Unravelling the Puzzle for Medical Devices: What Is Next for Industry?

Freitag A[1], Schmetz A[2], Sarri G[1]
[1]Cytel, London, UK, [2]BIOTRONIK SE & Co. KG, Berlin, Germany

Introduction

Healthcare decision-making for medical devices (MD) is associated with unique challenges, such as scarce high-quality trial data, and the presence of confounding factors that may impact a manufacturer's ability to demonstrate an MD's benefit on clinical outcomes.

So far, attention has been mainly placed on establishing general safety outcomes of MDs, such as the CE mark in the European Union (EU). Standardized evidence requirements and regulatory and reimbursement processes for MDs have long trailed behind those of pharmaceuticals.

Recently, there has been a shift towards higher evidentiary standards in regulatory setting for MDs. For example, in 2021, the EU's Medical Devices Regulation (MDR) restricted the use of evidence from existing devices in lieu of a formal evaluation of the new device, and set up increased MD assessment requirements. It is likely that health technology assessment (HTA) bodies will follow similar methodological trends when assessing MDs for reimbursement.

Objectives

To comprehensively capture the current assessment methods for MDs by regulatory and reimbursement bodies and describe any gaps in the methods and guidance provided.

Methods

We reviewed regulations, directives and formal active guidance documents from regulatory agencies and HTA bodies in selected countries (Canada, France, Germany, Italy, Spain, United Kingdom (UK), United States (US)) to describe current assessment frameworks and evidence requirements for MDs. All MDs other than in-vitro devices were considered as the latter tend to be captured by separate regulations.

Searches were undertaken using the websites of key organizations and the Google platform, and also through a snow-balling approach to identify other relevant sources. A list of organizations reviewed is provided in Table 1.

Findings across the identified documents were synthesized qualitatively and a thematic analysis was performed when results permitted (Figure 1).

Table 1. List of organisations reviewed

Jurisdiction	Regulatory Agencies	HTA Bodies / Payers
Canada	Health Canada	Canadian Agency for Drugs and Technologies in Health (CADTH)
EU	European Commission; Notified Bodies	*See member states*
- France		Haute Autorité de Santé (HAS)
- Germany		Federal Joint Committee (G-BA); Institute for Quality and Efficiency in Health Care (IQWiG)
- Italy		National HTA Program for Medical Devices (PNHTADM)*; National Agency for Regional Healthcare Service (AGENAS)
- Spain		Agency of Medicines and Medical Products (AEMPS); regional bodies
UK (England)	Medicines and Healthcare products Regulatory Agency (MHRA)	National Institute for Health and Care Excellence (NICE)
US	Food and Drug Administration (FDA)	Institute for Clinical and Economic Review (ICER)

* The Italian framework for the assessment of MDs involves multiple stakeholders and organizations

Results

Regulatory Frameworks

Operational Themes

Regulatory frameworks in the US (FDA), EU (MDR), UK (MHRA), and Canada (Health Canada) share similarities in many aspects when assessing MDs. The assessment process and corresponding evidence requirements for MDs are mainly driven by their categorization as determined by the level of risk for presenting potential harm to the user.

- **Class I and II devices (low to moderate risk)** often do not require a formal approval process or—if they are considered *"substantially equivalent"* to an existing device—they can go through an accelerated process without stringent evidence requirements.
- More stringent approval pathways are needed for **class III or IV (high risk) devices** where manufacturers must provide supporting evidence demonstrating the safety and effectiveness of the MD for the targeted population and its intended use.

In the EU, the MDR in 2021 expanded the scope of Notified Bodies (organizations tasked with evaluating MDs) for the assessment of MDs. Notified Bodies must meet stringent criteria for clinical competence to receive accreditation to conduct the conformity assessment. An MD must undergo the conformity assessment to receive the CE marking and be marketed in the EU.

In the UK, from 1 July 2023, the UK Conformity Assessment (UKCA) will replace the CE marking (excluding Northern Ireland).

Methodological Themes

- All four regulatory agencies provide detailed guidance on the evidence requirements needed for supporting the assessment of MDs.
- In many aspects, these share similarities with requirements for pharmaceuticals. Evidence should be identified from different published and unpublished data sources and include further data collection as needed.
- Similar to specific disease areas (e.g., rare diseases), US and EU frameworks specifically allow for other types of evidence (e.g., real-world evidence) apart from clinical data to be presented in MD initial assessments. In addition, evidence from a different manufacturer's device with similar operational technicalities and mode of action can also be used in support of the MD under investigation as long as the comparability between the devices can be established.
- The extent of post-marketing surveillance is based on the device class (detailed plans are needed for class II and above MDs), whether longer follow-up is needed to fully capture the safety profile or if there is uncertainty around the performance of the MD.
- As part of the MDR, *Eudamed* (European Databank on Medical Devices) is currently being expanded to further strengthen surveillance and transparency and monitor the safety and performance of MDs already available in the EU market.

HTA / Payer Frameworks

Our review showed some similarities in evidentiary requirements with those set up for pharmaceuticals, although this guidance was less clear:

- **Evidence generation:** all included HTA bodies require a thorough literature review as part of the evidence submission. Randomized trials are considered the gold standard study design for providing treatment effect estimates. However, the agencies acknowledge the limitations of conducting such trials for MDs due to ethical and practical reasons. NICE specifically notes that clinical expert opinion and patient experience can cover some of the literature gaps. IQWiG recommends that the limitations of traditional trials should be addressed during the trial design (e.g., outcome assessor blinding) when possible.

Results (cont.)

- **Economic analyses:** NICE uses a cost-minimization approach for MD evaluation by incorporating the NHS user-validation exercise. In Canada, cost-utility analyses are the preferred economic evaluation method, whereas in France, economic assessment is only needed if the manufacturer claims a high added clinical value or if a considerable impact on the health expenditure is expected.
- ICER acknowledges the specific limitations of cost-effectiveness analyses for MDs: evolution of devices and inherent changes to costs, differences in the patient populations likely to use the device.
- Reimbursement pathways for MDs in France further depend on whether the device is used in ambulatory or inpatient settings. While the Spanish reimbursement framework is being updated based on MDR requirements, Italy has been making efforts to tie the reimbursement of MDs to HTA via PNHTADM. This is yet in development.

Figure 1. Key themes identified

Regulatory agencies: ***Device classification determines the assessment pathway and evidence requirements. Devices with a higher risk of harm to the user are assessed against more stringent methodological criteria than those of lower risk classes.***

HTA Bodies: ***No clear distinction to guidance documents for pharmaceuticals. Separate guidance for MDs only exists for England and France; Germany uses criteria similar to those of pharmaceuticals for an MD specific evaluation pathway. Prior MD assessments showed a trend towards accepting lower evidence standards indirectly recognizing the methodological challenges around MDs. No differences in the requirements for economic evaluations, which depend on a country's HTA framework.***

Disease-specific guidance: ***Only the FDA has a specific pathway for MDs for rare diseases to address the specific evidence generation challenges.***

Post-marketing surveillance: ***Programs are generally aligned with those for medicines.***

Conclusion

- There is a **consensus across bodies that evidence generation activities for MDs face numerous unique challenges**, such as the inability to blind trials, how to assess investigator bias in outcome reporting due to increased training and experience of staff with the device and the rapid development of software technologies inherent to most high-risk devices that conflict with the time it takes to conduct clinical trials. A further, and less explored factor is the impact of continuous reprogramming of programmable devices to changing patient circumstances and condition (or lack thereof) and its influence on clinical outcomes.
- Regulatory agencies provide clear guidance considering these challenges in generating reliable outcomes for MDs and the impact in decision-making. However, **HTA bodies seem to fall behind**. Methodological guidance continues to overlap for both pharmaceuticals and MDs even though there is a recognition that they have very little in common with regard to evidence generation.
- **Data-generation challenges for MDs need to be acknowledged by HTA bodies**, so manufacturers may optimize evidence strategies outlining the true benefit of an MD, rather than accommodating methodologies which may be less fit for purpose.
- **Increased HTA attention to real-world evidence may facilitate the pursue of higher evidence standards for MDs**: by enabling better MD study designs, while respecting unique challenges, such as the possibility for MD evolution and by capturing real-life patient experience.
- **Recognizing these challenges will be vital for efforts like the EU Joint Clinical Assessment** to provide acceptable timely access for patients and incentivize evidence generation useful to the positive development of therapy.

Email: grammati.sarri@cytel.com | www.cytel.com | ISPOR 2022 | Poster ID 116259