Combination products: EU regulatory considerations

In this second continuing professional development supplement, we discuss considerations for determining the classification of products that combine both a device and medicinal product component, and outline the appropriate regulatory route for such combinations. We also examine the differences in approach between the medical device and medicinal product sectors.

KEYWORDS: CE certification; Medical device; Medicinal product; Usability; Borderline product; Ancillary medicinal substance; Drug delivery; Competent authority (CA); Notified body (NB).

The term “combination product” is a widely, but misused, expression, as there is no clear European definition, unlike in the US (FDA 21 CFR 3.2(e)). In Europe, for products that contain both a medical device and medicinal product element, the “combined” product is regulated as either a medical device or medicinal product and the scrutiny required differs significantly between the two routes.

Classification

The classification of a product as either a medical device or medicinal product depends on a few key factors, including: the presentation of the product on the market and product characteristics; the manufacturer’s intended purpose for the product; and the principal mode of action. The European definitions for both medical device and medicinal product are the key starting point to determining the appropriate classification of the combined product:

1. A medical device that is intended to administer a medicinal product, where the medicinal product is not integral, is regulated as a medical device under Medical Device Directive (MDD) 93/32/EC. An insulin pump is an example of such a device. Classification of the medical device is based on risk and is conducted following the classification rules detailed in Annex IX of MDD 93/32/EC as amended by 2007/47/EC.

2. A medical device that is placed on the market with an integral medicinal product is regulated as a medicinal product under Directive 2001/83/EC, eg, an autoinjector pen containing insulin.

3. A medical device that incorporates, as an integral part, a substance that if used separately can be considered to be a medicinal product or human blood derivative, but where the action of the medicinal product/blood derivative is ancillary, is regulated as a Class III medical device under Rule 13 of the MDD, eg, antimicrobial catheters, antibiotic-loaded bone cements.

4. A medical device that is placed on the market with an integral advanced therapy medicinal product (ATMP) is regulated under the Advanced Therapy Medicinal Product Regulation (EC) No 1394/2007, eg, autologous chondrocytes seeded onto collagen membrane to repair cartilage.

As a general rule of thumb, medical devices act by physical means while medicinal products act by pharmacological, metabolic or immunological means. However, it is also worth noting that Article 2(1) of Directive 2001/83/EC, as amended, states that: “In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a “medicinal product” and within the definition of a product covered by other Community legislation the provisions of this Directive shall apply.” This clause is often used in cases where there are insufficient scientific data available to provide clear evidence of the principal mode of action; in these cases the product shall be regulated as a medicinal product.

With technological advancements especially in the development of materials, the ease of differentiation of the principal mode of action between a medical device (physical) function and medicinal product action has become more difficult, with many more products falling into the borderline area requiring advice from competent authorities (CAs) or if necessary the working group on borderline and classification. This group is chaired by the European Commission and is composed of representatives of all member states of EU, EFTA and other stakeholders, with each product considered on a case-by-case basis. The working group issues a manual of borderline opinions on a bi-annual basis which provides non-legally binding guidance on a range of borderline products and the consensus of opinion reached by the group.

Procedure for a device containing an ancillary medicinal substance

In instances where the combination product is considered a medical device, ie, the device contains an ancillary medicinal substance or ancillary human blood derivative under Rule 13, the device must be CE marked before being placed on the market in the EU. The conformity assessment routes available for Class III medical devices are summarised in Figure 1 (overleaf). Most manufacturers follow the full quality assurance (FQA) and design examination (DE) route to conformity as detailed in Annex II of the MDD.

The alternative conformity assessment route for Class III medical devices is by following Annex III: Type examination by notified body (NB), and either Annex IV, in which every device/batch verified by an NB (for non-sterile products only) or Annex V: Production quality
assurance audit by an NB to ISO 13485:2016 (excluding design). However, the costs to set up and validate the testing required to conduct type examination testing are extremely high, making this a rarely followed conformity assessment route.

The conformity assessment process is conducted by an EU NB which must have scope for such assessment and Essential Requirement (ER) 7.4, Annex I of the MDD is applicable. Conformance to ER 7.4 requires that the “quality, safety and usefulness of the substance must be verified by analogy with the methods specified in Annex I to Directive 2001/83/EC.”

The NB is required to seek a scientific opinion from any CA designated by the EU member states or the EMA through Regulation (EC) No 726/2004. Note that an EMA consultation following Regulation (EC) 726/2004 is also applicable regulation and consultation route required for medicinal products developed by biotechnological processes, including recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells; and hybridoma and monoclonal antibody methods.

This supplement offers regulatory professionals an accessible way to use Regulatory Rapporteur as starting point for recording their LLH hours and help gain or maintain MTOPRA status.

Supplements will be archived online and will build up to become a repository of CPD exercises – pitched at different levels of regulatory experience – that members can access free as and when they require them.

CLASSIFICATION CONSIDERATIONS AND BORDERLINE CASES

Medicine

“Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.” (Medicinal Products Directive 2001/83/EC as amended, Article 1)

Medical device: “Any instrument, apparatus, appliance material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used on human beings for the purpose of:

- Diagnosis, prevention, monitoring, treatment or alleviation of disease
- Diagnosis, monitoring, treatment, or alleviation of or compensation for an injury or handicap
- Investigation, replacement or modification of the anatomy or of a physiological process
- Control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.” (Medical Devices Directive 2007/47/EC)

Food

“Any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be, ingested by humans…” Food shall not include... medicinal products within the meaning of Council Directive 65/65/EC (now Directive 2001/83/EC). (The General Food Law Regulation (EC) 178/2002, Article 2.)

Novel food

A food or food ingredient that does not have a significant history of consumption within the EU before 15 May 1997. (Novel Food Regulation 258/1997)

Food with health claims

These are foodstuffs which have health or nutritional claims associated with them based on their nutrient profiles. (Nutrition and Health Claims Regulation (EC) No 1924/2006)

Food supplement

“Foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiologica effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities.” (EU Food Supplements Directive 2002/46/EC)

Cosmetic

“Any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours.” (EU Cosmetics Regulation (EC) No. 1223/2009, Article 2 (1a))

Electronic cigarette

“A product that can be used for consumption of nicotine-containing vapour via a mouth piece, or any component of that product, including a cartridge, a tank and the device without cartridge or tank. Electronic cigarettes can be disposable or refillable by means of a refill container and a tank, or rechargeable with single-use cartridges.” (Tobacco Directive 2014/40/EU)

With the publication of the Medical Device Regulation now expected in May 2017, updates on any impacts of this new regulation on combination products will appear in later editions.

References

Case study:

Exploring the borders

The category of borderline products is an increasingly challenging area to work with. More combined products are entering the marketplace (such as drug-device combinations) and whole new product categories have been created, eg, electronic cigarettes ("e-cigarettes").

In order to determine the status of the product, it is important to: identify the primary intended purpose; establish claims; identify any pharmacological, metabolic or immunological properties of the ingredients (ie, what is the principle mode of action?); consider how it is presented; compare it with similar licensed or registered products (if applicable); and ensure company-wide agreement. In theory, this seems straightforward, but the reality can be quite different and hence it is important to be familiar with the definitions (see Classifications panel).

It can be extremely difficult to determine the status of a borderline product and on these occasions, it is important to seek advice. Many EU member states have a webpage dedicated to borderline products and it is often possible to complete an online form in order to obtain guidance.*

Example 1 – Weight-loss product: The primary intended purpose of a “slimming/dieting product” is to help someone to lose weight.

Scenario 1: The product claims that it will “make you lose weight by increasing your metabolic rate”. This is a medicinal claim, ie, it will “make you lose weight” and also it is modifying the body’s physiological function by “increasing your metabolic rate”. The packaging includes the brand name “Fat Burner” and images of decreasing dress sizes. “Fat Burner” implies an increased metabolic rate and the images further support this implied claim. Therefore, the product is a medicine.

Scenario 2: The product claims that “combined with a healthy diet and regular exercise it may help you to lose weight”. The label explains that the product acts as a bulking agent making you feel full and, therefore, you are likely to eat less. This is a physical action and does not modify the body’s physiological function. The brand name is “Gut-full” and the packaging includes a stomach with a smiley face drawn on it. This is still a “slimming/dieting product” but because of the way it is presented and its physical action, ie, bulking, in this instance the product is a medical device.

Example 2 – Spot/pimple product: The primary intended purpose of this product is to make the spot (or pimple) disappear.

Scenario 1: The product claims that it is a “tinted cream with antibacterial properties which will conceal and treat the spot”. From this it is clear that the cream is being used as a treatment to restore the skin back to normal and therefore is a medicine.

Scenario 2: The product claims that it is a “tinted cream which will conceal the spot”. In this instance, the cream is being used to cover up and disguise the spot and therefore it will “disappear”. Consequently, the product is a cosmetic because it is applied to the skin to change the appearance of the spot, ie, to conceal it.

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1. Which would be classed as a medicinal product under Directive 2001/83/EC?
   a) A Salbutamol dry powder inhaler device
   b) Drug-eluting coronary stents
   c) Heparin-coated catheters

2. Which of the following is not classified as a Rule 13 medical device?
   a) Biologic wound-care products containing antimicrobial agents
   b) Antibacterial-releasing dental restorative materials
   c) Autologous chondrocytes seeded onto collagen membrane to repair cartilage

3. An e-cigarette product advertisement states that it can be used in no-smoking areas to simulate smoking and although it does contain nicotine, it is less than 20 mg/ml of fluid. In this instance, no medicinal claim is being made and the level of nicotine is below the medicinal limit. Which directive must the e-cigarette must comply with?
   a) Tobacco Directive
   b) Medical Device Directive
   c) Local government regulators, for example, UK Trading Standards

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We hope you find this CPD supplement and the assessment useful. We welcome any feedback you may have on the content, format and assessment process. If you would like to contact us about any of the above or have a CPD-related question please email publications@topra.org.

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• Currently engaged in the field of regulatory affairs
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Contact membership@topra.org if you have any queries on moving from member to ‘registered’ member status.

*Please note: Employees in support companies, such as recruitment agencies, with no background, experience and/ or relevant qualification in healthcare regulatory practice are not eligible. Contact membership@topra.org if you have any queries.

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