



Regulatory Strategy for Drug-Device Combinations

By John Worroll

Introduction

Drug-device combinations have always been a challenge to the regulatory approval process. The main problem for the manufacturer can be determining on which side of the drug/device borderline the product falls and hence whether it will be regulated as a medicine or as medical device.

This article discusses the decisions taken during the early stages of product development which will have a crucial influence on the product's regulatory pathway and hence its time to market.

The basic options are either:

- CE marking as a medical device under the Medical Devices Directive 93/42/EEC or the Active Implantable Medical Device Directive 90/385/EC
or
- Licensing as a medicinal product under Directive 2001/83/EC, as amended

These two regulatory regimes are intended to be mutually exclusive and not to apply cumulatively. Which regime the product falls under depends on its intended purpose and mode of action. As the two regulatory regimes are radically different, the regulatory consequences of this decision can have a big effect on the time and cost of taking the product through the approval process and hence to market. The options, in order of increasing difficulty, are:

1. CE marking as a medical device below Class III; relatively straightforward. **Approximate time to market: 3-9 months**
2. CE marking as a medical device in Class III; a design dossier approval process is needed in addition to option 1. **Approximate time to market: 6-12 months**
3. CE marking as a medical device in Class III with a drug assisting the intended action; the notified body (NB) carrying out the design dossier approval must also consult a medicines competent authority. This can add several months to the timeframe relative to option 2. **Approximate time to market: 9-18 months**
4. Licensing as a drug; carried out through a drug regulator authority. This can be a long, arduous process especially for a company not experienced in this field. **Approximate time to market: 12-24 months.** The length of this process may drastically reduce the product's commercial viability.

In terms of time to market, options 1 and 2 are clearly preferable with option 3 taking a bit longer and option 4 to be avoided if at all possible. However, before setting off on any one of these paths, it is essential that the manufacturer and Notified Body are entirely comfortable with the agreed classification. Finding out half-way through that the approval process has to move up one or two notches can be inconvenient and expensive at best, and disastrous at worst. Therefore, it is best to stay away from the borderlines if at all possible, and the best time to ensure this is during the product specification phase.

Determining and Specifying the Product Intended Purpose

1. Definition of a medical device

In order for a product to fall under the medical devices directives, it must meet the definition of a medical device, given in Article 1.2(a) of 93/42/EEC, quoted below:

any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- *diagnosis, prevention, monitoring, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, 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.*

In other words, a medical device is anything (solid, liquid, gas or software) which has:

- a) a medical purpose and.....
- b) an action which is primarily physical as opposed to pharmaceutical

Copious guidance exists on what constitutes a medical purpose, so in this article we will focus on the device mode of action.

2. Definition of physical and pharmaceutical action

The part of the definition relevant to drug-device combinations is the last paragraph of the definition which says, in effect, that a medical device must achieve its principal intended action by means which are primarily physical as opposed to pharmaceutical. The relevant guidance is in MEDDEV 2.1/3 Drug Device Borderlines¹ which further defines “pharmaceutical”:

“Pharmaceutical includes pharmacological, immunological and metabolic ...”:

“Pharmacological means” *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. Although not a*

completely reliable criterion, the presence of a dose-response correlation is indicative of a pharmacological effect.

“Immunological means” 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 means” is understood as an action which involves an alteration, including stopping, starting or changing the speed of the normal chemical processes participating in and available for, normal body function.

The MEDDEV goes on to say that the fact that a product is itself metabolised does not imply that it achieves its principal intended action by metabolic means. In fact, there are many medical devices, such as absorbable sutures, which are absorbed into the body once they have achieved their (physical) purpose.

It is usually obvious if a substance is or is not acting pharmaceutically, but in cases of doubt it is best to seek expert advice, for example from a pharmacologist or a drugs regulatory agency such as MHRA.

3. Discussion of ancillary action

If a product is assisted in its function by a substance acting as a drug, the question is whether the assistance is ancillary with respect to the principal intended action of the product. This can be a subjective judgment and the claims made for the product can be crucial in deciding its “principal” and “ancillary” actions. A simple example is an anaesthetising lubricant for use with a urinary catheter where the decision may turn on whether the product is described as either:

- An anaesthetic gel with lubricant
- or
- A lubricating gel with added anaesthetic action

The first is clearly a medicinal product and will need to be licensed as a drug, while the second may well be a Class III combination medical device needing a Design Dossier review and a drug competent authority consultation.

The MEDDEV uses bone cements to illustrate the same point, saying that a plain bone cement without antibiotics is a medical device since it achieves its principal intended action (the fixation of a prosthesis) by physical means. However, some bone cements also contain antibiotics, while retaining the principal intended action of the fixation of a prosthesis. Such bone cements are classified as combination medical devices as the action of the antibiotic is clearly ancillary. Finally, if the principal intended action of the cement is to deliver the antibiotic, the product becomes a pharmaceutical and will need a Product Licence

Once it has been established that a product is a drug-device combination, and therefore falls under the medical devices directive, Rule 13 of Annex IX may apply:

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 the 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.

4. Discussion of “liable to act on the human body”

The crucial point in the above rule is whether the substance is **liable** to act on the human body, and not whether the manufacturer **intends** it to act on the human body. Therefore, a surgical drape coated with an antimicrobial agent might not fall under Rule 13, but surgical gloves coated with the same substance probably would. In the former case, it is unlikely that the antimicrobial would act on the patient, but in the latter case it is highly likely, even though that may not have been the manufacturer’s original intention.

The above point is also illustrated in the Commission’s Borderline Manual discussion of examination gloves coated with PHMB where it talks of the “risk” that the medicinal substance will act upon the human body, as distinct from the manufacturer’s intention.

Similarly, dressings containing silver (an antimicrobial agent) are classified as Class III under Rule 13 unless the manufacturer can prove via clinical and scientific data, using suitably rigorous testing, that the silver does not leach out of the device and thereby act on the patient. In the absence of such data, the default position is for the device to be classified as Class III under Rule 13.

5. Conclusions: How to reduce uncertainty?

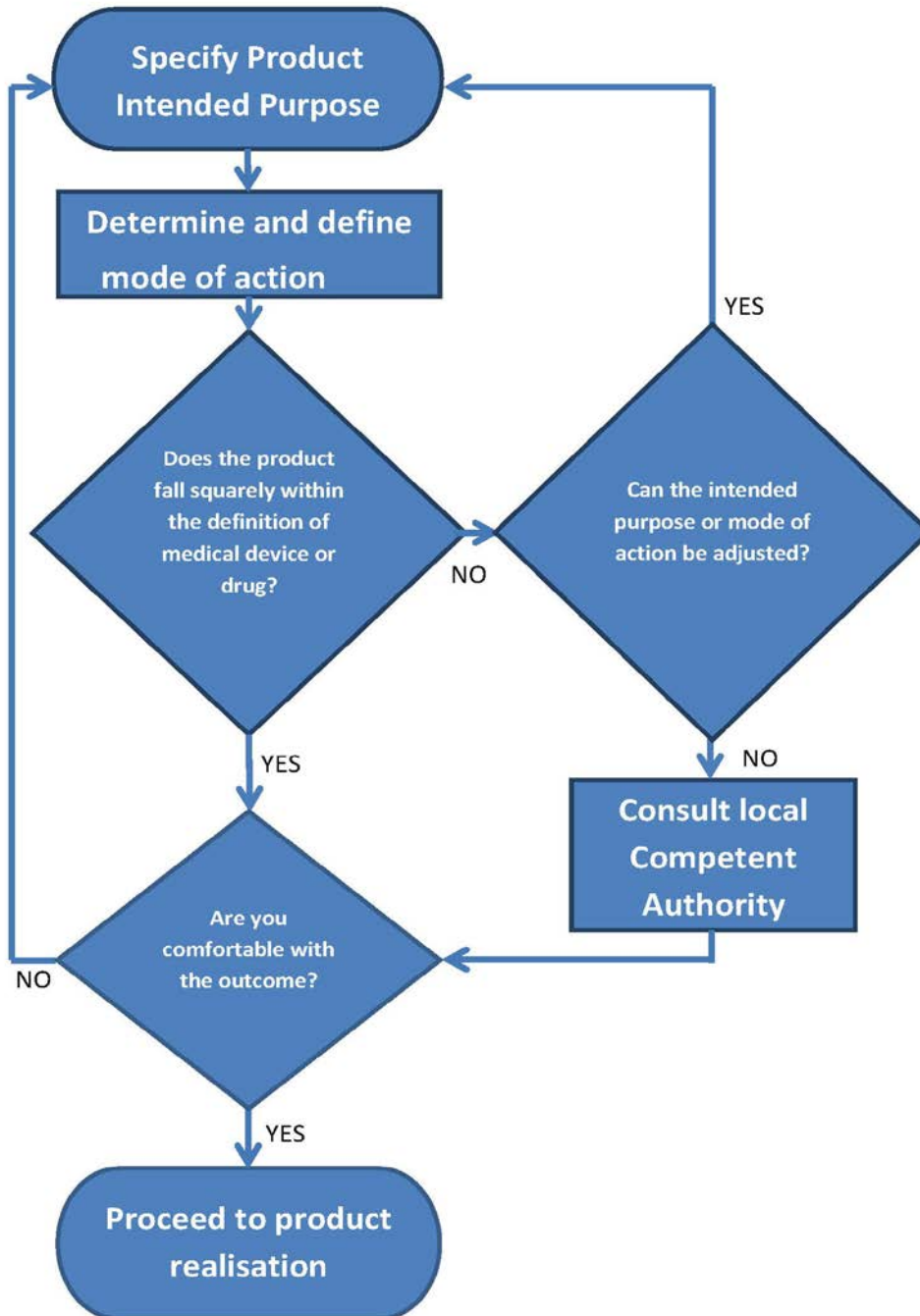
It is in the manufacturer’s interest to ensure that once it sets off on a regulatory pathway, there will be no surprises or challenges to impede progress to market. The following suggestions can be deduced from the discussion above:

- Take care that the intended purpose you specify is achieved physically and not pharmaceutically.
- Take early advice, e.g. from a pharmacologist, concerning whether a given substance or action is pharmaceutical in nature.
- If the product contains a pharmaceutical which is not intended to act on the patient, ensure there is good data to demonstrate that it is not liable to do so.
- Consult the guidance given in the references.
- If in doubt, discuss the issues with your Notified Body.

- If still in doubt, it is possible to ask MHRA or (other medical devices Competent Authority) for a judgment. Before doing so, it is advisable to gather as much data as possible so that the question can be put clearly and a definitive answer can be given. NB: the answer may not be the one which the manufacturer desires! In such cases it is usually not easy get a reversal.
- Finally, if still in doubt, the matter can be referred to the Commission Borderline Group (see reference 3) but this can be a lengthy process with no guarantee of an answer in the short term.

For more information about how [NSF HEALTH SCIENCES MEDICAL DEVICES](#) can support your regulatory strategy for drug device combinations, contact EUdevices@nsf.org

About the author: John Worroll is a senior consultant with NSF HEALTH SCIENCES Medical Devices, part of NSF Health Sciences, a division of NSF International. Before that, he worked for MHRA for 27 years in a variety of regulatory roles, followed by 8 years at the BSI Notified Body for medical devices where he was responsible for their regulatory compliance world-wide. He can be reached at EUdevices@nsf.org



Process for Specifying a Drug/Device Product

REFERENCES

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use

Council Directive 93/42/EEC of 14 June 1993 concerning medical devices

Council Directive 90/385/EEC on the approximation of the laws of Member States relating to active implantable medical devices

MEDDEV 2.1/3: Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative

MEDDEV 2.4/1 Classification of medical devices

MANUAL ON BORDERLINE AND CLASSIFICATION IN THE COMMUNITY REGULATORY FRAMEWORK FOR MEDICAL DEVICES. Version 1.13 (10-2012)

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