Introduction
What is a combination product? Is it a combination of more than one active pharmaceutical ingredient in a medicinal product dosage form, or can it mean a mixture of products such as a combination of a medical device and medicinal product?

The term “combination product” is a widely but misused expression, as there is no clear definition in Europe as to what a “combination product” is, unlike in the US where the FDA has a clear definition of a combination product in 21 CFR 3.2(e). The term is applied most commonly when referring to products having both a device and drug element. This is incorrect because, in Europe, such combinations are regulated as either a medical device or a medicinal product, the principle mode of action for the combination determining the classification of products that combine both device or medicinal product and the scrutiny required differs significantly between the two routes. The possible scenarios of where a medicinal product may be combined with a medical device and the regulatory option for that combination are as follows:

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 2010/83/EC. Examples include an autoinjector pen containing insulin, or a Salbutamol dry powder inhaler device.
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. Examples of these types of devices include drug-eluting coronary stents, heparin-coated catheters and wound-care dressings containing an antimicrobial agent.
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. An example would be autologous chondrocytes seeded onto collagen membrane to repair cartilage.

Key differences in devices vs medicines regulation
As mentioned above, the medical device sector is a very different world from that of the medicinal product sector, so the development of a product combining elements from both worlds does require the expertise from both sectors and often poses many challenges for development teams. For medical devices, development is usually based on the ongoing incremental improvements to the device design and speed to market is key. Time to market in the medical device sector is quite rapid and a three-month CE certification approval timescale from the application to a notified body (NB) is not unusual.

To place a medical device on the market in Europe a CE certificate is required, and once granted this allows instant market access across all EU member states and European Free Trade Association (EFTA) countries simultaneously. CE certificates are issued following the satisfactory evaluation of the technical documentation against the Essential Requirements (ER) of the MDD, ie, the “conformity assessment” process. CE certificates are issued by an NB who is designated to perform this task by the designating authority in their country.

Due to the vast variety in medical devices, the Directive has been written from a proportional perspective, eg, devices are classified based on risk, and the depth of scrutiny applied for conformity assessment depends on the classification and risk of the device...
The manufacturer's intended purpose for the product

The presentation of the product on the market and product characteristics

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.

A medical device as defined in Article 1(2)a of Directive 93/42/EEC, as amended, is as follows: "Medical device’ means any instrument, apparatus, appliance, material or other article, whether actuated by manual or mechanical means, but which may be assisted in its function by such means.”

Rule 13 of the MDD does allow for the incorporation of a known medicinal product or human blood derivative and states:

“All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 2001/83/EC, and which is liable to act on the human body with action ancillary to that of the devices, are in Class III. All devices incorporating, as an integral part, a human blood derivative are in Class III.”

Examples of medical devices that fall under Rule 13 of the MDD include drug-eluting coronary stents, dressings/plasters incorporating silver, antimicrobial catheters, antibiotic-loaded bone cements, antibacterial-releasing dental restorative materials, biologic wound-care products containing antimicrobial agents.

A medicinal product as defined in Article 1(2) of Directive 2001/83/EC, as amended, is as follows:

"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.

As a general rule of thumb, medical devices act by physical means while medicinal products act by pharmacological, metabolic or immunological means.

It is also worth noting that Article 2(2) 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.*”

The “in case of doubt” clause is often used in cases where there is 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 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, while this isn’t a legally binding document, does provide guidance on a range of borderline products and the consensus of opinion reached by the group.

Another point to note is that across the EU CAs, there are differing opinions in terms of product regulation whereby a product has a physical mode of action but is administered orally, such as products for constipation, simethicone products for flatulence or anti-reflux products. In general, these products are regulated as medicinal products; however, this opinion does vary across member states at this stage so it is important to be aware of the regional differences.

Given the complexity of many borderline products and the impact that taking an incorrect regulatory pathway could have on the costs and timelines, it is vital to consider the classification of products early on in the development process and where necessary discuss the details and regulatory strategy with either an NB or a CA.

**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.

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 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 13485:2003 (excluding design). Due to the complex

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**Figure 1: Class III medical device conformity assessment routes.**

Diagram showing the various routes to CE marking for Class III medical devices, including Annex II: Full quality assurance, Audit by a notified body to ISO 13485:2003, Annex III: Type examination by a notified body, Annex IV: Every device/batch verified by a notified body (non-sterile products only), Annex V: Production quality assurance audit by a notified body to ISO 13485:2003 (excluding design), with various permutations of these routes leading to the declaration of conformity and CE marking.
nature of such medical devices, 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 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 the 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
- Hybridoma and monoclonal antibody methods.

A common misconception is that the NB must use the CA in its own country; however, there are many factors that are taken into consideration when selecting the appropriate CA with which to consult, including but not limited to:

- CA’s knowledge of the active substance manufacturer and prior knowledge of the active substance master file (ASMF)
- CA’s experience of such consultations and resource availability to take on this work
- CA’s in-house technical expertise for certain medical device types.

The NB is responsible for seeking the opinion from the CA and prior to the submission of the consultation documentation, the NB must review the manufacturer’s documentation and verify the usefulness of the ancillary medicinal substance/human blood derivative within the device, including the provision of an opinion on the clinical benefit–risk profile for the incorporation of the substance into the device.

The consultation process can take up to 210 days following the receipt and validation of the documentation by the CA/EMA, with clock stops for questions. In reality, the average time for the conduct and completion of a consultation is nine months. On completion of the assessment, the CA issues a report to the NB detailing either a positive or negative opinion.

For devices containing ancillary human blood derivatives/recombinant DNA technology, a consultation with the EMA is mandatory and the EMA decision is final, therefore if the outcome is negative, the NB must not issue the CE certificate. While the Directive does not explicitly state this for consultations conducted with CAs, it would be extremely unusual for an NB to ignore the final opinion of a competent authority. In all cases, the NB is required to provide the CA/EMA with the conclusions of its assessment and the decision to either issue or not issue the CE certificate.

Changes made to devices post-CE certification
Changes are natural developments in any product lifecycle and are often introduced to make processes more efficient or add new suppliers or manufacturing sites. Where changes are made to a medical device containing an ancillary medicinal substance, the manufacturer should inform the NB of the proposed change prior to implementation. Depending on the impact of the change on the quality or safety of the ancillary medicinal substance, the NB may need to conduct a supplemental consultation with the medicines competent authority involved in the initial consultation, in order to confirm that the quality and safety of the ancillary substance is maintained. This supplemental consultation process is normally on a shorter timescale (one to three months); however, this timeline does depend on the significance of the change and potential impacts.

Common issues for medical device manufacturers
One of the greatest challenges that a medical device manufacturer may be faced with when developing a device containing an ancillary medicinal substance can be the active substance supply. Medical device manufacturers usually require much smaller quantities of drug substance as the amount loaded per device is usually far lower than levels used for pharmaceutical dosage forms, since the desired effect from the drug is usually local rather than reliant on absorption of the drug systemically with potential drug losses through first-pass metabolic action. Device manufacturers may only require gram quantities annually to satisfy their commercial scale production and find they are not considered a significant customer, making negotiations difficult, but it is important that device manufacturers obtain all the necessary quality information regarding the manufacture of the drug substance. A drug substance supply having a EDQM [European Directorate for the Quality of Medicines & HealthCare] certificate of suitability or a European ASMF are the ideal situations, otherwise a more extensive evaluation of the quality aspects for the drug supply will be required.

For devices utilising human blood derivatives, the EMA requires the device manufacturer to have full access to the Quality Module of the plasma master file, and include this as part of the application for consultation, even when the device manufacturer incorporates an already approved medicinal product. No exceptions to this are made, so it is a vital early-stage discussion when assessing potential drug suppliers.

Medicinal product approval route for a combination product
Medicinal product approvals are conducted either as a national application, via the mutual recognition, decentralised or centralised procedure (MRP/DCP/CP). The application is made by the manufacturer to CA and documentation on the quality, safety and efficacy of the medicinal product should be compiled in line with eCTD requirements.

For medicinal products with an integral delivery device element, the details of the device aspects are included in the Quality Module of the submission documentation and it is the responsibility of the CA to assess this documentation. The level of detail on the device that is required as part of the submission is unclear, and varies between CAs. Directive 2001/83/EC also does not appear to include any provisions for the assessment of the device aspects; however, the device should comply with Annex I of the MDD, This gap is widely recognised by CAs across Europe, with increasing focus being placed on the device assessment, especially as these devices increase in complexity.

In general, for medicinal products having a device element, CAs accept the CE certificate for many drug delivery devices, so if available these may be included in the medicinal product submission documentation. However, in the cases whereby the device is only placed on the market integral with the medicinal product, while CE certification of the device is not possible, an NB may evaluate the technical documentation for the device against the requirements of Annex I of the MDD and provide a detailed report of the assessment for submission to the CA.
Advanced therapies legislation

The known gap in Directive 2001/83/EC with respect to the assessment process for integral device aspects was addressed within the ATMP Regulation, which clearly details the expectations for the review process where an ATMP has an integral device aspect. Regulation (EC) 1394/2007 accepts the CE certification of such a device as part of the submission or, in the absence of CE certification, makes provision for EMA to consult with an NB on the device aspects and its conformity to the MDD.

The future for combination products in the EU

In the medical device sector, the long awaited Medical Device Regulation is nearing consensus and is anticipated to be finalised by early 2016, with a three-year transition period.

The Medical Device Regulation has many potential significant impacts for medical device manufacturers including the requirement for a “person responsible for regulatory compliance”, the possibility for a pre-market approval process and the concept of the designation of special NBs by the EMA for devices with ancillary medicinal substance/ utilising animal tissue or drug delivery devices. While we wait to see the final outcome in terms of implementation for many of the above concepts, it is acknowledged that the new Regulation appears to be moving closer to the concepts associated with medicinal product legislation.

With respect to medicinal products regulation, work is underway by CAs to provide better clarity on the assessment process for the medical device component when integral to a medicinal product, with the possibility of a consultation by CA with an NB. There is also increased emphasis on the data to support the usability of the device, following perhaps the FDA’s approach and guidance on this subject area.

The development of combination products continues to show good growth, with an estimated global value of US$115.1 billion in 2019; so the only certainty is that this area of health technology remains an exciting and challenging sector for medical device manufacturers, pharmaceutical companies, notified bodies and the regulatory bodies of the EU.

References