Commission guidance for the medical devices expert panels on the consistent interpretation of the decision criteria in the clinical evaluation consultation procedure

(Text with EEA relevance)

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1. **Introduction**

This document is intended to provide Commission guidance for expert panels established under Article 106 of Regulation (EU) 2017/745 ([1]) of the European Parliament and of the Council of 5 April 2017 on medical devices (hereafter: the MDR). This guidance aims to ensure a consistent interpretation of the criteria to be applied when deciding whether or not to provide a scientific opinion in accordance with Section 5.1, point (c) 'Assessment procedure for certain class III and class IIb devices' of Annex IX and section 6 of Annex X to that Regulation.

According to Article 54(1) of the MDR, the requirement for clinical evaluation consultation of the expert panels applies to the conformity assessment of:

— class III implantable devices;

— class IIb active devices intended to administer and/or remove medicinal products.

However, as stipulated in Article 54(2) of the MDR, those devices may be exempt from the clinical evaluation consultation procedure (CECP) under the following specific circumstances:

a) the renewal of a certificate issued under the MDR;

b) when the devices have been designed by modifying devices already marketed by the same manufacturer for the same intended purpose, provided that the manufacturer has demonstrated to the satisfaction of the notified body that the modifications do not adversely affect the benefit-risk ratio ([2]);

c) where the principles of the clinical evaluation of the device type or category have been addressed in common specifications (CS) and where the notified body confirms that the clinical evaluation of the manufacturer for this device is in compliance with the relevant CS for clinical evaluation of that kind of device.

According to Section 5.1, points (c) and (d) of Annex IX to the MDR, the expert panels shall decide within 21 days, under the supervision of the Commission, whether to provide a scientific opinion on the clinical evaluation assessment report (CEAR) of the notified body based on the clinical evidence provided by the manufacturer, in particular concerning the benefit-risk determination, the consistency of that evidence with the medical indication or indications and the PMCF plan. The decision shall be made on the basis of the following criteria:

(i) the novelty of the device or of the related clinical procedure involved, and the possible major clinical or health impact thereof;

(ii) a significantly adverse change in the benefit-risk profile of a specific category or group of devices due to scientifically valid health concerns in respect of components or source material or in respect of the impact on health in the case of failure of the device;

(iii) a significantly increased rate of serious incidents reported in accordance with Article 87 of the MDR in respect of a specific category or group of devices.

2. **Criterion 1: novelty and clinical or health impact**

This section provides guidance on how to assess the novelty of a device or its associated clinical procedure and how to estimate the possible major clinical and health impact of that novelty.

The novelty criterion relates directly to the device or the related clinical procedure under assessment and can therefore be evaluated based on the available documents, i.e. the CEAR prepared by the notified body as well as the accompanying documents, in particular the manufacturer's clinical evaluation report (CER).

Novelty typically means that there is a lack of experience in regard to the safety and performance of the device or specific features of the device or related clinical procedure, and there are no similar devices or insufficient experience with similar devices to enable straightforward appraisal of its future real-world safety and performance. However, in case of innovation based on modifications of previous variants of the device, relevant information coming from the post-market surveillance may be available and needs to be considered. To this end, the expert panel needs to estimate the clinical impact or health impact in conjunction with the novelty. Novelty alone is insufficient to trigger a scientific opinion. Rather, the panel needs to consider any possible major clinical and/or health impacts resulting from that novelty.

([1]) OJ L 117, 5.5.2017, p. 1.

([2]) MDCG 2019-3 Interpretation of Article 54(2)b rev 1; available at https://ec.europa.eu/docsroom/documents/40661

Conversely, potential clinical or health impacts that are not linked to a novel device (or novel features of a device) or a novel clinical procedure will not trigger a scientific opinion.

2.1. *Assessment of novelty dimensions*

When assessing novelty, relevant dimensions of a device in which novelty and innovation can be manifest may include, but are not limited to the ones listed below. To ensure consistency, experts should give due and systematic consideration to these dimensions when assessing the possible novelty of a device:

A) Procedure-related dimensions

- Novel clinical procedure or surgical procedure related to, inter alia, a novelty or a change in:
  - the mode of use or treatment option;
  - device-patient interface (including maintenance and adjustment);
  - interaction and control (existing technologies with a new interface or usage context, new way of device application);
  - deployment methods.

B) Device-related dimensions

- Novel medical purpose, including a new intended purpose of the device with regard to the clinical setting, severity and stage of disease, site in the body, target population (age, anatomy, physiology, sex) with a particular attention to devices used in paediatrics. For instance, novel devices may aim to meet previously unmet medical needs, whether for a disease as a whole or for specific indications or patient populations, within a broader intended purpose;
- Novel design, including new/modified specifications and properties such as physicochemical properties (e.g. mechanical properties, viscosity, surface characteristics, wavelength, type and intensity of energy), shape, size as well as software algorithms where these constitute an integral part of the functioning of the device;
- Novel mechanism of action, including due to new/modified physical or chemical properties. In case of a combination product, new pharmacological, immunological, metabolic properties of the medicinal substance need to be taken into account;
- Novel materials, including notably new/modified materials or substances in contact with human tissues or body fluids, changes in duration of contact, or in the release characteristics of substances, including degradation products and leachables. Materials also include the characteristics of the surface of the device such as specific coatings and surface treatments;
- Novel site of application for an established material, leading to new/modified contact with and/or mechanical loading of the same or different tissues;
- Novel components including parts, pieces or software that constitute an integral part required for the functioning of the device;
- Novel manufacturing process, including for example additive manufacturing, bio-printing, sterilisation processes, in relation to the state of the art.

It is expected that the information transmitted by the notified body to the expert panels may in some cases allow primarily for the estimation of novelty dimensions relating to the medical purpose and the clinical procedure involved.

Typically, no scientific opinion is required when the level of novelty is not high and there is no major potential negative clinical and/or health impact. Nonetheless, a scientific opinion is required when a major negative clinical or health impact is anticipated, independent of the estimated degree of novelty.

2.2. *Assessment of major clinical impact and health impact*

Once the expert panel has assessed the level of novelty, the possible clinical or health impact resulting from this novelty must be assessed.

A) Clinical impact: effects on an individual level

Based on the definition of the term 'clinical benefit' set out in Article 2(53) of the MDR, i.e. *'the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health'*, clinical impact in this context is understood as the totality of benefits, hazards and related risks at individual level. In the case of wholly new devices, information relevant for estimating the clinical impact will typically come from the clinical evaluation information obtained during the pre-market phase. For modifications of existing devices, evaluation of the clinical impact may in addition also draw on available post-market information, notably the PMCF report.

Clinical impact refers to:

— Clinical outcomes leading to changes in mortality, morbidity, health-related quality of life, burden of treatment, duration of hospitalization, mode of administration, severity, intensity, duration and timing of effects, need for medical or surgical re-intervention, and consideration of preferences, acceptability, usability as well as patient compliance where relevant;

— Clinical benefit or major contribution to care of individual patients or specific groups of patients, i.e. changes in clinical performance, and/or safety profile resulting in clinical advantages compared to existing state of the art methods;

— Negative clinical outcomes, clinical hazards and related risks;

— Risks related to potential severity, types, number and rates of adverse events, incidents, probability and duration of serious adverse events and of serious incidents (Article 2(57), (58), (64) and (65) of the MDR);

— Risks related to incompatibility with the use of other medical devices;

— Risks related to specific groups of patients, with a focus on vulnerable patient groups (e.g. children, elderly, pregnant women etc.);

— Risks related to medical device dysfunction due to reasonably foreseeable inappropriate conditions of use and misuse.

B) Health impact: effects on a population level

Health impact is understood, in this context, as net potential benefits and risks stemming from the clinical impacts on a population level and mainly in relation to post-market use of the device under real-world conditions. In particular:

— Effects on an individual level cumulatively expressed on a population level, i.e. assessing the size of the effects, the potentially exposed population and the duration of effects;

— Probability of serious public health threats (Article 2(66) of the MDR);

— Anticipating a justifiable high market penetration due to innovation, leading to a greater uptake of the device and subsequently to a higher number of patients being exposed to the device and, as a result, a higher overall probability of harms to occur leading to a higher net risk.

Risk is defined in Article 2(23) of the MDR as the combination of the probability of occurrence of harm and the severity of that harm.

C) Assessment of clinical or health impact

When assessing **possible major clinical or health impacts resulting from novelty**, in the context of the above guidance elements, the panel should take the following into consideration:

— **Focus on hazards, harm and risks**: The term 'impact' is a priori neutral and can encompass positive impacts (benefits) and negative impacts (hazards and related risks). Therefore, the focus of the assessment of impact should be on the evaluation and estimation of negative impacts or outcomes including the probability of occurrence and severity of specific harms. The CEAR should have sufficient information with regard to clinical risks, otherwise the notified body may be requested to present its conclusions concerning the benefit-risk determination;

— **Consideration of possible impacts:** In line with Section 5.1, point (c) of Annex IX to the MDR, assessment of clinical or health impact should also consider possible outcomes, i.e. effects for which there is no direct evidence (e.g. from clinical data) but which conceivably and realistically could occur with a high enough frequency under real-world conditions to lead to a major clinical and health impact. The concept of risk also incorporates the probability of a (negative) outcome occurring and therefore this probability should be considered. Finally, experts should carefully consider uncertainties in regard to estimations of the severity of harm and the magnitude of risks;

— **Estimation of the severity of impacts:** Section 5.1, point (c) of Annex IX to the MDR requires that possible major clinical or health impacts are considered. Thus, expert panels should perform an estimation of the severity of the impacts, based on their clinical experience and knowledge from the published literature regarding comparable cases. In addition, where useful and available, information provided in the context of the criteria set out in subparagraphs (ii) and (iii) relating to health concerns and increased rates of serious incidents of relevant groups or categories of devices should be considered.

For an estimation of severity, the following aspects should be taken into account:

— is there a possible significant public health risk related to morbidity and mortality?

— what is the estimated severity of possible undesirable side effects and their impact on mortality, morbidity, health-related quality of life?

— are there impacts that might cause life-threatening diseases and conditions?

— to which extent do the impacts have effects on safety or delivery of public health or patient care?

2.3. *Uncertainties*

The assessment of novelty and resulting clinical or health impacts may leave uncertainties. Although all medical devices should have clinical evidence of sufficient quantity and quality to support a positive benefit-risk conclusion, novel devices may have limited real-world data. This may lead to a change of the benefit-risk conclusion once the devices are made available to a wider patient population.

The panel is encouraged to record possible uncertainties in view of final decision making regarding the need for a scientific opinion.

When there are many uncertainties linked to novelty or clinical or health impact, the need for a scientific opinion will have to be taken on a case by case basis. For instance, high levels of uncertainty may justify the decision to have of a scientific opinion even when the novelty and the resulting negative clinical or health impact are not considered major. In case the expert panel considers it necessary to issue a scientific opinion due to high levels of uncertainty, it should provide a brief explanation, pointing in particular to the remaining uncertainties and why these are considered to be associated with risks.

While using its expert knowledge to the full extent, the expert panel is not expected to perform a risk assessment of the device, but base its decision on the information provided by the notified body.

3. **Criterion 2: scientifically valid health concerns**

Medical devices may be associated with health concerns due to a variety of reasons. Amongst these the MDR mentions, in the context of the second decision criterion set out in Section 5.1, point (c) of Annex IX, a significantly adverse change in the benefit-risk profile of a specific category or group of devices, due to scientifically valid health concerns in respect of components or source material or in respect of the impact on health in the case of failure of the device.

Health concerns often only become known once devices are on the market and used under real-world conditions. Information on such concerns may be relevant for the device under assessment, in particular when the device utilises components or source materials which have been associated with unacceptable levels of undesirable side effects or which may be affected by the same failure mode as devices known to have unacceptable levels of undesirable side effects.

Information relating to one specific device by one single manufacturer, amongst several manufacturers also using the same components and source materials or one single case, is typically insufficient grounds on which to trigger a scientific opinion. The available information needs to be sufficiently reliable and valid in order to trigger a scientific opinion.

3.1. *Indications for health concerns based on knowledge and expertise of the expert panel*

In specific cases, experts in the panels may have information on health concerns in relation to groups or categories of devices due to such concerns being known and/or discussed in the relevant scientific and clinical literature, including observational studies and information from relevant registries. Both the CER and the CEAR, which will provide the basis of the assessment, may also include references to relevant publications.

In cases where experts believe that there is evidence pointing to valid health concerns, the reliability of that evidence as well as the relevance for the device under assessment should be taken into account:

in regard to reliability, this should include:

— the quality of the data that led to the identification of a specific health concerns;

— the number of documented cases and, specifically, whether these have been systematically observed over time;

— the scientific plausibility of claimed causal links between device use and the respective health concerns;

— the robustness of such causal links.

in regard to relevance, this should include:

— whether the device is using the same or similar source materials and/or components as those used for the group or category of devices;

— whether the device failure reported for the group or category of devices is applicable also to the device under assessment;

— whether the device is used in a clinical procedure similar to a clinical procedure for which incidents have been reported for the group or category of devices.

In case the panel is satisfied that the available information is sufficiently reliable and relevant to trigger a scientific opinion, the panel should justify its decision as appropriate.

3.2. *Indications for health concerns based on information provided by the Commission secretariat*

Alternatively, relevant information may be provided to the panel by the Commission secretariat of the expert panels. This information would typically come from the following sources:

a) post-market surveillance and vigilance activities of manufacturers, notably the reporting of serious incidents individually or using the periodic summary reports (PSR) as well as field safety corrective actions (FSCA). Both need to be reported in the EU database for medical devices (EUDAMED) once operational and are accessible to Member States and the Commission (Article 87 of the MDR). Such information may allow the expert panel to draw conclusions on relevant health concerns, in particular where available for groups or categories of devices and in a manner that allows plausible causal links to be identified.

b) Depending on class, manufacturers must submit periodic summary update reports (PSUR) for devices. PSURs outline the conclusions of post-market surveillance data throughout the life cycle of the device. They need to include updates of the benefit-risk determination, main findings of PMCF studies and indications of volumes of sale, allowing, inter alia, the consideration of specific risks on a population level. Thus, for class III implantable devices they may constitute a source of information relevant for the expert panels;

c) Trend reports (Article 88 of the MDR) constitute another source of information. Manufacturers need to provide trend reports in case of statistically significant increases in the frequency or severity of *non-serious* incidents or expected undesirable side-effects that:

   a. could have a significant impact on the benefit-risk determination; and

   b. which have led or may lead to significant risks to the health or safety of patients, users or other persons and are unacceptable when weighed against the intended benefits.

Trend reports may thus point to specific health concerns relevant in the present context.

d) Manufacturers need to draw up a summary of safety and clinical performance (SSCP) for implantable and class III devices. SSCP need to outline the clinical evaluation and PMCF studies and include information on previous generations and variants of the device. This information may be relevant for possible health concerns in relation class III implantable devices (see Article 54.2(b) of the MDR).

4. **Criterion 3: significantly increased rate of serious incidents**

Information on significant increases of serious incidents reporting according to the legal obligations for manufacturers (Article 87 of the MDR) may be provided by the Commission secretariat, where available and in case such information is deemed relevant to the activities of the expert panels.

The expert panel should consider on a case-by-case basis, whether a given set of serious incident related information is relevant for the device under assessment. The panel should justify their reasoning in case the incident data set provided by the secretariat is considered sufficient to trigger a scientific opinion.

5. **Revision clause**

Based on the experience gained during the first term of office of the expert panels, the Commission may consider revising this guidance.