CEPs: What Does "State of the Art" Modify?

In a previous DL Regulatory Recap, "CEPs: Parameters vs clinical outcome parameters, what's the difference?" (Feb 2024), a logical interpretation of MDR Annex XIV, Section 1(a), 6th indent and its reference to "parameters" was discussed. This article builds on that discussion by explaining why the phrase "state of the art in medicine" in the same indent modifies "the acceptability of the benefit-risk ratio" and not "parameters."

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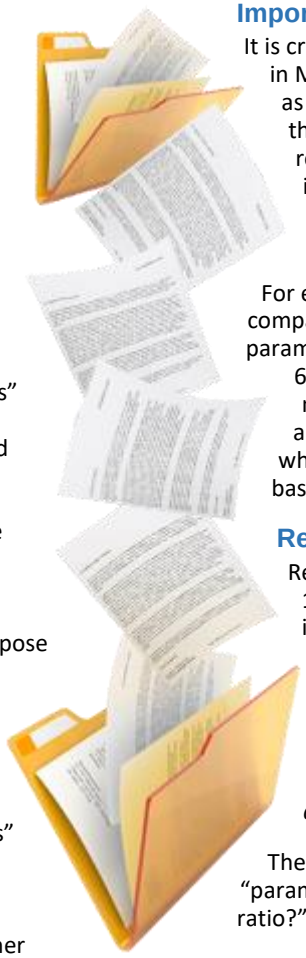
Source of varying interpretations

MDR Annex XIV, Section 1(a), 6th indent specifies that the clinical evaluation plan (CEP) must include:

"an indicative list and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device."

There are two aspects of MDR wording that lead to varying interpretations of the requirement. The first concerns "parameters" and whether that term refers specifically to "clinical outcome parameters" or is intended as a synonym for "criteria" to be used to determine the acceptability of a device's benefit-risk ratio. The second is whether the phrase "based on the state of the art in medicine" modifies "parameters" or "the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device."



The first aspect was addressed in some detail in the previous DL Regulatory Recap, which explained why "parameters" should not be interpreted as "clinical outcome parameters." Instead, "parameters" should be understood to mean all relevant criteria (e.g., intended purpose, indications, nature of clinical benefits, clinical outcome parameters, nature of residual risks, and other criteria) that a manufacturer uses to determine the acceptability of the benefit-risk ratio. Depending upon the particular device, clinical outcome parameters may indeed be one of the criteria or parameters used in this assessment. The point is that "parameters" in MDR Annex XIV, Section 1(a), 6th indent, is not synonymous with "clinical outcome parameters."

The second aspect, specifically, whether "based on the state of the art in medicine" modifies "parameters" or "the acceptability of the benefit-risk ratio," was only very briefly discussed in the earlier article. This article expands that discussion and its conclusions.

Importance of accurate interpretation

It is crucial to accurately interpret what "state of the art" in MDR Annex XIV, Section 1(a), 6th indent modifies, as precise understanding of regulations helps ensure that compliance aligns with the intent of the regulation. Accurate interpretation also helps avoid irrelevant questions being raised during conformity assessment reviews and unnecessary time spent on such matters.

For example, during conformity assessments, companies are sometimes asked to confirm that the parameters referred to in MDR Annex XIV, Section 1(a), 6th indent, are based on the state of the art in medicine. The points below will demonstrate that a more accurate request would be to address whether the acceptability of the benefit-risk ratio is based on the state of the art in medicine

Relevance of a key MDR requirement

Returning to the 6th indent of Annex XIV, Section 1(a), it requires that the clinical evaluation plan includes:

"an indicative list and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device."

The question is: Does "state of the art" modify "parameters" or "the acceptability of the benefit-risk ratio?"

Concluding that "based on the state of the art in medicine" applies to "the acceptability of the benefit-risk ratio" rather than "parameters" aligns with another fundamental requirement in the MDR.

Specifically, Annex I, Section 1 (GSPR 1) requires that any risks associated with the use of devices must "constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art."

Thus, interpreting that the 6th indent concerns the

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acceptability of the benefit-risk ratio based on the state of the art in medicine is entirely consistent with GSPR 1.

This is because GSPR 1 mandates that the generally acknowledged state of the art be taken into account when determining whether risks are acceptable when compared to benefits to the patient.

Grammatical analysis

The views presented in this article are based on the context of the text in question and on an interpretation of certain principles of English grammar (Quirk et al., *A Comprehensive Grammar of the English Language*, 1985), since the discussion concerns the English version of the MDR.

For ease of discussion, MDR Annex XIV, Section 1(a), 6th indent, is again presented, which is:

"an indicative list and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device."

The relevant sentence structure is as follows:

1. *"An indicative list and specification of parameters"* is the noun phrase that acts as the subject of the clause. This phrase identifies what needs to be included in the CEP.
2. *"To be used to determine"* is an infinitive phrase that describes the purpose or function of the "indicative list and specification of parameters." It explains why the parameters need to be listed and specified.
3. *"The acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device"* is the noun phrase that is the object of the infinitive "to determine." It is what the parameters are used to assess.
4. Finally, *"based on the state of the art in medicine"* is a prepositional phrase that serves as an adverbial modifier. Given its placement and grammatical function, it can be concluded that this phrase modifies "the acceptability of the benefit-risk ratio" rather than the earlier part of the sentence.

   Thus, the placement of this phrase immediately after "to determine" and before "the acceptability of the benefit-risk ratio" suggests that it provides additional context or criteria for how the acceptability should be determined. This conclusion is based on the principle that modifiers typically apply to the nearest relevant noun or phrase. In the case of the 6th indent, "based on the state of the art in medicine," directly precedes "the acceptability of the benefit-risk ratio," making it reasonable to conclude that it modifies this phrase.

Another way of analyzing the text of the 6th indent is that:

- The CEP must include a list and specification of parameters, which in this context, point to a range of criteria
- The parameters are used "to determine" something specific, i.e., "the acceptability of the benefit-risk ratio"
- The acceptability of the benefit-risk ratio must be "based on the state of the art in medicine".

Also, interpreting the phrase "based on the state of the art in medicine" as a modifier of "the acceptability of the benefit-risk ratio" aligns with the context of the regulation because it describes how the benefit-risk ratio should be evaluated and not how the parameters should be assessed.

Of course, it is acknowledged that certain parameters may include a type that should be subject to considerations of state of the art. For example, certain types of devices may require an evaluation of clinical data, where an evaluation of state of the art is relevant.

Conclusions

This article discusses why MDR Annex XIV, Section 1(a), 6th indent, should be interpreted to mean that the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device must be based on the state of art in medicine. A clear and consistent interpretation of this text will contribute to more effective compliance with the intended regulatory requirement and help prevent misunderstandings and inconsistencies during conformity assessment.

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