Understanding Pharmacovigilance challenges and complexities in Medical devices: US and EU perspective

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Objective

1. Understand how the management of safety for medical devices differs from other pharmacological agents
2. Differentiate between medical device pharmacovigilance regulations in the US and EU
3. Describe the challenges and complexities in the device regulations in the US and EU and, how the upcoming new rules will address them

Methodology

A review of the regulatory and PV systems literature for the US and EU was done with regards to medical device was done.

A comprehensive assessment of the safety reporting requirements in the medical device space was done for the US and EU to understand the differences and similarities amongst them in addition to the various challenges and complexities associated with it.

Classification of Medical Device

Class	US FDA	EMA
Class I	<ul style="list-style-type: none">• Low risk of injury/illness e.g., gauze, toothbrushes etc.• Manufacturers have to register their facilities, list the products they manufacture, and comply with GMPs	<ul style="list-style-type: none">• Low-risk, non-invasive devices e.g., sterile dressings, gloves etc.
Class II	<ul style="list-style-type: none">• Entail a moderate degree of risk e.g., suture, needles• Have to produce adequate assurance of safety and effectiveness	<ul style="list-style-type: none">Class IIa low-medium risk; e.g., surgical blades,Class IIb medium to high risk; e.g., ventilators, some implants
Class III	<ul style="list-style-type: none">• entail significant risk to the patient e.g., pacemakers, implantable defibrillators• Manufacturer must submit to the FDA a Premarket approval application (PMA)	<ul style="list-style-type: none">• Highest-risk devices, including all active implantable devices• Example: replacement heart valves and vascular stents etc.

Post Marketing reporting Requirements

US FDA	EMA
Known as Medical Device Reporting (MDR) reportable events <ul style="list-style-type: none">• These are events that manufacturers become aware of that reasonably suggest that one of their marketed devices may have caused or contributed to a death or serious injury, or has malfunctioned and the malfunction of the device or a similar device that they market would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. Timelines for Reporting <ul style="list-style-type: none">• Remedial Actions: 5-days reports (Form FDA 3500A)• Death, serious injuries and malfunctions: 30-day reports or initial reports (Form FDA 3500A) Reporting: <ul style="list-style-type: none">• Submitted to FDA electronically by:<ul style="list-style-type: none">• eSubmitter• Health Level 7 Individual Case Safety Reports (HL7 ICSR)	Known as an Incident <ul style="list-style-type: none">• Any event where the device is suspected to be a contributory cause of the incident, and which have led or might have led, to one of the following outcomes:<ul style="list-style-type: none">• death of a patient, USER or other person,• serious deterioration in state of health of a patient, USER or other person Timelines for Reporting <ul style="list-style-type: none">• Serious public health threat: immediately (but not later than 2 calendar days)• Death or Unanticipated serious deterioration in state of health: Not later than 10 elapsed calendar days• Others: Not later than 30 elapsed calendar days Reporting: <ul style="list-style-type: none">• Should be reported to the NCA in the CoI of the incident, unless specified otherwise in local regulations. This should also be reported to the appropriate notified body including any confirmation of receipt of the case sent by the CA and/or local CA reference number.• Manufacturers should also send any trend reports or summary reports to the notified body that they are communicating to the competent authority. Such reports may relate to issues affecting device certification.

Clinical trial safety reporting Requirement – By Sponsor to NCAs

US	EU
Unanticipated Adverse Device Effects <ul style="list-style-type: none">➤ Reported to FDA and all reviewing IRBs and investigators within 10 working days.	Reportable Events <ul style="list-style-type: none">➤ SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: Reported to NCAs immediately, but not later than 2 calendar days.➤ All other SAEs in a device clinical trial are reported in the form of a MEDDEV Table within 7 calendar days.

Clinical trial safety reporting Requirement– By Investigator to Sponsor

US	EU
<ul style="list-style-type: none">➤ Unanticipated Adverse Device Effects: Submit to the sponsor and the reviewing IRB as soon as possible but no later than 10 working days after the investigator first learns of the effect.	<ul style="list-style-type: none">➤ Reportable events: Submit to sponsor in acceptable timely conditions, but not later than within 3 calendar days after the occurrence of the event.

Specific Challenges in US and EU

Topic	US	EU	Comments
Oversight of Public health	Considering a public concern over adverse events, and for the oversight of public health, the FDA was given a mandate for the assurance of the safety and effectiveness of medical devices.	Notified Bodies are not designed to work as public health agencies.	EU assessment made by manufacturers and Notified Bodies; provides less insight into clinical end points for high-risk devices
Centralization	Central approval process also provides publicly searchable listings and databases of adverse events	Though individual Notified Bodies may be motivated to provide a predictable and streamlined approach to attract customers, there may be inconsistency in the process for approving similar devices among Notified Bodies.	Standardization and harmonization of premarketing and post-marketing evaluation are theoretically simpler and easier to implement in the US
Transparency	Open presentations to advisory committees describe particularly novel, complex, or high-risk devices, and Summary of Safety and Effectiveness Data provides the justification for approval as well as discussion of adverse events.	In the European Union, Notified Bodies have no obligation to publish their decision-making process or the evidence provided by sponsors.	Public access/ transparency to evidence in the EU is limited.
Access	For high risk medical devices, clinical premarketing testing and for SMDN clearance, delays patient access to these devices	EU patients may have access to certain high-risk devices sooner than in the United States, subject to limitations by payers.	EU patients have faster access to certain devices, but these products are marketed with less rigorous proof of effectiveness and may have a greater chance of later-identified adverse events

Commission priorities

Implementation: Priorities

*is chaired by the commission. The MDCG is the main body supporting the commission representatives from national competent authorities and

New rules

On March 7 2017, the Council of the European Union adopted new rules that will update the regulatory framework for the approval and marketing of medical devices and in vitro diagnostics in Europe.

The European Parliament is expected to adopt the MDR and the in vitro diagnostics regulations (IVDR) next month. Then after being published, the new rules for medical devices will have a three-year transition period and will take effect in 2020.

• **Clinical trials**
The new regulations would withdraw the principle of equivalence and require further clinical trials in medical devices, which would especially affect class III devices

• **Increased transparency of the Devices**
Eudamed database will provide patients, healthcare professionals and the public with comprehensive information on devices placed on the EU market.

• **Reformation of Notified bodies**
To make the position of notified bodies stronger in relation to manufacturers, with more knowledgeable and experienced personnel to conduct assessments of medical devices. Stricter monitoring of notified bodies by competent authorities in the member states and a new joint assessment of notified bodies by experts from other member states and the European Commission

• **Increased traceability of the devices**
It will be possible to ensure that it will be possible to identify economic operators to whom the devices are supplied or from whom the devices are purchased.

EUDAMED

Notified body designation timeline

Reporting workflow for Device and Combinations Products in the US

Managing Medical Device/combination products

Conclusion

Although medicines and devices are regulated under European Union and the United States law, the regulatory regimes are very different. The safety reporting timelines for the devices are stringent and based on the remedial actions taken for them. The United States and the European Union approach the challenges in different ways. Whereas the United States has always relied on a strictly centralized process through one agency, FDA, the European Commission synchronized the regulations of 28 different countries as they combined to create the European Union. The FDA historically developed as a consumer protection agency, whereas the regulations from the European Commission arose out of a need to harmonize inter-state commercial interests while preserving national "autonomy." The EU system has drawn criticism for conflicts of interest in its evaluation process, and a recent recall of a popular silicone breast implant that was approved only in the European Union has reinforced European concerns about the clinical evaluation of high-risk devices. In order to strengthen the regulations in medical devices, the European Parliament adopted two new regulations on 5 April 2017. They will be published in the Official Journal. The new rules will apply three years after publication with regards to the medical devices. US FDA too at the same time is taking initiatives to ensure that safety monitoring is robust both preapproval as well as post approval.

Central approval process in the US allows post-market phenomena in one generation of devices to inform later applications and study designs. This also provides publicly searchable listings and databases of adverse events. Though individual Notified Bodies may be motivated to provide a predictable and streamlined approach to attract customers, there may be inconsistency in the process for approving similar devices among Notified Bodies. Additionally, review of Notified Bodies not made public; post-marketing data shared among Competent Authorities but not with the public. Open presentations to advisory committees describe particularly novel, complex, or high-risk devices, and Summary of Safety and Effectiveness Data provides the justification for approval as well as discussion of adverse events. In the European Union, Notified Bodies have no obligation to publish their decision-making process or the evidence provided by sponsors. E.U. patients have faster access to certain devices, but these products are marketed with less rigorous proof of effectiveness and may have a greater chance of later-identified adverse events. The new rules in the EU which will apply three years after publication with regards to the medical devices will bring significant changes in the system. The position of notified bodies will be made stronger. There will be strict monitoring for them. Eudamed database will provide patients, healthcare professionals and the public with comprehensive information on devices placed on the EU market. Also, the new regulations would withdraw the principle of equivalence and require further clinical trials in medical devices, which would especially affect class III devices.