Bridging the Gap Between ERs and GSPRS

How to make the transition from MDD to MDR go as smoothly as possible.

To establish compliance with the Medical Device Regulation (EU) 2017/745, manufacturers need to establish conformity to all relevant GSPRs.

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The **Medical Device Regulation** (EU) 2017/745 came into effect on May 26, 2021, and now all the device manufacturers have to **comply with these requirements**mdr to place and market their devices in the European Union. The Essential Requirements of the Medical Device Directives (93/42/EEC) have been repealed by the General Safety and Performance Requirements (GSPR). To establish compliance with the Medical Device Regulation (EU) 2017/745, manufacturers need to establish conformity to all relevant GSPRs and herein lies the challenge.

How does the manufacturer determine the relevant GSPRs? What data is required for demonstrating conformity with the different GSPRs? How different are the GSPRs from the ERs? What additional data is required when transitioning from the ERs to GSPRs? These are some of the questions that need to be considered when establishing MDR compliance for any medical device.

One of the main components of establishing compliance with the EU MDR lies in providing the appropriate evidence and data to prove conformity with the relevant GSPRs that are in line with the device's intended purpose. It is of utmost importance that all evidence, which includes data from non-clinical or clinical studies held by the manufacturer, data from published literature, data from PMS activities, is correctly identified and analyzed.

Article 61(1) of the MDR states – "Confirmation of conformity with relevant general

safety and performance requirements set out in Annex I under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk ratio referred to in Sections 1 and 8 of Annex I, shall be based on clinical data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III. The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device, clinical risks, and its intended purpose.

To that end, manufacturers shall plan, conduct and document a clinical evaluation in accordance with this Article and Part A of Annex XIV".

As is apparent from the above clause, demonstrating conformity to the GSPRs is the cornerstone of establishing compliance with the EU MDR. There are no significant differences between the ERs of the MDD and the GSPRs of the MDR, but some of the requirements under the GSPRs are more stringent and require more clinical data to be presented and analyzed. There is a total of 23 GSPRs, while there were 13 ERs under the MDD and 16 ERs under the Active Implantable Medical Device Directives 90/385/EEC (AIMDD).

The requirements of GSPR are covered in Annex I of the MDR with three (03) chapters, such as:

- Chapter 1 – General requirements
- Chapter II – Requirements regarding design and manufacture
- Chapter III – Requirements regarding the information supplied with the device

The new GSPRs have expanded requirements under the labeling and risk sections. There is also an enhanced emphasis on cybersecurity for programmable electronic systems. Some of the new requirements relate to combination products, where there is a combination of a drug and device that contain substances of biological origin.

The new requirements are in line with the current industry standards or guidance and manufacturers may very well be compliant with these requirements but are now burdened with having to provide adequate data to support this. The state-of-the-art requirements mentioned in the harmonized standards are incorporated into the MDR's GSPRs. Under the MDR, the acceptability of the benefit-risk ratio banks on consideration of available alternate treatment options and the applicable and relevant data from post-market surveillance.

An essential part of the Clinical Evaluation Report (CER) is an objective analysis of data presented within the report to establish conformity with the GSPRs. A simple gap analysis between the ERs and GSPRs with confirmatory statements is not enough. A detailed analysis of the data citing what GSPRs are applicable and tracing the corresponding documents and/or data demonstrating compliance is required. It is also required to provide suitable justifications for GSPRs which are not applicable. The GSPRs 1, 3, 4, 6, and 8 are related to establishing the safety and performance

of the device. It includes establishing the benefit risk profile and the acceptability of the risk profile. Thus, the GSPRs are considered universally applicable to all medical devices.

Some of the significant updates in the GSPRs in comparison to the ERs are described below:

Devices Without a Medical Purpose

Devices without a medical purpose were out of the scope of MDD and AIMDD but are within the scope of MDR; hence understanding how to apply the GSPRs pertaining to safety and performance is challenging. The GSPR 9 covers the details of this requirement, which mentions that the device must not exceed the 'maximum acceptable risk' and must be consistent with a high level of safety and protection of health. However, what would be considered as the maximum acceptable risk is not clearly defined in the MDR. It is expected that common specifications would be available that would provide clarity on this issue. Until these specifications become available, the manufacturer must justify the determined maximum acceptable risk and justify by referencing available industry standards pertaining to similar devices with a medical purpose.

Chemical, Physical and Biologic Properties

The GSPR 10, which is related to a medical device's chemical, physical and biological properties, is an expansion of the ER 9 and requires additional evidence or data to establish conformity. Some of the other requirements under this GSPR include having to show compatibility between different parts of an implantable device, establishing the validity of the intended purpose of the device followed by modeling or biophysical research, where applicable, mechanical properties of the materials used, surface properties and confirmation that the device meets all the pre-defined chemical and physical specifications.

Having physical and chemical characterization of the device to establish safety is an important addition that needs to be considered when presenting data in the CER. There should be a robust justification if the characterization is unavailable or deemed not required.

The GSPR 10.4 on Hazardous Substances is especially important and is considerably different from the earlier requirements in the ER. This GSPR now mandates a detailed material characterization, leachable testing, and degradation analysis for devices that have the property of degradation or leaching. One must perform the extractable testing and make the related data available for analysis in the CER. If the material used for construction contains any toxic, Carcinogenic, Mutagenic, or toxic to Reproduction (CMR substances) or endocrine-disruptor substances, a robust justification must be provided for their presence. It must also be demonstrated that they do not lead to unacceptable effects when used under normal conditions.

Devices Incorporating Materials of Biological Origin

For devices that have derivatives of animal origin, there are additional requirements that are detailed under GSPR 13.1. A new requirement under the GSPR for devices in this category is that the manufacturers are expected to provide data to show that the processing, manufacture, design testing of the product has been carried out to ensure its safety to the user, the patient or any other person involved in the handling of the product, including persons involved in the waste disposal.

Software as a Medical Device

The GSPRs also have much more detailed requirements for Software as a Medical Device (SaMD). There are specific requirements pertaining to the management of risk related to software as a system, including validation, cybersecurity, network potential risks, etc. When preparing a CER for software, the data to be included and analyzed must be in line with these requirements. Thus, it is necessary to provide the verification and validation reports in the CER to show the established conformity with the GSPRs.

Details regarding the quality management system must also be adequately highlighted in the CER to provide evidence to support the relevant GSPRs, which directly decide the conformity assessment route. For example, for Class I devices it is not normally required to submit a clinical evaluation report to the Notified Body for assessment. However, they are still required to conform to the requirements of the MDR, demonstrate conformity to the GSPRs and suitability for the intended purpose and acceptability of benefit-risk profile which requires a clinical evaluation.

Thus, a clinical evaluation report must still be drafted for all Class I devices, and they must be written with the sufficient data to establish compliance with the MDR, especially for Class I devices that are supplied sterile and have a measurement function or are reusable surgical devices since they will be subject to audit by a Notified Body.

Conclusion

It is quite common for manufacturers to overlook some of the newer requirements under the GSPRs, some of which may warrant new clinical or non-clinical testing to be carried out by the manufacturer in order to be compliant. The manufacturers may also be required to update the risk management procedures and the related documents. The MDR must be carefully read and understood to ensure that the data is not inadvertently overlooked or misrepresented.

The best way to avoid non-conformity is to develop a detailed checklist that can help to track the documents/data. Also, the route that is being considered to establish conformity to the GSPRs i.e., the harmonized standard or the common specifications can help to avoid non-conformity.

References:

[1] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF
[2] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745
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