Digital health regulations – overcoming the challenges

Introduction
The digital health sector encompasses a large and different set of technologies to make health information and intervention more accessible beyond traditional care systems. Artificial intelligence and advanced algorithm systems are becoming more active in supporting clinical decisions. Digital health, digital diagnostics and consumer wearables form a part of this growing market. At its core, digital health forms a junction between data science and healthcare, supporting clinical decisions. Digital health, digital diagnostics and advanced algorithm systems are becoming more active in disease management and in control of their health.

The US and EU are the major hubs of the global medical device industry. Each maintains their own unique requirements with similar regulations in relation to a medical device classification in the route to registration. Hence, the adoption of a generally converging strategy to define device-collected patient-reported outcomes (PROs).

Pioneering technology companies face numerous challenges when attempting to register Class I and II devices, which this article seeks to explore. Moreover, it strives to illustrate the application of existing regulatory frameworks to support rapid innovation in today’s highly iterative world of digital device development and the cost benefits to the healthcare systems around the world regulation may bring.

US and EU regulations
Table 1 shows comparisons of relevant features of medical device regulations between the EU and US.

US regulations
The US FDA rules for medical devices are administrated by the Medicinal Device Amendments (1976) and, more precisely, by the Centre for Biologics Evaluation and Research (CBER). Broadly, medical devices are classified into Class I to III. Class I devices or low-risk devices, known as “general devices”, are usually exempt from pre-market notification, 510(k). However, some Class I devices may require pre-market clearance by the FDA. Most Class II devices are classified as medium-risk devices and require pre-market notification 510(k) clearance, while most Class III devices are classified as high-risk devices and require pre-market approval (PMA). Notably, device classification also depends on the device’s intended use.

The medical device clearance process is directly related to device classification with Class I devices cleared, without any clinical or preclinical data based on their assumed safety and efficacy or the risk to patients. Exempt devices (either Class I or II) require no pre-market notification application or FDA clearance before sale of the device in the US. However, the manufacturer must register its institution with the FDA in order to ensure that good manufacturing practice is followed. Class I, II or III devices, which are not exempt, are cleared via the 510(k) clearance process. Devices within these classes are marketed as least safe and effective, or “substantially equivalent” to a legally marketed device. Moderate-risk devices are deemed substantially equivalent to an existing device and are to be cleared through the 510(k) clearance pathway without requiring clinical data. However, some Class II moderate risk devices or some 510(k) submissions can require clinical data to support a marketing clearance from the FDA.

All Class III devices require PMA that consists of clinical data demonstrating safety and effectiveness of the device. Therefore, these devices require a PMA application under section 515 of the

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Keywords
Medical devices; Device classification; Data extrapolation; Patient-reported outcomes (PROs); Non-compliant patient; Artificial intelligence.

Abstract
Although established regulatory frameworks, such as those for medicines and diagnostics development, have been around for a long time, the regulatory pathways related to the use of medical device technology and validating patient-reported outcomes in clinical trials are not always clearly defined. Biotech start-ups often have to balance a limited budget against high expectations from stakeholders in terms of product performance and claims. Taking a stepped approach to the regulatory path can be a way of demonstrating quick and cost-effective regulatory progress, while opening up the potential of efficiently collecting real world evidence data. EU (UK) and US tech and device companies confront numerous challenges in relation to obtaining regulatory device approvals from regulatory agencies and good practice (GxP) approvals for use in clinical trials at large. This article examines challenges of the application of current regulations within the biotechnology sector using three real case examples, each facing different challenges, and describing how these have been overcome.

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Following approval or release of products, the NB can require companies to perform post-market studies as part of the CE mark certification, if the long-term safety of the device is unknown.

Food, Drug, and Cosmetic Act in order to obtain marketing approval. It may be worthy to note that some Class III pre-amendment devices may also require a Class III 510(k). Following approval or release of the device into commercial distribution, medical devices continue to be monitored in accordance with the Safe Medical Devices Act 1990, focusing on the reporting of serious adverse events or deaths to manufacturers and the FDA. It may be useful to highlight that US market electronic devices, most of which are physical digital health products, would also require Federal Communications Commission registration to enable the product to be legally marketed in the US.

**EU regulations**

The existing regulatory process has been in place since 1990 with the following directives in current use: Active Implantable Medical Device Directive (AIMDD) (90/385/EEC), General Medical Device Directive (MDD) (93/42/EEC) and In Vitro Diagnostic Medical Device Directive (IVD MDD) (98/79/EC). Most companies are already audited under the Medicinal Device Regulation (MDR) system, which will come into effect in 2020. However, during the transition period from May 2017 to May 2020, current Council Directives 90/385/EEC and 93/42/EEC and Directive 98/79/EC are in use until rescinded by Regulation (EU) 2017/745 and (EU) 2017/746 for Medical Devices and in vitro diagnostic (IVD) medical devices, respectively. Presently, the EU operates its device regulations through decentralised pre-market controls. Each country has a competent authority (CA), which requires one or more notified bodies (NBs) in any given country to act as third-party assessors of a manufacturer’s compliance. For low-risk devices, Class A IVD medical devices or Class I medical devices without sterile or measuring function, manufacturers must submit applications to respective CAs, this takes the form of a self-certification. For medium- and high-risk devices, the conformity assessment is undertaken by the NBs. All medical devices must be registered with a CA in the place of the manufacturer’s business.

In contrast to the US, the EU follows a five-class scheme. Devices are classified into Class I–III division, with Class I and II being further subdivided into I and Im and IIA and IIB, respectively. As in the US, Class III products are ranked as the highest risk products. Medical devices that are non-implantable and considered low risk are “self-certified” by applying the CE marking. These include good manufacturing practices, labelling and adequate packaging and storage. However, medium- and high-risk devices must undergo a more extensive external review. Device approval applications can be filed in any member state and reviewed by an NB established within that state and authorised by that state's CA to assure conformity.

### Table 1: Comparisons of relevant features of medical device regulations (EU and US).

<table>
<thead>
<tr>
<th></th>
<th>EU Medical Device Directive (MDD)</th>
<th>US The Federal Food Drug and Cosmetic Act</th>
<th>Minimum technical data required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory authority</td>
<td>National competent authorities member states</td>
<td>US FDA</td>
<td></td>
</tr>
<tr>
<td>Risk classification</td>
<td>Class I and Im</td>
<td>Class I</td>
<td>Literature review, preclinical device performance</td>
</tr>
<tr>
<td></td>
<td>Class IIa</td>
<td>Class II</td>
<td>Literature review, preclinical and clinical device performance</td>
</tr>
<tr>
<td></td>
<td>Class IIb</td>
<td>Class III</td>
<td>Literature review, preclinical and clinical device performance (safety and effectiveness)</td>
</tr>
<tr>
<td></td>
<td>Class III</td>
<td>Class III</td>
<td></td>
</tr>
<tr>
<td>Approval pathway</td>
<td>Medical device manufacturers need to exhibit CE marking on their products in order to ensure that devices are safe and fit for their intended use</td>
<td>510(K)</td>
<td>Premarket approval (PMA)</td>
</tr>
<tr>
<td></td>
<td>Multiple pathways</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality management systems requirements</td>
<td>ISO 13485 or as per applicable Annex of 93/42 EEC</td>
<td>21 CFR Part 820</td>
<td>US FDA</td>
</tr>
<tr>
<td></td>
<td>Notified Body</td>
<td>22 CFR Chapter 1</td>
<td>21 CFR Chapter 1 Subchapter H</td>
</tr>
<tr>
<td></td>
<td>MDD (93/42/EEC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AIMDD (90/385/EEC)</td>
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<td>IVDMDD (98/79/EC)</td>
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with requirements of the relevant EC Directive. Following approval or release of products, the NB can require companies to perform post-market studies as part of the CE mark certification if the long-term safety of the device is unknown. The CAs in each of the EU countries manages post-market surveillance of safety. Since 2011, it has been mandatory to include all adverse events in the European Databank on Medical Devices (EUDAMED).

Real world cases

*At-home monitoring of heart failure*

Heartfelt Technologies is a small medical device company in Cambridge, UK, founded in 2015. It has developed an intelligent camera system for automatically detecting and reporting the signs of heart failure from the patient's home. The camera is designed specifically with non-compliant patients in mind, those who do not take their medicines regularly, or self-monitor and self-report their symptoms as instructed by their medical team. Such non-compliance can stem from many issues, for example, early stages of dementia. Regardless of the cause of non-compliance, from a medical device design perspective, the aim is to make a device that requires no user interaction which functions entirely passively. This is achieved by running a neural network on the camera system to register the presence of the patient automatically. It then collects, quantifies and reports the signs of worsening heart failure, in particular, the change in volume of the feet that occurs in over half of heart failure patients about a week before admission to hospital. This volume change is directly related to the change in weight that compliant patients are asked to self-monitor and self-report, with the same clinical intervention provided when observed (a simple course of diuretic tablets). In the majority of cases, this intervention will prevent complications leading to hospital admission. Reduced admission represents not only a significant escalation of care needed resulting from a lengthy hospital stay.

The company has a comprehensive quality management system for the design and manufacture of medical devices (ISO 13485). From an EU regulatory perspective, the Heartfelt Technologies device is a “Class I with measuring function” (Class IIm) device, according to rule 12 in accordance with annex IX of the MDD 93/42/EEC as amended by directive 2007/47/EC. The measuring function attribute is due to the quantification of a medically relevant parameter, which means that the accuracy and precision of this measurement must be covered by the quality system, and regularly inspected by an NB. From the US perspective, the intended use of the device is the monitoring of foot volume, which is analogous to the monitoring of weight via an internet-connected set of weighing scales. On this basis, the FDA chose to exercise “enforcement discretion” over the device, provided that no diagnostic claims are made. This means that the device could get to market and begin helping patients in a matter of months rather than years. This highlights the importance of carefully considering the exact medical claims that a device could make. If the company were to claim that exactly the same device was for use in monitoring the progression of heart failure as a disease, (ie, making a diagnostic claim), it is likely that the device would be considered a Class IIA device in the EU and, therefore, would need to pass through a much lengthier process in the US. Such diagnostic claims would likely require extensive real world patient data which, of course, can be collected using the patients monitored by the device under the lower regulatory burden. Such an approach would almost avoid the vast majority of enormous clinical trial costs that would be necessary, if the company directly proceeded to those medical claims.1,3,4

An important aspect for the entire category of remote patient monitoring devices is getting the product to market in a cost-effective manner. Therefore, gaining real world patient-use data can be dramatically accelerated by careful consideration about the specific claims made around the device. The adoption of a two-step regulatory strategy in which the same device can be brought to market rapidly, followed by enhancement of clinical claims using real world patient data, can dramatically shorten time-to-market and significantly reduce costs. Moreover, real world user feedback is gained more rapidly, meaning that any iteration of the device can be performed faster and less expensively under the lighter regulatory regimen. More importantly, the cost-effectiveness of the device is underpinned by its meeting of the regulatory guidelines.

Digital technology for rare diseases

Aparito is a UK/Dutch company founded in 2014. Its aim is to gather patient-generated data in rare diseases. For Aparito, there are few regulatory approved endpoints for compound registration using solutions such as video, voice and photo capture, wearable devices linked via bluetooth devices and disease-specific mobile apps developed with patients and for patients. Therefore, its device is currently utilising a PRO concept.

The Aparito platform Atom 5 device is operating as a Class 1 certified device with a quality management system under ISO 13485. The device also aligns with good practice requirements of auditability and accountability used in clinical trials. Engagement with the European Medicines Agency (EMA) and the FDA is planned as part of a qualification procedure in the near future. Aparito’s strategy is to enable remote and continuous data collection for physician decision-making and clinical trial use. Early plans are under way for developing algorithms for automated alert of patient decision making, which would increase the regulatory requirements to Class IIA.

To support the emergence of patient-generated data in a robust and compliant way, Aparito proposes to base its methodology using global extrapolation strategies as operated under the EMA extrapolation concept paper and the ICH E17R1 guidance.5,6 The EMA extrapolation reflection paper7 mentions that data sources, other than those from clinical trials, can be used and may prove complementary to well-designed prospective studies that track the
current standard of care. The methodology used in one therapeutic area with specific novel and patient-designed endpoints can be applied to other therapeutic areas. These methods allow for a more refined approach towards paediatric development, relying on three main areas: pharmacology, disease manifestation and progression, and clinical response to treatment. Such data have the potential to track and quantify the child’s development longitudinally and the response to treatment in a meaningful way, which remains a frontier at the moment. The combination of Aparito’s technology and the application of the Extrapolation Regulatory Framework align paediatric research with the new era of rapidly developing technology and precision medicine, where medical practice will be based on detailed genetic and other molecular understanding of the patient and the disease.

Seizure detection using AI algorithms
Empatica, an MIT Media Lab spin-off company based in Massachusetts, US, focuses on epilepsy management using a high quality digital worn wrist watch called Embrace.

The approval path and the clinical trial were originally designed for a De Novo pathway. The Embrace watch also obtained an expedited access pathway designation by the FDA for a faster review process. However, by the end of the trial, a predicate received approval in the same field. Therefore, it was possible to initiate the filing through a 510(k) pathway with a reduction in time for the overall clearance process. Embrace was self-certified in Europe as a medical device for seizure detection in April 2017. In January 2018, Embrace received FDA clearance for seizure monitoring in adults, making it the world’s first epilepsy smart watch to be cleared by the FDA. In December 2018, Embrace received FDA clearance for use in a paediatric population, aged six and older, making it the first non-electro-encephalography (EEG) based physiology signal seizure monitoring system to be cleared for such use. The latest regulatory approval highlights the potential of AI to detect seizures and monitor seizure activity in the home setting.

A machine learning algorithm able to recognise accelerometers and electrodermal activity signatures of convulsive seizures-like events has been developed and trained on data from epilepsy patients experiencing generalised tonic-clonic seizure in epilepsy monitoring units (EMUs), labelled using gold-standard video-EEG in level IV epilepsy centres.

For clinical validation and FDA clearance purposes, an additional prospective EMU clinical trial with a “fixed and frozen” algorithm was performed in multiple level IV epilepsy centres in the US and Europe. The rigorous requirements for clearance included the revision of the video EEG data by three different epileptologists. The detection algorithm had to blindly predict the reviewers’ agreement based on a majority rule, while keeping the false alarm rate at acceptable levels.

Clinical testing was carried out in an EMU among 141 patients diagnosed with epilepsy, of which 80 were paediatric patients, aged 6–21 years; and the rest were adults (61). A total of 53 out of 54 generalised tonic-clonic seizures were detected by Embrace (accuracy rate=98%) during the clinical testing, with the overall false alarm rate (endpoints required by the FDA for approval in seizure detection) for adults being 0.67, and the one for paediatrics being 1.35.

Empatica operates with a single artificial intelligence algorithm for the entire epilepsy population, whereas, in the future, it plans to use a more advanced machine learning algorithm to enhance a self-adaptive learning mechanism.

Conclusion
The current strategic vision for the technology sector is to continue expanding partnerships with regulatory authorities. This is to ensure that the medical devices of tomorrow are regulated under a framework that allows rapid access to innovative technologies that give patients what they need now and in the future.

The US and EU regulations bear many similarities in terms of device classifications. In both systems, devices are classified based on increasing risk from class I to class III. The registration strategies used by the pioneering technology companies discussed in this article were based on an initial registration in the EU and, as such, medical devices need only to demonstrate safety and performance. Although the EU requirements may change due to the May 2017 MDR, clinical performance will be required to support intended purpose of an IVD or medical device.

An important consideration for device development – whether it is wearable or non-wearable – is its potential for acceleration to market entry. This may be achieved by following a two-stage regulatory strategy in which data claims are expanded in tandem with real world evidence data collection processes. However, it is important that limitation claims for the device are carefully aligned with the device potential.

High quality digital products which monitor patient care are the most important aspect of regulation today. Moreover, the current requirements of regulation seek to ensure a high quality digital device that is safe to use and cost-effective to produce as illustrated by the case studies examined in this article.

On the horizon, there are the EU’s MDR May 2020 regulations which will, no doubt, bring further application challenges for our present and future companies and their innovative digital products.

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