Combination Products: A Difficult Balance Between Drug and Device

Combination products (CPs) are integral to the patient experience - but, under a changing regulatory landscape, what classifies as a CP, and what are the differences between permitted daily exposure and tolerable intake?

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Inhalers, pre-filled syringes, pens, and nebulisers, along with autoinjectors are CPs used in the everyday life of many patients: any combination of a drug, a device, and a biological product could be considered a CP.

A Challenging Regulatory Landscape

Under 21 CFR 3.2(e) of the FDA's Food, Drug, and Cosmetic Act, combination products include (1):

- A product comprised of two or more regulated components
- Two or more separate products together in a single package, or as a unit, and comprised of drug and device products, device and biological products, or biological and drug products
- A drug, device, or biological product packaged separately that, according to its investigational plan or proposed labelling, is intended for use only with an approved, individually-specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect – and where upon approval of the proposed product the labelling of the approved product would need to be changed
- Any investigational drug, device, or biological product packaged separately that according to its proposed labelling is for use only with another individually-specified investigational drug, device, or biological product, where both are required to achieve the intended use, indication, or effect

The FDA designated a specific office for these products: Office of Combination Products (2). In the EU there is no official definition of 'combination products' but there are:

- Medical devices which incorporate a medicinal substance with an ancillary action as an integral part
- Medical devices which incorporate an ancillary human blood derivative as an integral part
- Drug delivery products, where the medicinal substance and the medical device form an integral part

A Flowchart to Help Determining the Regulatory Status in Europe

"Integral" is cited several times in MDR (e.g., Article 1 (8) 1st and 2nd paragraph, Article 1 (9) – 2nd paragraph). MDCG 2022 – 5 provides clarity in the definition of this term and suggested a flowchart for determining the regulatory status of combination products (in **Figure 1**) (2, 3).

In both jurisdictions, the Primary Mode of Action (PMOA) leads the regulatory pathway. However, the testing pathway does not have a clear leader and there is no unique test panel fits for all CP.

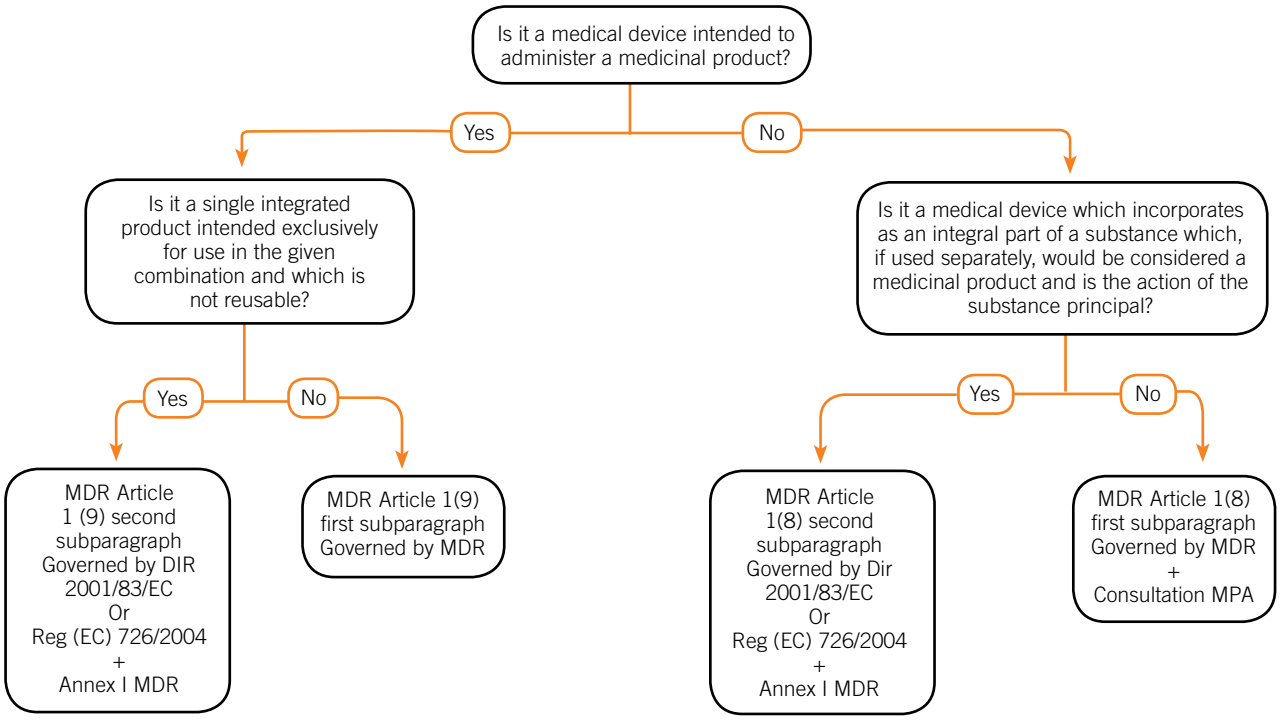

Figure 1: Flowchart for determining the regulatory status of CP

Image Credit: bubutu@123RF

	USP <1663>	ISO 10993-18
Extraction solutions	Simulant solvents customised on the product (drug formulation)	Minimum of two extraction solvents of differing polarity (three are suggested in case of implantable device: polar, semi-polar, and non-polar solvents)
Solvent compatibility	Usually not necessary	Advisable. Deleterious effects to the materials (such as degradation) or the extractables profile (such as chemical alteration of the extractables) should be avoided
Contact time and temperature	To be evaluated on a case by case basis	Case by case basis based on contact category; exaggerated at least
Product state	Solid, liquid, gas	Not specifically addressed
Total Daily Intake (TDI)	TDI usually well-defined Easy AET calculation	Number of devices/day not always definable

Table 1: Study Design for extractable study

Medical devices and drug products refer to different standards and guidelines and, therefore, testing approaches. The process of bringing together (bio)pharmaceuticals and medical devices to create a combination product requires specific testing on all product constituents.

What About Extractables and Leachables?

Using chemical characterisation as paradigm, USP chapters <1663> and <1664> are used to assess extractables and leachables (E&Ls) associated with drug packaging and delivery systems, while ISO 10993-18:2020 is the standard for chemical characterisation of medical devices within a risk management process (4, 5, 6). A first misalignment can be seen in the definition of leachables: the focus on storage if USP <1664> ("under normal conditions of storage and use or during accelerated drug product stability studies") is lost in ISO 10993-18 ("clinical use condition").

A rough comparison of a study design per USP <1663> and ISO 10993-18 is reported in **Table 1**. One approach is not contradicting the other, but some precautions should be taken into account when designing an extractable study.

In any case, the extractable study should provide qualitative and quantitative data about the compounds a patient could be exposed to. These data are the input for a toxicological risk assessment (TRA), defined as the "act of determining the potential of a chemical to elicit an adverse effect based on a specified level of exposure" (6).

Toxicological Risk Assessment, Step by Step

For both drug and medical devices, a TRA includes as a first step a hazard identification for each chemical inherent property of a chemical constituent to induce one or more adverse health effect in humans, as well as the conditions (e.g., route, duration, frequency, gender, age) necessary for the chemical constituent to elicit the adverse health effect. In parallel, the exposure assessment is used to estimate the actual quantity of a chemical that contacts (external dose) or enters (internal dose) the patient's body. Then, the Margin of Safety (MoS) is calculated and finally the toxicological risk is assessed. An exposure dose of a constituent is without appreciable harm to health when MoS exceeds 1 and the contributing values to the MoS are demonstrated to be conservative. The MoS is the ratio of the constituent's Tolerable Contact Level (TCL), Tolerable Intake (TI), Tolerable Exposure, Permitted Daily Exposure (PDE), or Threshold of Toxicological Concern (TTC), and its exposure dose.

Pharma	Medical Devices
• Arbitrary adult human body weight for either sex of 50 kg. • It is recognised that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE. • For paediatric use, an adjustment for a lower body weight would be appropriate **Derived from (9)**	• 70 kg body weight for adult men • 60 kg for adult women, which is also representative of all adults in a worst-case assumption • 10 kg for children (>1 year to ≤ 16 years of age) • 3.5 kg for infants (<1 year) • 1.5 kg for very low birthweight infants • 0.5 kg for very low birthweight neonates (e.g., preterm neonate) **Derived from (9)**
• For lead, the paediatric population is considered the most sensitive population, and data from this population were used to set the PDE • The PDEs are considered appropriate for pharmaceuticals intended for paediatric populations **Derived from (9)**	

Table 2: Patient body weight

> *A PDE value is conservative for any exposure duration, while TI is specific for the device's exposure*

Permitted Daily Exposure or Tolerable Intake?

The PDE, mainly used in pharma, represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at, or below, this dose every day for a lifetime (7). Meanwhile, the TI (used for medical devices) estimates the daily exposure of an identified constituent over a specified time period (e.g., acute, subacute, subchronic, or chronic) on the basis of body weight, that is considered to be without appreciable harm to health (8). In short, a PDE value is conservative for any exposure duration, while TI is specific for the device's exposure.

Body Weight Considerations

A further difference in the approach is related to the patient's body weight, summarised in **Table 2**.

Other Factors to Be Considered

When determining a toxicological value and therefore extrapolating a point of departure to individuals who can be exposed to a chemical of toxicological concern, numerical values that account for uncertainties are used. Here, using pharma or medical device point of view, some differences apply.

For medical device, three factors (intraspecies, interspecies, and quality and relevance) are/were usually used per ISO 10993-17:2002, but the proposed revision of the standard will introduce *n* factors (e.g., route-to-route, exposure duration, point of departure); for pharma, just five factors are used (11, 8). The numerical value for the same factor could be dissimilar and even the order is different (e.g., inter-individual variability as UF1 for medical devices and F2 for pharma).

This brief overview underlines some differences between analytical approaches for the two worlds (pharmaceutical and medical devices) which could mine the approval of a combination product. For this reason, having total familiarity with the drug and the device, and having a clear understanding of the regulatory status, are essential to reach the market sooner and avoid regulatory pitfalls.

The author would like to thank Simone Carrara and Daniele Lioi for their highly valuable inputs.

References

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European Registered Toxicologist with a MS in Applied Toxicology and Biomedical Engineering, **Paolo Pescio** has over 15 years of experience in biological evaluation of medical devices and toxicological risk assessment for pharmaceutical products.

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