosmetics if the content is above 10 ppm in leave-on products and 100 ppm in rinse-off products,[1] whereas no labelling is required on pharmaceuticals and medical devices, as the safety can be assessed on a case-by-case basis for these product categories.

Safety and efficacy

Safety assessments of pharmaceutical products must be approved by the competent authorities before such products are placed on the market, whereas no external approvals are required for Class I medical devices or cosmetics. However, safety assessments of higher-risk medical devices have to be approved by the notified bodies prior to certifications of conformity. The new Cosmetics Regulation includes clearer requirements for manufacturers to conduct a safety assessment and supply a product safety report prior to placing a cosmetic product onto the market. In order to increase safety and to facilitate the safety assessments of cosmetics, more than 1,000 substances are identified as forbidden in cosmetic products and almost 300 substances may be used only in accordance with the restrictions laid down in the Regulation.[1] In addition, approximately 150 colourants, almost 30 ultraviolet filters and almost 60 preservatives are approved for use in cosmetics.[1] However, the animal testing ban on cosmetic products and ingredients makes the future assurance of safety more complex. The testing ban on finished cosmetic products has long been in effect, while the testing ban on ingredients or combinations of ingredients will apply step by step as soon as alternative methods are validated and adopted, but with a maximum cut-off date of six years after the Directive comes into force, ie, March 2013, irrespective of the availability of alternative non-animal tests.[5]

The safety assessment of cosmetics does not cover risk identification, as is the case for pharmaceuticals and medical devices. This means there is less chance of detecting possible adverse effects prior to market launch of a cosmetics product. However, while not required at this point in time, the methodology may well be applied to cosmetics in the future, as a number of ingredients with pharmacological effects are used in cosmetics.

For example, anti-ageing products which claim to contain ingredients with effects on skin structure, cell differentiation, etc, may well increase the risk of unwanted effects. Tretinoin (retinoic acid) is one of few substances with proven effects on symptoms of ageing skin, but this drug substance is banned in cosmetics.[1]

Market surveillance

The intergovernmental rapid alert system, Rapex, which operates when unsafe consumer products appear on the market within the EU, has previously identified illegal levels of a carcinogen in an eyeliner and skin-lighteners containing glucocorticoids.

For the three product categories, the responsible manufacturer needs to have a post-market surveillance and vigilance system in place which describes the processes for collection of complaints/incidents and potential product recalls. The vigilance system for pharmaceuticals is regularly inspected and approved by the competent authority, whereas for cosmetics and Class I medical devices it is the responsibility of the company to fulfil the legal requirements and produce evidence on inspection. With the new Cosmetics Regulation, serious undesirable effects now need to be notified to the authorities[1] in a manner similar to that which has long been required for pharmaceuticals and medical devices.

The future

The differences in regulatory requirements between the three different topical product categories are gradually being erased by the increase in requirements on the less regulated categories, ie, medical devices and cosmetics. However, the complexity and regulatory burden for topical pharmaceuticals are also being increased. It is therefore likely that the market share will grow for medical devices and cosmetics which target both diseases and changes of the physiological functions of the skin. It is important that users of these products and those approving and recommending such products to patients and consumers are aware of the differences in the level of evidence regarding efficacy and safety. A transparent system that enables both consumers and professionals to understand the scientific evidence regarding claimed effects on the skin, as well as of the safety assessment and potential adverse effects, should facilitate informed product choices.

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