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The ISO 10993-17:2023 Revision Impact on Combination Products

Introduction and Regulatory Framework

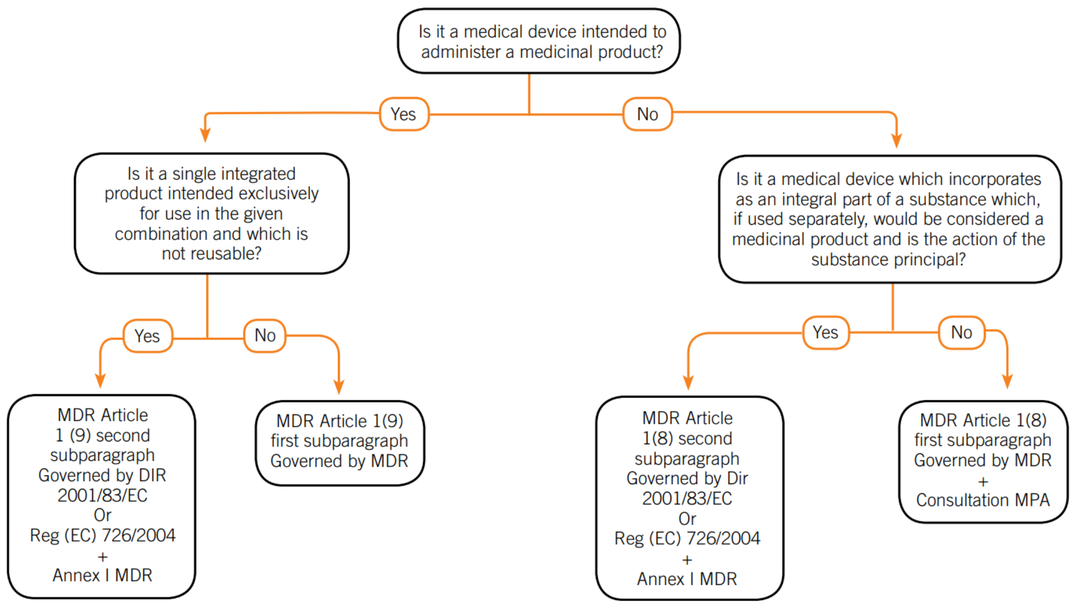
Medical Device and Medicinal Product Combinations, called also Combination Product (CP) combine drugs, devices, and/or biological products and can have a wide range of clinical applications. They configure when at least two constituent parts co-exist (e.g., drug/device in an insulin injector pen; drug/biologic in a preparate composed by a therapeutic drug and a monoclonal antibody).

In the EU there is no official term "*Combination Products*" but there are:

-Medical devices incorporating as an integral part a medicinal substance with an ancillary action;

-Medical devices incorporating as an integral part an ancillary human blood derivative;

-Drug delivery products, where the medicinal substance and the medical device form an integral part.



Flowchart for determining the regulatory status of CP as per MDCG 2022 – 5

In Europe, various CP are subject to different regulatory requirements since they can be either regulated as a medicinal product or a medical device on the base of their primary mode of action.

As per the Regulation (EU) 2017/745 of the European Parliament and of the Council: "*Products which combine a medicinal product or substance, and a medical device are regulated either under this Regulation or under Directive 2001/83/EC of the European Parliament and of the Council. The two legislative acts should ensure appropriate interaction in terms of consultations during pre-market assessment, and of exchange of information in the context of vigilance activities involving such combination products. For medicinal products that integrate a medical device part, compliance with the general safety and performance requirements laid down in this Regulation for the device part should be adequately assessed in the context of the marketing authorisation for such medicinal products.*"

A drug/device Combination Product shall include in its marketing authorisation dossier the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I of the Medical Device Regulation (MDR) contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a Notified Body.

ISO 10993-17 revision and toxicological evaluation of Combination Products

In the context of assessing the biological safety of the device component in a drug/device combination product, ISO 10993-17:2023 serves as a pertinent standard since outlines the necessary requirements for conducting toxicological evaluations.

The new revision introduced the following relevant principles:

- *Toxicological Screening Limit* (TSL): cumulative exposure dose (expressed as µg) to an identified constituent over a specified time period that is without appreciable harm to health;
- *Worst-case Estimated Exposure Dose* (EEDmax): exposure dose (expressed as µg/kg/day) that is a maximum value for a specified intended clinical-use scenario;
- *Margin of Safety* (MoS): ratio (unitless) of the constituent's Tolerable Contact Level (numerator), Tolerable Intake (numerator) and its Exposure Dose.

The new revision of the Standard also requires determining multiple EEDmax and MoS values on the base of the intended clinical-use scenario of the device under evaluation.

Period of assumed exposure to the constituent	Calculation of MoS value for toxicological endpoints to be addressed[d]			
	Acute[c]	Subacute[c]	Subchronic[c]	Chronic[c]
≤1 d[a]	X	Not applicable	Not applicable	Not applicable
2 d to 30 d[ab]	X	X	Not applicable	Not applicable
31 to 365 d[ab]	X	X	X	Not applicable
≥366 d[ab]	X	X	X	X

X indicates toxicological endpoint shall be addressed unless otherwise justified (see Clause E.1).

[a] This applies when Formula (E.1) is used to estimate an exposure dose.

[b] This applies when Formula (E.3) is used to estimate the worst-case estimated exposure dose for assumed exposure periods.

[c] Acute, subacute, subchronic and chronic refer to the duration of exposure for which the TCL or TI is protective (see 9.2.1 NOTE 1).

[d] See 6.1 for toxicological endpoints to be addressed.

MoS values to consider when constituent release kinetics data are not available

The crucial role of Worst-Case Exposure Dose Estimation (EEDmax)

The determination of EEDmax is directly affected by the Total Quantity of each constituent, the Body Weight of the patient population considered and the assumed release duration.

$$EED_{max} = (TQ \times SF_{a.r.}) \,/\, BW_{L} \,/\, R_{d}$$

The Standard provides default Rd values that can be selected as is here reported:

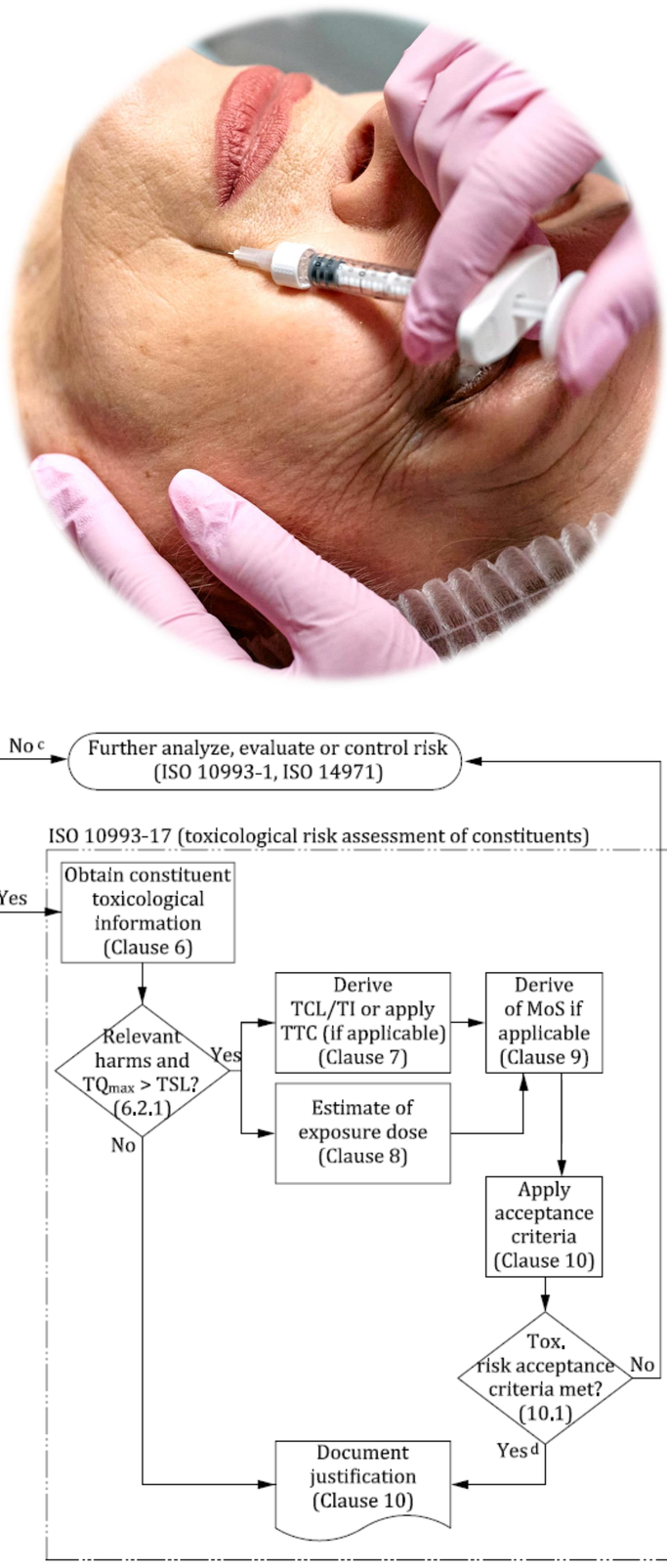
Medical device contact duration category	R_d for each time period of assumed constituent exposure duration, d			
	≤1 d	2 d to 30 d	31 d to 365 d	≥366 d
Prolonged (≤30 d)	1	2	Not applicable	Not applicable
Long-term (31 d to 365 d)	1	2	31	Not applicable
Long-term (≥366 d)	1	2	31	366

R_d value indicates when it is used to calculate a worst-case estimated exposure dose unless otherwise justified.

Selection of default Rd values

In evaluating a CP, its mode of use (i.e., posology) shall be considered. Indeed, single-use disposable medical devices where the cumulative exposure duration can exceed 30 days require to deviate from the default Rd values. To help navigate these particular cases, the Standard provides examples in the Annex E (the data presentation has been adjusted):

Time Period days	Disposable devices with long term exposure		
	Repeated use every 24 hours	Repeated use every 3 days	Repeated use every 60 days
≤ 1	1	1	1
2 to 30	1	2	2
31 to 365	1	2	31
≥ 366	1	2	31



Biological evaluation process (according to ISO 10993-1 on ISO 14971)

Case study: when the posology is not canonical

Toxicological evaluation of a single-use pre-filled syringe with the subsequent posology: 1 treatment session followed by a control visit and a possible touch up after 15 days; 1 treatment session 30 days after the first injection, followed by a control visit and a possible touch up after 15 days; possibly followed by maintenance session each 3 months.

Given the mode of use of the evaluated product, every time that it is applied it shall be considered as an *ex-novo* application of the product. Therefore, the attribution Rd values here presented has been deemed pertinent.

Time Period days	Rd days
≤ 1	1
2 to 30	2
31 to 365	2
≥ 366	31

Conclusion

Among many new concepts, the new revision of ISO 10993-17 provides the requirements for a process for specifying a level of exposure to a constituent of a medical device that is without appreciable harm to health and extends the previous version by clarifying how to calculate worst-case estimated exposure dose values.