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Expert report

# Comparison of the regulatory systems in the USA and EU with respect to medical device safety

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# Executive Summary


Initial situation

Switzerland depends on foreign medical devices for healthcare. Since 1996 Switzerland has accepted - subject to certain conditions - CE-marked devices that are approved for the European Union (EU). This also continues to apply without an update to the Mutual Recognition Agreement (MRA) between the EU and Switzerland. However, the introduction of a new EU Medical Device Regulation (MDR), the delay in provision of the infrastructure required and the associated reduction in product portfolios are leading to a decline in the availability of CE-certified devices. Established existing devices and more particularly new innovative devices are affected by this development.

To extend Switzerland's scope for action and to ensure the long-term healthcare of its population, the Swiss Parliament commissioned the Federal Council on 28 November 2022 to amend the law to allow the recognition of medical devices from non-European regulatory systems with comparably strict requirements, in particular from the United States (USA). In the parliamentary procedure, the Federal Council was sceptical as to whether this would sufficiently guarantee patient safety.

Methodology

Swiss Medtech commissioned the Johner Institut Schweiz GmbH to examine the US American and EU regulatory system for medical devices, in particular with respect to selected safety-relevant aspects. To this end, the regulatory requirements for, among others things, approval or conformity assessment processes, safety and performance requirements as well as market surveillance were compared with each other and further examined by evaluating relevant publications and expert assessments on lived legal practice.

Results

The comparison of the regulatory systems has shown that no significant safety-relevant differences exist between the USA and the EU with respect to legal and normative requirements. The requirements for market access and post-market surveillance are risk-based and both systems place great value on evidence of safety and performance. A substantial difference is that medical devices in the USA are uniformly investigated, approved and monitored by the U.S. Food and Drug Administration (FDA), a central authority with law enforcement powers. By contrast, investigation and examination in the EU is conducted on a decentralised basis by national authorities and state-authorised private-sector institutions known as Notified Bodies, which can lead to an inconsistent interpretation of the regulations and hence to differences in the understanding of device conformity. Another characteristic feature is the acceptance of predicate devices. In the USA, the 510k approval process facilitates a simplified approval of medical devices with moderate risk using the equivalence principle, without compulsory demands for specific clinical data. A large proportion of US devices are

approved in this manner. With the introduction of the MDR, the equivalence process in Europe has been significantly restricted such that its application to CE-marked devices is now limited and hence EU devices require significantly more device-specific data as evidence of safety and performance prior to market clearance.

Summary

Overall, no substantial safety concerns could be identified. Medical devices from both jurisdictions are developed, manufactured and monitored to comparably high standards. From today's perspective, medical devices approved by the FDA for the USA are generally at least as safe as CE-marked medical devices that comply with EU regulations. In the comparison undertaken in this expert report, the examination of the regulatory systems had overriding importance. Accordingly, it cannot be concluded across the board that no differences exist for individual devices.

Concluding comment

It should be taken into consideration that the MDR only came into force in 2017 and, as a result of transitional arrangements in place until 2027 or 2028, has not yet been fully applied to all devices. As a consequence, data, including empirical data, about how the system functions in practice are missing. In addition, there are not enough publicly accessible data from the EU for this expert report to compare the regulatory requirements as well as quantify their effectiveness. These data will only become available when the EUDAMED is introduced as the central database and is fully functional. For this reason, it is not possible for this expert report to give a conclusive quantitative assessment of the safety of devices on the market.

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# 1. Background and questions

Switzerland depends on foreign medical devices for healthcare. In the past, this requirement was covered by CE-marked devices that are approved for the European Union (EU). As of 2002, there has been a legal agreement on the mutual recognition of conformity procedures between Switzerland and the EU which has facilitated free trade in medical devices. This Mutual Recognition Agreement (MRA) has not been updated, which has made the mutual import and export business more difficult. CE-marked devices are still recognised in Switzerland but EU manufacturers require a Swiss-authorised representative (Swiss Medical Device Regulation MedDO Article 51 f.).

Moreover, numerous factors are leading to a general decline in CE-marked medical devices. This is true of both established existing devices and new innovative devices. A new Medical Device Regulation (MDR) has been in force in the EU since 26 May 2021 (1). The higher requirements, particularly for documentation and clinical assessment, as well as the time and effort required to make all existing device documentation compliant with the MDR are causing many manufacturers to reduce their portfolios and are resulting in fewer innovation activities (2,3). The problem will be further exacerbated because the infrastructure required, such as the central EUDAMED database, is not fully available yet. In particular, the capacities of the conformity assessment bodies, known as Notified Bodies, are limited, which is delaying documentation checks.

Through the referral of motion 20.3211 "For more room for manoeuvre in the procurement of medical devices for the care of the Swiss population" (5) from Damian Müller, member of the Council of States, the Swiss Parliament ordered the Federal Council on 28 November 2022 to amend national legislation so that Switzerland recognises not only medical devices with the CE marking but also devices from non-European regulatory systems with comparably strict requirements, in particular those approved by the U.S. Food & Drug Administration (FDA) for the United Sates (USA) in order to increase Switzerland's room for manoeuvre and to overcome potential supply bottle necks (4).

During the parliamentary procedure, the Federal Council was sceptical (5,6) about whether patient safety would be sufficiently guaranteed in this case. To assess the concerns of the Federal Council, Swiss Medtech commissioned the Johner Institut Schweiz GmbH to look at the following questions in an expert report:

1. How do the systems for the regulation of medical devices in the EU and the USA differ with respect to the approval or conformity assessment process, safety and performance requirements and market surveillance?

2. Do these differences affect device safety?

In the comparison of the regulatory systems in the USA and EU undertaken in this expert report, it is important to remember that the MDR only came into force in 2017 and, as a result of transitional arrangements which obtain up to 2027 or 2028, has not yet been applied in full to all devices (see Annex 1). Data, including empirical data, about how the system is functioning in practice are either missing or very sparse. The

conclusions of this expert report are based on the assumption that both regulatory systems are established for all devices and are fully used and implemented.

# 2. Methodology

This expert report compares the USA and EU legal systems for regulating medical devices with respect to safety-relevant aspects and analyses the differences found with respect to their potential impact on device safety.

For this comparison, the currently valid provisions of the Federal Food, Drug, and Cosmetic Act (7) and Regulation (EU) 2017/745 on medical devices (1) as well as official websites, in particular the FDA website (https://www.fda.gov/), were examined. To be able to better assess the safety-relevant aspects, a literature search was carried out on Pubmed (https://pubmed.ncbi.nlm.nih.gov/) for relevant scientific publications (peer-reviewed). Assessments by the following experts on lived legal practice were also collected:

- **Irvin Bislimi (M.Sc.)**
  Head of Regulatory Affairs at Aesculap AG (B. Braun Group)

- **Luca Salvatore (M.Sc.)**
  Luca Salvatore has been in charge of International Regulatory Affairs at the Johner Institut GmbH since 2015. He has helped numerous medical device manufacturers worldwide to establish regulatory strategies and approvals and is an expert on FDA approvals.

- **Prof. Dr. Ariel Dora Stern**
  Harvard Business School and Harvard-MIT Center for Regulatory Science
  Prof. Stern's research focuses on technology management and innovation in healthcare. Her projects cover the regulation, strategy and economics of healthcare and focus on understanding the driving forces behind the development of new devices in companies and the factors which determine how new medical technologies are accepted and used in practice. Prof. Stern has expertise in the intersection of regulation, company strategy and the economics of healthcare. She also investigates the digital transformation of medical technology and healthcare and looks at the political, social and economic issues arising from the growth in digital health and the digital transformation of medicine.

# 3. Comparison of the regulatory systems USA vs. EU

A comparison of the regulatory systems for medical devices in the USA and EU allows conclusions to be drawn about safety-relevant factors. To this end, different regulatory aspects are examined. These include the general statutory framework, the requirements for market access and post-market surveillance.

## 3.1 Regulatory framework

### 3.1.1 Legal systems and accountabilities

To guarantee the safety of patients, medical devices are strictly regulated and monitored in both the USA and EU.
In the USA, medical devices are regulated by section 201(h) of the **Federal Food, Drug, and Cosmetic Act (FD&C Act)** (7). This law was passed by the US congress in 1938 and has been amended many times since, also with respect to the medical device regulation. The amendments serve, among other things, to extend the field of application to other device groups and to allow for technical developments and other new findings, e.g. with respect to the safety of medical devices (8).

The implementation of and compliance with regulations is monitored by the **U.S. Food and Drug Administration (FDA**), a central authority with law enforcement powers (9). The establishment of the FDA as a central authority responsible for both the approval and the surveillance of medical devices means that the regulation of devices in the USA is always very consistent and that "in-house" experts are available for device assessments. Moreover, a large amount of data and information are centrally recorded and made accessible to the general public through the Freedom of Information Act, which results in a highly transparent regulatory system.

In the EU, the regulatory framework for medical devices is enacted by the European Parliament and Council. In 2017, the new **regulation (EU) 2017/745 on medical devices (MDR)** (1) came into force, replacing Directive 93/42/EEC on medical devices (MDD) (10) and Directive 90/385/EEC on active implantable medical devices (AIMDD) (11). For existing devices placed on the market under the MDD, the transition periods end in 2027 or 2028 in certain circumstances (see Annex 1).

In contrast to the USA, there is no central regulatory authority in the EU for medical devices. Surveillance is conducted on a decentralised basis by national authorities and state-authorised private sector institutions known as **Notified Bodies** (see section 3.1.6). The manufacturers are responsible for declaring that their devices conform with the MDR (Article 10 MDR). For devices associated with higher risk, a Notified Body must be part of the conformity assessment process (see section 3.1.5), which means that a large proportion of medical devices in the EU are also investigated using the four-eyes principle.

### 3.1.2 Use of standards and guidelines

In both the USA and the EU, the legal requirements for safety and performance are supplemented by standards and guidelines considered to be state of the art on both aspects. Standards contains specific requirements for the safety and performance of particular device types and ensure that medical devices are developed and manufactured to high levels of quality. The standards are prepared worldwide by standards committees, for example the International Organization for Standardization (ISO) or the International Electrotechnical Commission (IEC) in collaboration with representatives from different countries. The benefit of standards as a supplement to legislation is that standards are able to look at specific requirements in detail, e.g. at a particular field of application. Moreover, standards can be amended more easily and quickly than legislation to reflect ongoing developments in the state of the art.

The standards relevant to medical devices, e.g. ISO 14971 (risk management), IEC 62304 (medical device software), IEC 62366-1 (usability) and the IEC 60601 series (medical electrical equipment) are, for the most part, recognised to the same extent by the FDA and the EU. Officially recognised standards are published as **recognized consensus standards** (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm) in the USA and as **harmonised standards** (https://single-market-economy.ec.europa.eu/single-market/european-standards/harmonised-standards/medical-devices_en) in the EU. As a result of the changeover from the MDD/AIMDD to the MDR, many standards for medical devices are not yet included in the list of harmonised standards. The deadline for implementation of the standardisation proposal is 27 May 2024 (12). However, this is just a formality, as the Notified Bodies already expect compliance with the standards which reflect the state of the art called for by basic safety and performance requirements (Annex I MDR). In addition to the officially recognised standards, there are also other standards in the USA (13) and the EU which medical device manufacturers can refer to. In both systems, manufacturers must give the authorities their reasons for using or not using a standard.

Both the USA and the EU have the right to define other binding specifications if there are no recognised standards or the recognised standards are inadequate. These are available as FDA-specific **performance standards** in the USA and as **common specifications** in the EU.

In addition to the standards of the official standardisation committees and the binding specifications, there are also other guidelines. These are not legally binding either but compliance with these guidelines is generally expected by the testing bodies, which makes them binding in practice. These guidelines are issued by official organisations such as the FDA and the European Medical Device Coordination Group (MDCG) as well as by testing bodies such as the Notified Bodies and other representatives of the sector such as the Association for the Advancement of Medical Instrumentation® (AAMI) and MedTech Europe. In the USA, the Guidance Documents from the FDA play an essential role. The FDA uses these guidelines to present its standpoint on certain topics such as how to perform certain device investigations. Generally speaking, the FDA guidelines very specifically refer to a certain device or device type and ensure consistent expectations and testing of these devices. The MDCG (https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en) guidelines published to date have, hitherto, tended to be used to interpret the legal requirements.

Safety level is normatively and to a large extent consistently defined through the use of standards and guidelines, independently of the manufacturer's risk assessment. This ensures that devices globally comply with comparable safety levels. Hence, the buyer of a medical device, for example ECG equipment, can assume that its safety and diagnostic performance is the same regardless of whether it was purchased from a US American or a European manufacturer.

### 3.1.3 Qualification of medical devices

Qualification is the process of defining whether a device is considered to be a medical device or not. The definition of a medical device is more or less the same in both legal systems (see Table 1). An essential difference though is that, in the USA, the FD&C Act includes the regulation of devices for the veterinary sector, while in the EU the definition excludes them. The qualification of medical devices is thus comparable in both regions.

*Table 1: Definition of medical devices USA vs. EU*

| **Definition of medical devices** | |
|---|---|
| **USA** | **EU** |
| A “medical device” is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:<br><br>1. recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,<br>2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, **in man or other animals**, or<br>3. intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.<br><br>The term "device" does not include software functions excluded pursuant to section 520(o). | "Medical device" is any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:<br>• diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,<br>• diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,<br>• investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,<br>• providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations<br><br>and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or **on the human body**, but which may be assisted in its function by such means.<br><br>**(Article 2 MDR)** |

| | |
|---|---|
| **(Section 201(h) of the Food, Drug, and Cosmetic Act)** | |

### 3.1.4 Classification of medical devices

In both the USA and the EU, medical devices are divided into risk classes. Classification into risk classes regulates market access in both systems. High-risk classes result in stricter regulation and surveillance.

In the USA, medical devices are assigned to risk classes I to III by the FDA. Class I covers devices with a low risk of disease or harm to the patient, class II devices with a "moderate risk" and class III devices which perform a life-sustaining or supporting function essential to the prevention of harm to health or which pose a potential, inappropriate risk of disease or harm" (14). Medical device manufacturers can research the class of their devices using a device code in the FDA database: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm.

In the EU, the classification is rule-based and, among other things, depends on the type of device and the nature of the application, duration and location. It ranges from the lowest to the highest risk in classes I, IIa, IIb and III. In addition to basic class I devices, class I contains three further sub-classes categorised as class I*: Im *(measure)*, Is (*sterile)* and/or Ir (*reusable)* medical devices. The manufacturers undertake the classification on the basis of rules (Annex VIII MDR) and guidelines. However, they do not have a completely free hand as the classification is checked by the Notified Body. The classification of devices placed on the market without the Notified Body can also be checked by national authorities.

The advantage of the US system is that it is easier for the FDA to make changes to the classification if market data provide evidence for another risk assessment. This makes it easier to react to new technological developments in the USA if necessary (15). By contrast, changes to the classification rules in the EU must be made by amending legislation.

*Table 2: Summary of the classification USA vs. EU*

| | **USA** | **EU** |
|---|---|---|
| Classes | I, II, III | MD: I, I*, IIa, IIb, III |
| Classification | Risk-based assessment by the FDA | Rule-based risk classification |
| Flexibility | is regularly reviewed and adjusted as necessary | rigid, can be adjusted only by amending legislation |

### 3.1.5 Approval or conformity assessment process

The biggest difference between the regulatory systems in the USA and EU is that medical devices in the USA are usually approved following testing by the FDA (depending on the approval process this is known as "clearance" or "approval"), whereas manufacturers in the EU declare that their devices comply with the MDR themselves. As approval is in the form of a licence issued by an authority, the FDA confirms compliance with all regulations in the USA. By contrast, the EU conformity assessment process essentially places the responsibility with the manufacturer and this must be verified by a Notified Body depending on the risk (from class I* onwards).

#### *US approval process*

In the USA, each device undergoes its own approval process to obtain market access. There are three main procedures by which medical devices are examined by the FDA (fig. 1):

1. Premarket Notification (510(k))
2. De Novo Classification Request
3. Premarket Approval (PMA)

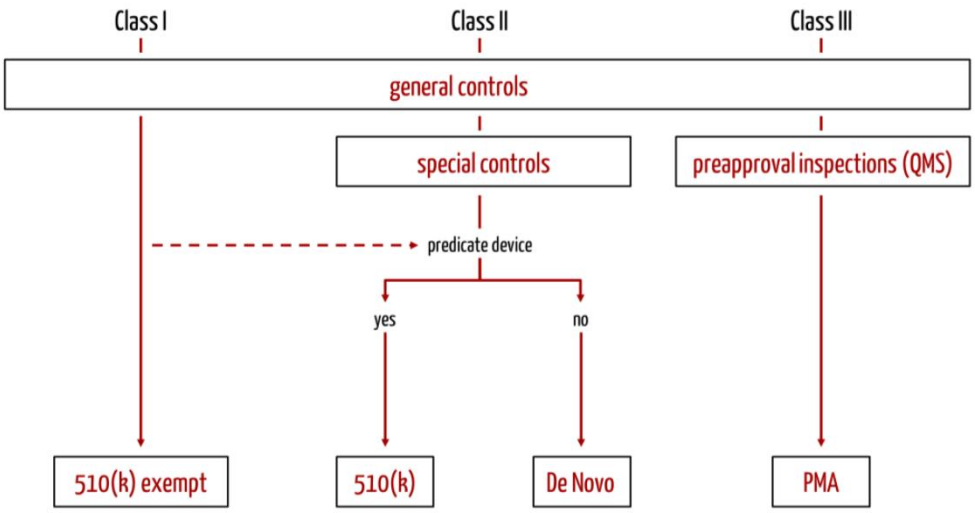


***Fig. 1: US approval process***

The standard processes are presented for classes I, II and III. Special cases for certain devices, e.g. class III devices which have been granted a 510(k), as well as special processes e.g. Humanitarian Device Exemption (HDE) are not illustrated.

### Premarket Notification (510(k))

The premarket notification (14,16) approval process, better known as the 510(k) process, is based on a comparison with a similar device, the so-called predicate device, which is already lawfully placed on the market in the USA. As a result of substantial equivalence, it is assumed that the device is as safe and effective as the predicate device. This process can usually only be used for devices with a moderate risk (class II, or in few instances, class I).

Devices are considered equivalent if they have the same intended use and the same technical characteristics, or if they have the same intended use but different technical characteristics that do not, however, affect safety or performance. Manufacturers must prove equivalence using relevant FDA data. These data can be clinical as well as non-clinical (laboratory) data, and include technical performance tests, sterility, electromagnetic compatibility, software validation, biocompatibility assessment and other data. Accordingly, substantial equivalence does not imply that the new device and the predicate device must be identical.

The 510(k) process is the process used to approve most medical devices in the USA. In 2017, 3,173 devices were approved via the 510(k) path, which corresponds to 82 per cent of all approved devices (17). On average, 2,825 devices are approved via the 510(k) process each year.

### De Novo Classification Request

New types of devices with a low or moderate risk (class I or II) and for which no *predicate device* exists, can be approved via the De Novo process (14,19). If this is used, the manufacturer must assess whether the *general* and, if applicable, the *special controls* (see section 3.2.2) are suitable for guaranteeing the safety and

performance of the device. Moreover, the manufacturer must demonstrate the safety and performance of the device through clinical data, performance assessments and other data, including biocompatibility, sterility and electronic safety. In addition, a benefit-risk analysis is required. Devices which have been approved via the De Novo process can be used in future as *predicate devices* for comparable devices within the scope of the 510(k) process.

**Premarket Approval (PMA)**

For devices with a high-risk (class III), the FDA has specified that general and special controls on their own are not a sufficient guarantee of the safety and performance of these devices. For FDA approval via the Premarket Approval (PMA) process (14,20), the manufacturer must provide sufficient scientific, in particular clinical evidence, that the device is safe and effective when used according to directions. On average, 31 devices are approved via the PMA process each year (18).

**Other processes**

Most class I devices and a small proportion of class II devices are graded by the FDA as so uncritical ("**exempt**" status) (21) that no testing of safety and performance is required by the authority in question and hence none of the above-mentioned approval processes needs to be used for these devices. This applies to, among other things, many software devices. These devices are listed in this FDA database: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm.

In addition to the three approval processes described here, there are other special processes. For example, niche devices used to treat or diagnose diseases affecting less than 8,000 people annually in the USA can be approved via the **Humanitarian Device Exemption (HDE)** process (14,22). No scientific proof of performance is needed for these devices. The manufacturer only needs to show that there is a probable benefit for the patients and that this benefit outweighs the risks. As this and other special processes play only a very minor role, they are not examined any further in this expert report.

The approval of medical devices by the FDA is permanent. This means that once devices are lawfully placed on the market in the USA, they are allowed to be marketed without restriction provided that they are not significantly changed or show any serious safety problems, even if regulatory or normative requirements change. This is known as grandfathering.

## *EU conformity assessment process*

The MDR specifies in chapter 5, section 2 that every manufacturer must conduct a conformity assessment process before a device is allowed to be placed on the market. These processes are described in Annex IX to XI and can be summarised as follows:

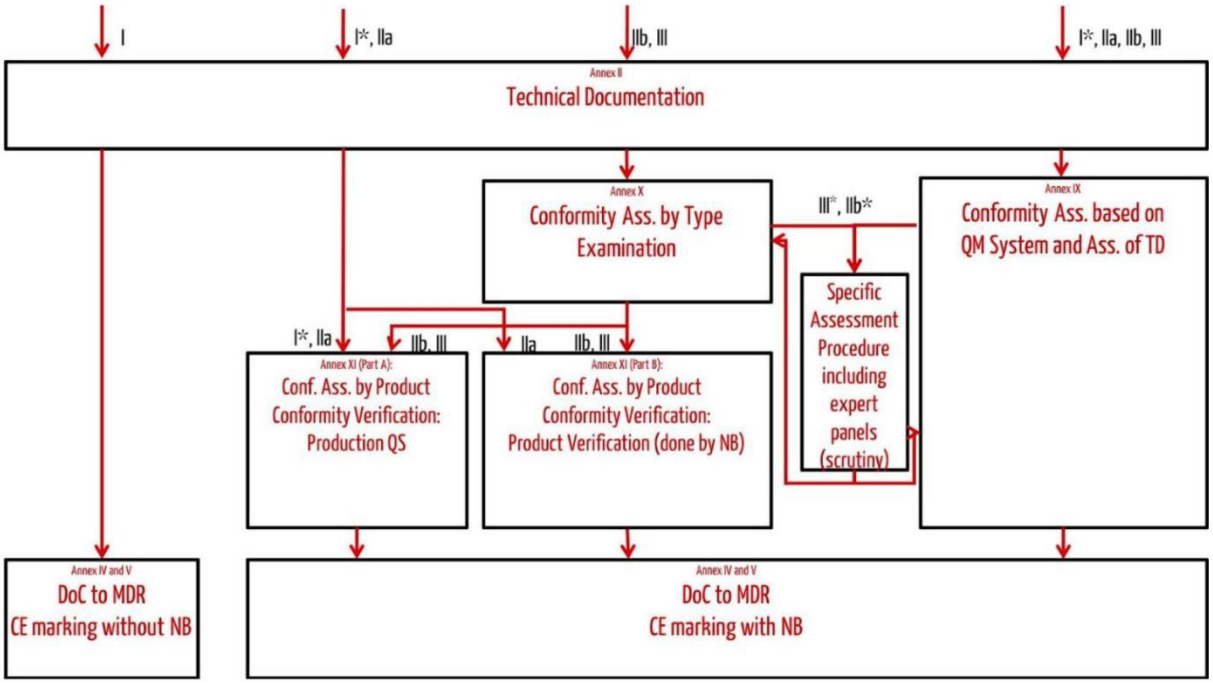


***Fig. 2: EU conformity assessment procedure according to MDR (23)***

The standard procedures are shown for classes I, I*, II and III. Special procedures, e.g. special productions based on Annex XIII are not depicted (DoC = Declaration of Conformity; NB = Notified Body; TD = Technical Documentation; QM = Quality Management; QS = Quality Assurance).

An absolute prerequisite for all assessment procedures is technical documentation in accordance with Annex II. This usually contains a device description, clinical assessment, risk management documentation, usability documentation, operating instructions and labelling information. Depending on the device type, the technical documentation is extended to include additional information, for example, software or biocompatibility documentation.

For class I devices, the manufacturers undertake the conformity assessment procedure themselves by writing the technical documentation and subsequently declaring conformity without examination by a Notified Body according to Annex IV and V (self-declaration).

For all other (higher) classes, including class I*, the technical documentation is at least partly reviewed by a Notified Body. A list of all Notified Bodies is available on the EU's NANDO (New Approach Notified and Designated Organisations) database website: https://webgate.ec.europa.eu/single-market-compliance-space/#/notified-bodies/notified-body-list?filter=legislationId:34.

Depending on the selected procedure, the following reviews are conducted:

- Manufacturers of class IIa devices which are not special productions or investigational devices, are subject to a conformity assessment in accordance with Annex IX chapters I and III, including an assessment of the technical documentation in accordance with section 4 of the same Annex for at least one representative device in each device category. Alternatively, the manufacturer can opt to produce the technical documentation in accordance with Annexes II and III, in combination with a conformity assessment in accordance with Annex XI section 10 or section 18. The assessment of the technical documentation applies to at least one representative device from each device category.

- Manufacturers of class IIb devices which are not special productions or investigational devices, are subject to a conformity assessment in accordance with Annex IX chapters I and III, including an assessment of the technical documentation in accordance with section 4 of the same Annex for at least one representative device from each generic device group. For implantable class IIb devices, with the exception of sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips and connectors, the assessment of the technical documentation in accordance with Annex IX section 4 applies to each device. Alternatively, the manufacturer can opt for a conformity assessment based on a type examination in accordance with Annex X, in combination with a conformity assessment based on a verification of device conformity in accordance with Annex XI.

- Manufacturers of class III devices which are not special productions or investigational devices are subject to a conformity assessment for each device in accordance with Annex IX. Alternatively, the manufacturer can opt for a conformity assessment in accordance with Annex X, in combination with a conformity assessment in accordance with Annex XI.

In addition, the so-called "scrutiny process" has been introduced as part of the MDR. This process is also known as the consultation process and provides for Notified Bodies to include an expert committee in the conformity assessment. The consultation process is used only for class lll implantable devices or active class llb devices which administer or remove a medicinal product from the body.

The certificates are issued by the Notified Bodies and are valid for 5 years. During this time, the companies are monitored and regularly checked by the Notified Bodies (see section 3.1.6).

With CE marking, manufacturers declare that their devices conform with all applicable legal requirements. If the state of the art or the regulations change, manufacturers must allow for and implement these changes. As a matter of principle, there are no exceptions for post-market devices. Manufacturers are usually granted transition periods for implementation, as is the case with the MDR for certain existing devices (24).

***Table 3: Summary of the conformity processes USA vs. EU***

| | **USA** | **EU** |
|---|---|---|
| Are medical devices approved? | Yes, they are approved by the FDA. | No, manufacturers declare conformity with the regulations themselves. Depending on the device class (apart from class I, without I*), clearance must be issued by a Notified Body as part of the conformity assessment process. |
| Are the requirements classified by risk? | Yes | Yes |
| Are all devices examined by a testing centre? | No, devices with a very low risk can be exempted from the approval (*exempt* status). All other devices are examined by the FDA. | No, class I devices (apart from I*) are not examined by a Notified Body. The manufacturer takes responsibility for the declaration of conformity. However, the national competent authorities also investigate class I devices by random sampling.<br><br>Under Annex IX, the examination of documentation by the Notified Body is partly based on random sampling. For certain high-risk devices, the documentation of each device is reviewed. |
| Is market placement via a predicate device possible? | Yes, the majority of devices are cleared via the 510(k) process on the basis of predicate devices. | Yes, under MDR, the pathway via predicate devices is possible, to a considerably lesser extent than with the MDD however. |
| Are device-specific clinical data required? | Depends on the device class and whether a predicate device exists. Mandatory for high-risk devices. | Depends on the device class and available clinical data. Mandatory for high-risk devices. |
| How long is the approval or the certificates valid for? | The approval is unlimited as long as no significant changes are made to the device and there are no indications of adverse effects relating to safety or performance. This also applies even if the regulations change. | Certificates are issued for a duration of 5 years.<br><br>At the time of shipment, it must be proven that each device is state of the art. This means that even devices that are manufactured in the same way post-market must be recertified if, for example, the regulations change. |

### 3.1.6 Authority market surveillance

In both the USA and the EU, manufacturers are monitored by the authorities to ensure that they comply with the regulatory requirements, in particular with respect to the quality management system (QMS; see section 3.2.1).

The FDA routinely inspects the manufacturers of class ll and lll medical devices (*routine inspections*) in accordance with a risk-based timeline (FD&C Act §360 (h) (2) and (4)). On these occasions, the QMS is inspected in two of the four areas of management, development, corrective and prevention actions (CAPA) and control of the production and processes. The FDA also reviews compliance with other regulations, including part 806 (Reports of Corrections and Recalls), part 803 (Medical Device Reporting), part 807 (Registration and Listing) and part 821 (Tracking). Following incidents or in the event of inspectional findings, the FDA conducts compliance follow up inspections to check whether earlier violations have been adequately corrected by CAPA, to document ongoing violations or to support future regulatory actions. If specific problems are reported to the FDA, the latter will use “for cause” inspections to investigate them in detail (25).

In the EU, market surveillance is organised on a decentralised basis by member states and carried out within the scope of surveillance programs if conformity violations are suspected or following serious incidents. In accordance with Article 101, the member states name a competent authority which cooperates with the competent authorities of the other member states and with the Commission (Article 102 MDR) and hence coordinates European-wide market surveillance activities. It is up to the member states to decide whether to hand over the entire responsibility to a single authority or whether to use other subordinate authorities in addition to a superordinate authority. The market surveillance activities are described in Article 93 of the MDR and cover in particular checks on the conformity of device characteristics and performance conducted through, among other things, examinations of the documentation, physical controls and laboratory tests on the basis of appropriate samples. In doing so, risk management, vigilance data and complaints are taken into account.

Authority market surveillance in the EU is supported by the surveillance activities of the Notified Bodies. These bodies carry out annual QMS surveillance audits for manufacturers of devices in classes I* to lll, and in accordance with the selected conformity assessment process. The Notified Bodies also continually evaluate the technical documentation on the basis of a random sampling plan. Unannounced audits must also be conducted at least once every five years or as required, for example following vigilance reporting (Annex lX 3.4 MDR).

***Table 4: Summary of authority market surveillance***

| | **USA** | **EU** |
|---|---|---|
| Are medical device manufacturers monitored by the authorities? | Yes, the FDA routinely conducts inspections in accordance with a risk-based timeline and following incidents and specific problems. | Yes, the competent authorities carry out checks as part of surveillance programs if conformity violations are suspected or following serious incidents.<br>In addition, manufacturers of class I* to III devices are audited annually by their Notified Body. |
| Which classes are monitored by the authorities? | All classes, with particular risk-based focus on higher classes. | All classes, with particular risk-based focus on higher classes. |

## 3.2 Regulatory requirements for market access

### 3.2.1 Quality management system (QMS)

In the USA and the EU, manufacturers of medical devices are required to set up a quality management system (QMS). Important aspects of a QMS for medical device manufacturers include compliance with safety and performance requirements, risk management, clinical assessment, post-market surveillance system, vigilance, the management of corrective and preventative actions as well as device improvements.

In both legal systems, no substantial differences can be identified in the requirements for the QMS which could have a significant impact on device quality (15). The differences predominantly lie in vigilance, with the FDA requirements being specific to the American system, and in the traceability of documents.

The international standard ISO 13485 helps manufacturers to set up a functional QMS. ISO 13485 is already harmonised in the EU under the MDR. FDA requirements are currently being aligned with those of ISO 13485 to reduce further the differences between the two legal systems in future (26).

In the USA, the FDA always checks, as a matter of principle, the QMS of medical device manufacturers during their routine inspections (see section 3.1.6). Prior to market placement, the QMS is checked only for manufacturers of new high-risk devices during the PMA process as part of pre-approval inspections (25). Individual non-sterile class I or II devices are exempt from the obligation of a QMS ("**GMP exempt**"). These devices are listed in this FDA database: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm.

In the EU, all manufacturers are required to have a QMS which is monitored (annually) in accordance with Article 10 MDR (see section 3.1.6). Whether this has to be officially certified according to ISO 13485, for example, and inspected pre-market by a Notified Body depends on the selected conformity assessment process (see section 3.1.5).

### 3.2.2 Evidence of safety and performance

The FD&C Act requires that medical devices must be safe and effective without specifying this in more detail. On top of this there are basic rules, known as the general controls, which apply to all devices (27). They contain specifications on fakes, false labelling, device registration and listing, pre-market reporting, forbidden devices, reporting on activities in the field including repair, replacement or returns, recordings and reports, impaired devices as well as compliance with good manufacturing practice (*GMP*). Class ll devices must comply with other device-specific rules known as special controls (28). These include performance standards, post-market surveillance, patient registers, special requirements for labelling, requirements for pre-market data and device-specific guidelines.

Annex I of the MDR describes in detail fundamental safety and performance requirements which, provided that they apply to the device in question, must always be complied with. These are subdivided into general requirements (chapter I, e.g. risk management), requirements regarding the design and manufacture (chapter II, e.g. biocompatibility and usability) and requirements regarding the data supplied with the device (chapter III).

Demonstrating the safety and performance of medical devices takes place in two stages. Firstly, clinical data must be systematically collected and assessed (**clinical assessment**). Clinical data can either be data collected from clinical studies or from public data published in scientific literature or for predicate devices (29). The requirements of clinical studies are largely regulated in the same way in both the USA and the EU. Secondly, manufacturers use recognised standards that specify the device requirements and examination criteria.

Whereas in the USA the pathway via predicate devices (510(k) process) is used for the majority of devices (see section 3.1.5), in the EU this pathway has been significantly restricted since the introduction of the MDR (30). Clinical assessment via CE-marked equivalence devices is still possible only if no significant differences exist in terms of the safety and clinical performance of the devices, technically as well as biologically. Moreover, manufacturers must be able to prove unequivocally that they have access to the predicate data, which means this pathway is practically impossible for competitor devices.

## 3.3 Regulatory requirements for manufacturers regarding post-market surveillance

To guarantee that medical devices are safe and efficient to use, manufacturers must monitor their post-market devices to identify problems and, if necessary, react to incidents.

### 3.3.1 Post-market surveillance in the USA

In accordance with 21 CFR part 820.198. manufacturers selling devices in the US American market are required to define a process for dealing with incoming reports in the form of complaints and claims, for investigating and assessing them and, if applicable, for drawing the conclusions required from them about any preventative and corrective actions required (CAPA) as per 21 CFR part 820.100. Reportable incidents, so-called Medical Device Reports, must be reported to the FDA in accordance with 21 CFR part 803. In addition to the manufacturer's obligations, there are further reporting obligations in the USA which require health institutions (in the same way as in Switzerland) to report incidents to the manufacturer and FDA (14). The FDA monitors reported serious incidents involving devices and investigates whether the manufacturers implement adequate CAPA actions. If the FDA decides that the devices do not (or no longer) comply with the regulatory requirements and/or that the safety and performance of the device is no longer guaranteed, a device recall can be ordered and the device can no longer be sold.

There are public databases for reports from manufacturers and health institutions (MAUDE: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm), as well as for reports of device recalls and safety warnings issued by the FDA (https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts)

In accordance with 21 CFR part 822.1, the FDA can also demand proactive post-market surveillance (PMS) activities if the medical device belongs to class II and III and

- a malfunction could lead to serious adverse effects on health
- or the device is allowed to be implanted for longer than one year
- or the device is life-supporting or life-sustaining
- or the device is likely to be frequently used in paediatric populations.

The FDA can impose this requirement at the time approval is applied for or at a later time. PMS is defined as "The active, systematic, scientifically valid collection, analysis, and interpretation of data or other information about a marketed device" (21 CFR part 822). A corresponding guidance document (31) contains instructions about what actions manufacturers should take to comply with the requirements of 21 CFR part 822.

Supplementary to the legal regulations, the ISO 14971 standard on risk management for medical devices recognised by the FDA requires, as a matter of principle, PMS for all devices (15).

### 3.3.2 Post-market surveillance in the EU

To ensure that manufacturers can react strategically to incidents involving their devices and hence reduce the likelihood that a (negative) event occurs again, a reactive vigilance system is also obligatory for the EU market (MDR chapter VII section 2). The EU requirements regarding vigilance as well as the reporting obligations for manufacturers are regulated in a way comparable to the USA. The reporting obligations for health institutions in the EU are not regulated by the MDR but by special national laws, for example in Germany by §§ 3 (2) and 5 (2) of the Medizinprodukte-Sicherheitsplanverordnung (MPSV) (Medical Devices Safety Plan Regulation). Reportable events are monitored by the *competent authorities* as well as the Notified Bodies. If necessary, device recalls can also be ordered.

At the time of writing, reports are not collected in a public database in the EU. Instead, medical device manufacturers must report incidents to the competent authority (e.g. Swissmedic in Switzerland or BfArM [Federal Institute for Drugs and Medical Devices] in Germany) who document the applicable national corrective measures in the field. The information exchange between the individual national authorities takes place via the non-public Eudamed2 database system. At some time in the future, the reports should be centrally recorded in the new **EUDAMED** (https://ec.europa.eu/tools/eudamed/#/screen/home) database which is partly accessible to the public.

With the MDR, the EU also focuses strongly on proactive systematic post-market surveillance (PMS) which collects and analyses all available data about the device to detect potential problems (promptly) and, if applicable, resolve them before serious incidents occurs (MDR chapter VII section 1). The requirements for this are substantially more detailed and specific than under MDD.

In accordance with Article 83 and 84 of the MDR, this active post-market surveillance must be systematically planned and undertaken for all devices regardless of their risk class. This systematic surveillance must fulfil the following objectives:

- Update of the benefit-risk analysis and improvement of risk management,
- Update of the design and manufacturing information, operating instructions and labelling,
- Update of the clinical assessment (post-market clinical follow-up or post market performance follow-up),
- Update of the summary on safety and clinical performance,
- Determination of the requirement for preventive, corrective or safety corrective actions in the field,
- Determination of the options for improving the usability and the safety and performance of the device, if applicable as a contribution to the surveillance of other devices,
- Detection and reporting of trends.

The data generated and collected during this process will be used, among other things, to update the device's technical documentation. Moreover, the manufacturers are required to write a post-market surveillance report (PMS report) or a detailed periodic safety update report (PSUR). The PMS report is mandatory for class I devices. A PSUR is required for all other classes. Both reports are used to determine whether the planned

device-specific surveillance has actually been carried out. The reports must contain the following as a minimum:

- Summary of the collected and assessed results
- (Any) conclusions drawn from the results obtained
- Corrective and preventative actions undertaken (with reason)

and additionally in the PSUR:

- Conclusions about the benefit-risk analysis
- Number of sales, applications and patients

The risk class of the respective device determines not only the required content but how often the reports are written:

- MDR class I: PMS report, as required
- MDR class IIa: PSUR, as required but at least every two years
- MDR class IIb and lll: PSUR, as required but at least once a year

***Table 5: Summary of post-market surveillance USA vs. EU***

| | **USA** | **EU** |
|---|---|---|
| Do manufacturers have to monitor post-market devices? | Yes, manufacturers must define a process for all reports, i.e. for how they investigate and assess reports and complaints, and, if applicable, initiate corrective actions and send reports to the FDA. | Yes, manufacturers must define a process for all reports, i.e. for how they investigate and assess reports and complaints, and, if applicable, initiate corrective actions and send reports to the competent authorities. |
| Is a proactive PMS system (based on the EU specification in the MDR) mandatory for all devices? | There is no basic legal obligation to set up a proactive PMS system. The FDA can, however, order PMS actions for class II and class III devices in certain circumstances. In addition, the recognised standard (ISO 14971) on risk management requires PMS for all devices and is hence mandatory in practice. | Explicitly required from the manufacturers in the MDR and mandatory for all device classes, but with different requirements regarding the granularity and frequency of the report depending on the device class. ISO 14971 is also harmonised for the MDR |
| Who is responsible for reporting serious incidents? | Manufacturers must report problems and reportable incidents centrally to the FDA, and there are extended reporting obligations for health institutions. | Manufacturers must report problems and reportable incidents to their competent authorities in the member states. The reporting obligations for health institutions are not regulated by the MDR but by national laws |
| Are reports of serious incidents transparent? | In the USA, there are public databases for reports from manufacturers and health institutions (e.g MAUDE) as well as for reports on device recalls and safety warnings from the FDA. | Information exchange between the individual national authorities takes place via the non-public Eudamed2 database system. At some time in the future, the reports should be centrally recorded in the new EUDAMED database which is partly accessible to the public |

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# 4. Discussion

As the Swiss regulation of medical devices (MedDO) essentially corresponds to EU requirements, a comparison of the regulatory systems in the EU and the USA was undertaken to examine to what extent the regulations differ and whether the discovered differences could potentially impact the safety of devices.

## 4.1 The system comparison reveals no substantial safety-relevant differences

Because of their high priority and their potential risk to human health, medical devices in both the USA and EU are strictly regulated and monitored. Regulation is risk-based in both legal systems (see section 3.1.4) and the use of international standards ensures a comparable level of safety for all devices, regardless of where they are sold (see section 3.1.2).

There is much common ground in the construction and implementation of the regulations and only specific differences which are discussed below. However, we were unable to find any indication that these differences could lead to significant safety concerns.

### 4.1.1 Approval vs. conformity assessment processes

Depending on the risk class, medical devices have to undergo certain processes to obtain market access (see section 3.1.5). There is a substantial difference here between the two legal systems. In the USA, devices are usually approved by the FDA, i.e. the authority confirms compliance with all regulations. In the EU, by contrast, the manufacturers are responsible for declaring conformity with the valid regulations. However, depending on the risk class, a state-authorised Notified Body must be included in the conformity assessment process which issues a certificate confirming that parts of the manufacturer's technical documentation have been inspected for completeness and correctness.

While there is a simplified special process such as the HDE process in the USA for niche devices (see section 3.1.5), the MDR makes no provision for a comparable process. Accordingly, all devices in the EU essentially have to undergo a significantly more expensive standard conformity assessment process. This may mean that devices are placed late or even not placed on the EU market, which can restrict patient care and hence patient safety.

Because of their low risk, class I devices in both the USA and the EU are exempted from the costly and time-consuming approval or conformity assessment process, but are monitored by the authorities. This ensures that, in both legal systems, there is more capacity available for monitoring higher risk devices.

### 4.1.2 Quality management system (QMS)

A QMS specifies how the process and product quality is reviewed, maintained and, if applicable, improved in the company over the entire life cycle of the device. The installation of a QMS is mandatory in both regions for almost all devices. In the USA, individual devices with a low risk are exempted from the obligation (GMP exempt). The requirements for QMS are already comparable today and will be further harmonised through the alignment of the FDA requirements to the ISO 13485 (see section 3.2.1). This ensures that manufacturers in the USA and the EU set up processes which, among other things, comply with the regulatory requirements, monitor the quality and safety of their devices and actively react to incidents with corrective and preventative actions.

One difference lies in surveillance. In the USA, the QMS (with the exception of the PMA process) is only investigated post-market as part of the inspections by the FDA (apart from GMP exempt). In the EU, all manufacturers who have opted for the conformity assessment process per Annex IX (which most have) must have their QMS certified pre-market by their Notified Body. Moreover, an annual surveillance by the Notified Body is mandatory in the EU, while in the USA the FDA uses a risk-based inspection plan with longer intervals between inspections.

There are no indications in the literature that the differences in surveillance of the QM systems has an impact on device safety.

### 4.1.3 Evidence of safety and performance

In both legal systems, manufacturers must demonstrate the safety and performance of their devices (see section 3.2.2).

The basic safety and performance requirements are described in great detail in the MDR. By contrast, the requirements in the USA are not written in detail into law but are specified in the FDA guidelines. The FDA guidelines usually focus on specific individual device groups or technologies so that more detailed specifications are not possible here (15,32). The advantage of the US system is that changes can be made more easily and hence it is possible to react more quickly to technological developments for example. Changes are also possible in the EU via common specifications, for example, but, based on experience, they require considerably more time to be implemented.

Moreover, the manufacturers in both systems provide evidence of safety and performance through the use of device-specific (international) standards. In this way, comparable device safety is guaranteed, supplementary to the regulatory requirements.

Manufacturers must clinically assess their devices in both the USA and EU. Provided that sufficient data are available, e.g. from scientific literature or an equivalence device, clinical data specific to the device are not absolutely essential except for high-risk devices.
Another difference, however, is the acceptance of predicate devices. In the USA, the majority of devices (17, 18) are approved as part of the 510(k) process on the basis of what are known as predicate devices (see section 3.1.5). There are concerns about whether the equivalence comparison in the 510(k) process is suitable as a sufficiently reliable demonstration of the safety and performance of medical devices (33,34). Critics of the 510(k) process complain that, just because an almost identical predicate device exists, this does not automatically guarantee the safety and performance of the new device (35). However, as part of the 510(k) process, manufacturers must demonstrate that, at the time of approval, the safety of the device complies with all currently applicable standards and guidance documents as well as with the currently valid legal specifications. In the EU, the pathway via equivalence devices is severely restricted under the MDR. This means that manufacturers have to demonstrate performance and clinical effectiveness in particular via other pathways. Often, the public clinical data are insufficient so that more clinical trials will probably have to be conducted in the EU.

Another criticism of the USA approval process is that there are medical devices assigned to class lll which should only be approved via the PMA process. However, some of these PMA devices, for example certain hip protheses (36), are not regulated on the basis of their risk class but are approved via the 510(k) process (34). From the FDA's standpoint, these devices do not place patients at greater risk, which means that they do not prioritise a new classification.

On the whole, devices in the USA can remain on the market after their first approval through what is known as grandfathering (see section 3.1.5). They do not have to comply with the currently valid regulations, provided that no changes are made and there are no indications of impaired safety and performance (for example, via the reporting process for US devices). However, devices in both the USA and the EU must comply with the requirements of the ISO 14971 standard on risk management which ultimately reflects the state of the art.

The recall data published by the FDA show that the American system works. In absolute terms, the majority of recall devices are in class II which were approved via the 510(k) process (37). If these data are compared with the total number of approved devices, it becomes clear that the high-risk devices approved via the PMA process have a significantly higher recall rate (almost 30%) than devices approved via the 510(k) process (approx. 11%) (18). The higher recall rates of high-risk devices can be explained by the nature of the devices. To date, there are no comparable data for the EU.

The specific implementation of the ways in which manufacturers demonstrate safety and performance is monitored in both markets by the authorities, and the normative and legal requirements are, as already described, very similar. Surveillance differs though in several ways. While the Notified Bodies mainly look for complete compliance with the regulatory requirements of the MDR, the FDA focuses on the practical implementation of the guidance documents and standards. Organising experts within an authority - together with their expert knowledge - into a device code-specific expert panel, ensures that even the supporting

documents are often subject to very intensive scrutiny. If problems are detected, devices in both systems can be recalled if necessary to guarantee patient safety.

### 4.1.4 Post market surveillance by manufacturers

In both regulatory systems, medical device manufacturers are required to identify risks from medical devices through market surveillance (see section 3.3).

Comparable requirements exist in the USA and the EU for dealing with serious incidents. However, the USA has a more active reporting system for cultural reasons (15). Additionally, users and patients in the USA can directly and publicly report possible incidents without requiring an assessment by the manufacturer.

The legal requirements regarding proactive market surveillance are more extensive in the EU than in the USA. However, the FDA has recognised the ISO 14971 standard on risk management for medical devices in which PMS is required and hence the differences are smaller in practice than they appear at first glance (15). Moreover, there have been no analyses to date on how much PMS is necessary, particularly with respect to the device risk and in comparison with the required effort.

All in all, a comparable level of safety can be assumed.

## 4.2 The central role of the FDA leads to more consistency and transparency in the regulation of medical devices

In the USA, placing all the responsibilities for regulating medical devices with the FDA leads to consistent regulation of the devices (see section 3.1). The central publication of guidelines, data and information results in more clarity and transparency for all market participants. Moreover, the FDA provides close interaction with manufacturers in order to organise device approvals more efficiently (15,32).

In the EU, the decentralised approach using private-sector Notified Bodies is frequently criticised as being inconsistent and, in the past, as being to some extent, more business- than patient-oriented (38). Currently, the picture that emerges tends to be one in which the Notified Bodies are too critical in their investigations in some cases and make demands that go beyond the scope of the valid regulations (39). The inconsistent interpretation of the regulations leads to discrepancies during device review and to uncertainties about the requirements, among other things, for manufacturers (15,32,39).

This means that, in the USA, the same device from different manufacturers is always investigated using the same criteria. By contrast, due to its decentralised structures, it is impossible to guarantee in the EU that devices from different manufacturers are always investigated with same strictness.

## 4.3 Effect of MDR transitional arrangements on safety

Although the MDR officially came into force on 26 May 2021, it has not yet been fully applied to all devices.

All devices, including those that have already been on the market for many years without incident, must always comply with the current regulations as the MDR has not, as a matter of principle, made any special provisions for existing devices. The re-examination and higher requirements of the MDR regarding clinical evidence means that manufacturers are reassessing their portfolios and that established devices, particularly those in the niche sector, are disappearing (or could disappear) from the market without an alternative in some cases and that, as a result, patient care can no longer be guaranteed to the same degree (2,3).

Beside the re-certification of devices, all Notified Bodies must be re-informed. Here too, requirements have increased so that currently, under the MDR, there are significantly fewer Notified Bodies (39 MDR Notified Bodies as of July 2023) than under the MDD (49 MDD Notified Bodies), which is causing a certification bottleneck. To avoid supply bottlenecks, the EU Commission has extended transitional deadlines for existing devices with an MDD certificate from 2024 to 2027/28 in certain circumstances (see Annex 1). During this period, these devices can still be placed on the market with an MDD certificate. Requirements under the MDR have to some extent increased. The MDR has higher requirements for post-market surveillance (PMS) than the MDD. Manufacturers who place their devices on the market under the transitional arrangements must have already set up a QMS in accordance with MDR, as well as comply with all the surveillance activities required by the MDR.

## 4.4 Regulatory science (would be) important for evidence-based regulation

To guarantee the healthcare of their population, countries should adequately consider all aspects of patient safety when making decisions about medical device regulation and supply evidence-based reasons for them.

Regulatory science (40), a science which deals with regulation and its impact, has been established at the FDA for many years. The goal of regulatory science is an evidence-based assessment of the regulations as well as the regulatory amendments required for the ongoing development of the market and technologies. The FDA is currently working to make the regulation more flexible and hence more up-to-date with respect to product development cycles (41). Based on previous statements from the FDA, it is to be assumed that no serious additional safety concerns were detected in the system during the intensive research.

To date, there exists absolutely no scientific examination of this kind within the EU. In the EU, the approach taken would appear to be that more extensive regulation is better, but there is no evidence whatsoever to this effect. This approach takes too one-sided an approach to patient safety as only the potential risk of a medical device is assessed. The consequences of unavailable devices, devices that are too expensive or the delays in placing new devices on the market are not considered here (42). However, it is precisely these problematic consequences for supply security which have been emerging in the EU since the introduction of the MDR (2,3). The lack of availability and consistency of EU data on market placement and recalls of medical devices has made it more or less impossible both in the past (35,37) as well as in the present to carry out quantitative comparisons of the two regulation systems.

In our literature research, we failed to find any reports about systemic safety problems with devices from the USA or the EU. Only a few publications carried out quantitative comparisons of device safety under the US and EU systems during the time of the MDD. Davis et al., 2011 (43) analysed vigilance data from the USA and the EU in the period from 2005 to 2009. They discovered that, in absolute terms, the number and type of device recalls in both systems were more or less identical. Hwang et al. 2016 (37) examined safety warnings and recalls for new cardiovascular, orthopaedic and neurological medical devices that were awarded a CE marking between 2005 and 2010. In contrast to Davis et al., they found that the rate of reports was almost three times higher up to 2016 if these devices were first placed on the market in the EU. It should be taken into account though that significantly more devices were first placed on the market in the EU and that about a third of the examined devices were not marketed in the USA. No comparable studies have been published to date for the MDR.

# 5. Summary

The comparison of the regulatory systems in the USA and EU show that they have much in common but that there are also some differences in the processes. Both systems have some challenging aspects but seem to function well overall. In both legal systems, the safety and performance of the devices as well as their surveillance are of central importance. In the USA, the central role of the FDA guarantees a consistent investigation and surveillance of the devices. By contrast, the decentralised approach in the EU requires in some cases a more extensive description of the regulatory requirements to guarantee appropriate examination and surveillance.

In the EU in particular, a lack of data makes it impossible to carry out analyses that go beyond the system comparison. In addition, the MDR has not yet been fully applied (transitional arrangements) so that only the future will show whether and to what extent the MDR leads to an improvement in the device or patient safety compared to the MDD.

Overall, no substantial safety concerns could be identified. Medical devices from both jurisdictions are developed, manufactured and monitored to comparably high standards. On the basis of this system comparison, medical devices approved by the FDA for the USA are at least as safe as CE-marked medical devices that comply with EU regulations. It should, however, be taken into account that the regulatory systems were compared overall and not in terms of individual devices in this expert assessment. Accordingly, it cannot be concluded in general terms that no differences exist for individual devices. This must be examined separately.

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# Annex 1: MDR transition periods according to Regulation (EU) 2023/607

Originally and in accordance with Article 120, the MDR provided a transitional period up to 26 May 2024 for the market placement of existing devices with a valid MDD/AIMDD certificate. To guard against impending supply bottlenecks from existing products, Regulation (EU) 2023/607 (24) was enacted on 15 March 2023 to continue to permit, in certain circumstances, the market placement of existing devices until the end of 2027 (class lll devices and (with exceptions) class IIb implantable devices) or until the end of 2028 (remaining class llb, class lla and l devices) (see Fig. Annex 1). Prerequisite for this is that the manufacturers set up a quality management system in accordance with Article 10 Paragraph 9 MDR by 26 May 2024 at the latest and that a written agreement for a timely MDR certification with a Notified Body exists by 26 September 2024. In addition, MDR requirements for post-market surveillance, market surveillance, vigilance and the registration of economic stakeholders must be complied with. The Notified Bodies continue to be accountable for the appropriate surveillance of all applicable requirements in the transition period.

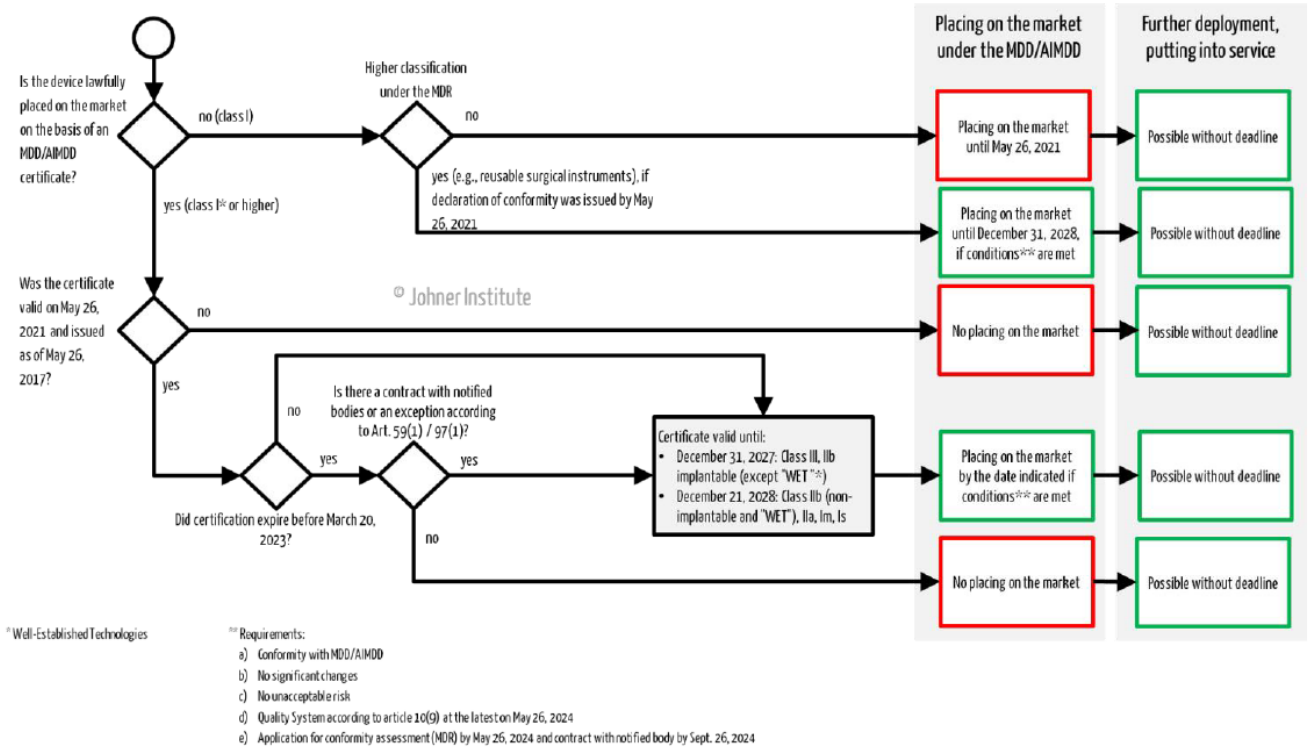


***Fig. Annex 1: Transition periods for existing devices in accordance with Regulation (EU) 2023/607 (44)***

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# Annex 2: Tabular summary

| Comparison of the regulatory systems | | | |
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| | **USA** | **EU** | **Summary** |
| **Regulation** | | | |
| **Are medical devices regulated?** | Yes, by the Federal Food, Drug, and Cosmetic Act (FD&C Act). | Yes, mainly by Regulation (EU) 2017/745 on medical devices (MDR). | Medical devices are strictly regulated both in the USA and the EU. |
| **Are international standards and guidelines recognised?** | Yes. Officially recognised standards are published as recognised consensus standards. In addition, there are voluntary consensus standards, performance standards and other guidelines e.g. from the FDA or the Association for the Advancement of Medical Instrumentation® (AAMI). | Yes. Officially recognised standards (i.e. standards which are compatible with the technical requirements of the relevant EU rules, namely the MDR) are published as harmonised standards*. In addition, there are non-harmonised standards known as common specifications as well as other guidelines, e.g. from the European Medical Coordination Group (MDCG) or professional associations such as MedTech Europe.<br>*The list of MDR-harmonised standards is currently still incomplete. Harmonisation should be completed by May 2024. However, this is just a formality as investigational sites already expect compliance with the standards. | Standards and guidelines reflect the state of the art for certain processes, e.g. risk management or specific device types, e.g. software. A global harmonisation of safety levels is achieved through international standards.<br><br>The standards relevant to medical devices are, for the most part, recognised to the same extent by the FDA and the EU.<br><br>Standards and guidelines (but not *common specifications)* are not legally binding but compliance with them is generally expected by the testing centres, which makes them binding in practice. This also applies |

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| | | | to standards which have not yet been harmonised under the MDR. |
| **Qualification (definition of medical devices)** | | | |
| **How are medical devices qualified?** | A «medical device» is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:<br>recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,<br>intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or<br>intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being | "Medical device" refers to any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:<br>▪ diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,<br>▪ diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,<br>▪ investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,<br>▪ providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the | The definition of a medical device is basically the same in both legal systems.<br><br>One essential difference is that, in the USA, this regulation also applies to devices for the veterinary sector, which are excluded from the definition in the EU. |

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| | metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o).<br><br>**(Section 201(h) of the Food, Drug, and Cosmetic Act)** | human body, but which may be assisted in its function by such means.<br><br>**(Article 2 MDR)** | |
| **Classification** | | | |
| **How are medical devices classified?** | In risk classes | In risk classes | In both the USA and the EU, medical devices are divided into risk classes. |
| **What are the classes?** | I, II, III<br><br>Class I: devices with a low risk of disease or harm to the patient.<br><br>Class II: devices with a moderate risk.<br><br>Class III: devices which perform a life-sustaining or supporting function essential to the prevention of harm to health or which pose a potential, inappropriate risk of disease or harm. | I, I*, IIa, IIb, III (from lowest to highest risk)<br><br>Class I* contains three sub-classes: Im (measure), Is (sterile) Ir (reusable). | Even though the classification is risk-based in both legal systems, the assignment to risk classes is not identical so that the same devices might be assigned to a higher or lower class in the USA than in the EU. The requirements for the risk classes also differ slightly.<br><br>In both legal systems, the classification controls the type of market access and the extent to which an testing centre is involved in device assessment both pre-market and during the market phase. |
| **How is the classification done?** | Risk-based assessment by the FDA. | Risk-based classification is rule-based and, among other things, | In the EU, a generically constructed set of rules for determining the |

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| | The assignment of the device categories to the classes is done by the FDA. Medical device manufacturers can research the class of their devices using a device code in the FDA database. | depends on the device type and on the nature, duration and location of application (see Annex Vlll MDR). | classes results in a generally binding grouping but, in some cases, also to discussions about the exact allocation.<br>By contrast, the US authority determines the class depending on the device. |
| **How flexible is the classification?** | Flexible: the classification is regularly reviewed and changed if necessary. | Rigid: change only possible by amending legislation. | The advantage of the US system is that the FDA can make changes to the classification if market data provide evidence for another risk assessment. This also makes it easier to react to new technological developments in the USA.<br>By contrast, changes to the classification rules in the EU must be made by amending the legislation. Although this is possible, it is a lot more complex. |

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| Approval or conformity assessment process | | | |
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| **Are medical devices approved?** | Yes, they are approved by the FDA.<br><br>In the USA, there are three main approval processes used by the FDA to examine medical devices:<br><br>▪ Premarket Notification (510(k))<br>▪ De Novo Classification Request<br>▪ Premarket Approval (PMA) | No, manufacturers declare conformity with the regulations themselves. There are different conformity assessment processes for this and they are described in the MDR Annexes IX to XI. | The biggest difference between the regulatory systems in the USA and EU is that medical devices in the USA are approved following examination by the FDA, while manufacturers in the EU declare the conformity of their devices with the valid regulations themselves.<br><br>As approval in the USA takes the form of a licence issued by an authority, this authority confirms compliance with all regulations. By contrast, the EU conformity assessment process essentially places the responsibility with the manufacturer. |
| **Are the requirements classified by risk?** | Yes | Yes | |
| **Are all devices examined by an testing centre?** | No. Devices with very low risk can be exempted from the approval (exempt status). Most class I devices and a small proportion of class II devices are graded by the FDA as so uncritical (“exempt” status) that no evidence of safety and performance is required. This applies to, among other things, many | For class I devices, apart from I*, the manufacturer takes responsibility for the declaration of conformity without involving a Notified Body in the process. Examinations based on random sampling are also carried out for class I devices by the national competent authorities. | Both legal systems have adopted the approach of "the lower the risk, the less strict the surveillance of the device". This is sensible as it means more available capacity for the surveillance of higher risk devices. |

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| | software devices. These devices are listed in an FDA database.<br><br>All other devices are examined by the FDA as part of the approval process. | During the conformity assessment process as per Annex IX, the documentation review is based on random sampling to some extent. For certain high-risk devices, the documents on each individual device are reviewed. | |
| **Is market placement via a predicate device possible?** | Yes, the majority of devices are approved via the 510(k) process on the basis of predicate devices. | Yes, under the MDR the pathway via predicate devices is possible but to a considerably lesser extent than with MDD. It can only be used if the device has the same technical, biological and clinical characteristics as the predicate device, and the manufacturer has access to the relevant data on the predicate device and can also evidence these. | The challenge of the 510(k) process lies in the suitability of the predicate device to demonstrate safety and performance with sufficient reliability and that some devices may become serial predicate devices. Post-market devices are monitored by both the FDA and the manufacturer, however, and will be recalled by the FDA if problems are detected.<br><br>The limitation of the equivalence comparison in the EU means that more clinical trials will probably have to be conducted, which delays market placement. |

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| **How long is the approval or the certificates valid for?** | The approval is not time-limited as long as no significant changes are made to the device and there are no indications of adverse effects relating to safety or performance. This also applies even if the regulations change. This is known as "grandfathering". | The certificates issued by the Notified Bodies are valid for five years.<br><br>With CE marking, manufacturers declare that their device complies with the currently valid regulations. At the time of shipment, they must therefore demonstrate the state of the art. This means that changes must also undertaken for devices manufactured in the same way post-market if the regulations change. This also applies during the lifetime of the certificate.<br><br>As a matter of principle, there are no exceptions for existing devices*<br><br>*Until 2027/28, the transition periods for the changeover to the MDR apply to existing devices in certain circumstances. During this period, the MDR requirements (with respect to documentation and clinical assessment) do not have to be fully complied with. | The EU system guarantees that all devices placed on the market comply with the current state of the art and the currently valid regulations.<br><br>By contrast, in the USA devices can still be placed on the market even though they no longer comply with the current regulations.<br><br>However, all post-market devices are monitored so that it can be assumed that problems with existing devices will be detected. If necessary, the FDA can recall devices.<br><br>The MDR does not take into account that existing devices have already been on the market for many years without incident and that another examination and higher requirements (could) result in good and safe devices, particularly in the niche sector, disappearing from the market without an alternative in some cases, and that patient care can no longer be guaranteed to the same extent. |

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| Regulatory surveillance | | | |
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| **How does regulatory surveillance work?** | Medical devices are consistently approved and monitored by the U.S. Food and Drug Administration (FDA), a central state authority with law enforcement powers.<br><br>Every two years, the FDA routinely inspects the QMS of manufacturers of class II and III medical devices.<br><br>In addition, inspections are conducted because of incidents or if specific problems are reported to the FDA. | Compliance with the regulations is monitored on a decentralised basis by national authorities and state-authorised private-sector institutions known as Notified Bodies.<br><br>The Notified Bodies carry out annual surveillance audits of the manufacturers of class I* to III devices during which the QMS is investigated together with the documentation on a random basis. This audit must be carried out unannounced at least once every five years or following a vigilance report if required. | Surveillance in the USA and EU is risk-based. In both legal systems, class I devices (excluding I* in the EU) are less strictly monitored.<br><br>The establishment of the FDA as a central authority means that the regulation of devices in the USA is always very consistent and that "in-house" experts are trained and available for device assessments. Moreover, a large amount of data and information are centrally recorded and made accessible to the general public through the Freedom of Information Act, which results in a highly transparent regulatory system.<br><br>The decentralised structures in the EU system result in an inconsistent interpretation of the regulations, which could lead to different critical assessments of comparable medical devices. This is one disadvantage of the EU system. |

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| Regulatory requirements for market access - quality management system (QMS) | | | |
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| **Are manufacturers required to set up a QMS?** | Yes, with different kinds of surveillance (see next question).<br><br>Individual non-sterile class I or II devices are exempt from the obligation of a QMS ("GMP exempt"). These devices are listed in an FDA database. | Yes, with different kinds of surveillance (see next question). | The setting up of a QMS plays an important role in both the USA and the EU.<br><br>No notable differences can be identified in the requirements for the QMS which could have a significant impact on device quality.<br><br>In future, these differences will be even smaller as the requirements of the FDA are currently being harmonised with those of ISO 13485 standard (Medical devices - Quality management systems - Requirements for regulatory purposes) which represent the state of the art in the EU. |
| **How is the QMS monitored?** | Only the QMS of manufacturers of high-risk devices is reviewed by the FDA and it does this as part of the PMA process prior to placement on the market.<br><br>As part of the inspections, the FDA reviews the QMS of all manufacturers with the exception of GMP exempt. | Whether the QMS has to be reviewed and certified by a Notified Body before placement on the market depends on the classification and the selected conformity assessment process. As most manufacturers opt for the pathway via Annex IX MDR, this means that the QMS is also certified beforehand for the majority of manufacturers.<br><br>For manufacturers who have to involve a Notified Body in their conformity assessment process (from | The QMS is regularly monitored in both judicial areas.<br><br>The biggest difference is that in the USA, the QMS (except for PMA) is only reviewed post-market as part of the inspections by the FDA, whereas in the EU the QMS of manufacturers must be certified beforehand by a Notified Body via Annex IX certificate. |

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| | | class I* onwards), the QMS is audited annually by the Notified Body.<br>For class I manufacturers, the QMS can be reviewed as part of the investigations undertaken by the competent authority. | |
| **Regulatory requirements for market access - evidence of safety and performance** | | | |
| **What are the requirements set by the regulations regarding evidence of safety and performance?** | The FD&C Act requires that medical devices must be safe and effective without specifying this in more detail. On top of this, there are basic rules, known as general controls, which apply to all devices. Class II devices must comply with other device-specific rules known as special controls. | Compared with what obtains at the FDA, Annex I of the MDR describes significantly more comprehensive fundamental safety and performance requirements which, provided that they are applicable to the device in question, must always be complied with.<br>This allows the Notified Bodies to investigate the conformity assessment on a detailed basis. | To prove the safety and performance of medical devices, clinical data must be systematically collected and assessed (clinical assessment).<br>Clinical data can either be data obtained from clinical studies or from public data published in scientific literature or published for predicate devices. The requirements of clinical studies are largely regulated in the same way in both the USA and the EU.<br>Additionally, the recognised standards and guidelines and hence the state of the art would have to be complied with in both markets. In the USA, officially, this occurs only when the device is submitted or changes are made to it. In the EU it occurs regularly. |

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| **Are device-specific clinical data required?** | This depends on the device class and whether a predicate device exists.<br>Device-specific clinical data are mandatory for high-risk devices. | Depending on the device class and the available data, device-specific clinical data are not absolutely essential for the clinical assessment.<br>Device-specific clinical data are mandatory for high-risk devices. | In the USA and the EU, manufacturers must conduct a clinical assessment (examination of safety, performance and effectiveness) for all devices (except for GMP exempt devices in the USA). Depending on the device class, device-specific clinical data are not absolutely essential for this, provided that the evidence can be provided in another way, e.g. through equivalence devices or scientific literature.<br>High-risk devices are examined using device-specific clinical data in a comparably strict manner in both judicial areas. |
| **Post market surveillance** | | | |
| **Do manufacturers have to monitor post-market devices?** | Yes, manufacturers must define a process for all reports, i.e. for how they investigate and assess reports and complaints, and, if applicable, initiate corrective actions and send reports to the FDA. | Yes, manufacturers must define a process for all reports, i.e. for how they investigate and assess reports and complaints, and, if applicable, initiate corrective actions and send reports to the competent authorities. | In both the USA and the EU, manufacturers are required to monitor post-market devices to identify problems and, if necessary, react to incidents. |

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| **Is a proactive PMS system (based on the EU specification in the MDR) mandatory for all devices?** | There is no basic legal obligation to set up a proactive PMS system. The FDA can, however, order PMS actions for class ll and class lll devices in certain circumstances. In addition, the recognised standard (ISO 14971) on risk management requires PMS for all devices and is hence mandatory in practice. | Explicitly required from the manufacturers in the MDR and mandatory for all device classes, but with different requirements regarding the granularity and frequency of the report depending on the device class. ISO 14971 is also harmonised for the MDR. | Proactive PMS activities can uncover potential risks from medical devices. The requirements for manufacturers regarding post-market surveillance are much more comprehensive in the EU than in the USA. However, the FDA has recognised the ISO 14971 standard on risk management for medical devices, as has the EU. This standard requires a proactive PMS and hence the differences are smaller in practice than they appear at first glance. |
| **Who is responsible for reporting serious incidents?** | Manufacturers must report problems and serious incidents centrally to the FDA, and there are extended reporting obligations for health institutions. | Manufacturers must report problems and serious incidents to their competent authorities in the member states. The reporting obligations for health institutions are not regulated by the MDR but by national laws. | Both in the USA and the EU, manufacturers are required to report problems and critical incidents involving their devices. These reporting obligations are comparably regulated in both judicial areas. |
| **Are reports of serious incidents transparent?** | In the USA there are public databases both for reports from manufacturers and health institutions (e.g MAUDE) as well as for reports on device recalls and safety warnings from the FDA. | Information exchange between the individual national authorities takes place via the non-public Eudamed2 database system. At some time in the future, the reports are to be centrally recorded in the new EUDAMED database which is partly accessible to the public. | In the absence of MRA, Switzerland has access only to the publicly accessible parts of the databases i.e. only to US data at the moment until EUDAMED is fully functional. |