GSMA mHealth

Understanding Medical Device Regulation for mHealth
A Guide for Mobile Operators

Foreword

Mobile technologies will make a significant contribution to addressing the enormous challenges of healthcare provision worldwide. Early efforts in mobile health saw many trials funded by network operators, NGOs and other interested bodies with mixed results.

We are now in a transition phase in the development of this market. A number of mobile health propositions have gained acceptance and are being more widely adopted. The market is developing and this growth is accompanied by a rapid increase in the number of software solutions, 'Apps' that potentially offer new modalities of care, blurring the distinction between a more traditional provision of clinical care by physicians, and the self-administration of care and well-being.

Network operators, equipment suppliers, software vendors, and healthcare professionals all seek clarity on the roles they could play in the value chain for mobile health. But importantly, they also seek clarity in the responsibilities each may have under the regulatory requirements for healthcare.

This document serves as a guide to the GSMA and its members on the evolving realm of medical device regulation as it applies to mobile healthcare. This guide provides an overview of the key terminology that is central to medical device regulation. It also provides a more detailed overview of the regulatory landscape of mobile health in US and EU, and their implications from a mobile operator perspective. Some case studies that explore these regulations and a detailed glossary of terms is provided.

GSMA is continuing to build its understanding of medical device regulation as it applies to mobile healthcare and would be very interested to receive any comments on the contents of this paper. Please email: mhealth@gsm.org

Contents

1. Introduction

As the market for mobile medical devices reaches the next stage in its development, greater consideration is being given to the regulatory frameworks that will govern their promotion and use. In contrast to models for regulation in the telecommunications industry, to those unfamiliar, medical device regulations can appear complex and burdensome. They may appear to be a hindrance to innovation and product development and yet despite this apparent complexity, it is estimated that there are over 1.5 million different medical devices available on the market worldwide. With the rapid pace of technology advancement and innovation, medical devices comprise one of the fastest growing and vibrant industries, with a global market value today of around US$250 billion.

"Intended Use" is a cornerstone of device regulation

Medical device regulations, whilst broadly similar, do vary from country to country. However, a governing principle in medical device regulation in both EU and US is that of "Intended Use". Any determination regarding applicability of medical device regulations to a product or service will be based on the intended purpose of the product and its mode of action.

Considering a product's intended use in conjunction with the regulators definition of what constitutes a medical device (discussed later) enables manufacturers to decide with reasonable clarity, whether the product will fall within the scope of the regulations where there are no claims made regarding the suitability of a network or a mobile device for medical purposes. This principle should generally relieve both mobile network operators and vendors of mobile communications equipment of any burden in medical device regulation.

There is much guidance available to manufacturers on FDA (USA) and MHRA (UK) websites on this, and many other aspects of device regulation.

Risk Assessment and Medical Device Classification

Medical devices by their very nature have the potential to present a hazard - to be a source of harm in normal use, and more so if misused. Regulations are therefore a necessary instrument to safeguard users from undue and unnecessary risks and are based on the principle of mitigating, to an acceptable level, the potential of a device to cause harm.

Determination of the potential to cause harm (risk assessment) and implementation of appropriate risk reduction measures through the design and development process is an essential requirement under the regulations.

Regulators recognize that there are many different types of medical devices with a correspondingly wide range of associated risk. Medical devices are therefore assigned to a particular class (National regulations typically identify three or four device classes). The classification is made according to a set of rules within the regulations and is based on device design complexity, use characteristics, and potential for harm in normal use and foreseeable misuse situations. So the extent to which regulatory controls are applied varies progressively from class to class, in proportion to the potential hazard they present.

The regulations acknowledge that:

- Absolute safety cannot be guaranteed
- It is a risk management issue
- It is closely aligned with device effectiveness / performance
- It must be considered throughout the life span of the device

So, regulations place obligations on manufacturers, but also provide a supporting framework for product development, facilitating design and development of products that are for fit for purpose and that provide an acceptable risk-benefit balance.

Standards

The use of standards has been a key element in establishing medical device regulations. The International Organization for Standardization (ISO) defines a standard in the medical device domain as follows:

"Standards are documented agreements containing technical specifications or other precise criteria to be used consistently as rules, guidelines or definitions of characteristics, to ensure that materials, products, process and services are fit for their purpose".

Standards can establish a wide range of specifications for products, processes and services

- Prescriptive specifications obligate product characteristics, e.g. device dimensions, biomaterials, test or calibration procedures, as well as definitions of terms and terminologies.
- Design specifications set out the specific design or technical characteristics of a product, e.g. operating room facilities or medical gas systems.
- Performance specifications ensure that a product meets a prescribed test, e.g. strength requirements, measurement accuracy, battery capacity, or maximum defibrillator energy.
- Management specifications set out requirements for the processes and procedures companies put in place, e.g. quality systems for manufacturing or environmental management systems.

Prescriptive design and performance specifications have been commonplace in standards for some time and management specifications have also rapidly gained prominence. Recent years have seen the development and application of "generic management system standards", where "generic" means that the standards' requirements can be applied to any organization, regardless of the product it makes or the service it delivers, and "management system" refers to what the organization does to manage its processes.

Two of the most widely known series of generic management system standards are the ISO 9000 series for managing quality systems, and the ISO 14000 series for environmental management systems. ISO13485 and ISO13488 are specific ISO quality systems standards for medical device manufacturing. As indicated earlier, there is wide ranging information and assistance relating to these standards and their application available on regulatory and standards organizations websites.

The Role of the Manufacturer

The term 'Manufacturer' has specific meaning within medical device regulations and is worthy of clarification here owing to the potential for misinterpretation. 'Manufacturer' means the legal company with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under the company name, regardless of whether these operations are carried out by that company itself, or on their behalf by a third party.

Put simply, if you or your company place a medical device on the market, you or your company are the legal manufacturer and you are thus responsible for compliance with the applicable medical device regulations. This is true, irrespective of what your route to market is - the distributor, for example, has no responsibility here, and nor does the component manufacturer. In addition, as the manufacturer, you are responsible for post-market surveillance; monitoring and acting upon any adverse events or complaints in the field. It must be clear to the consumer therefore, how they can contact the manufacturer (again, not the distributor) in order to report such events.

Device, Accessory and Component

Beyond intended use, regulators make a distinction between a medical device, an accessory and a component; each of which is regarded and managed differently in the regulations. The elements of a mobile health solution may include sensors, software, a mobile phone and an associated network infrastructure, each of which could be classified as a device, accessory or component, depending on the construction of the specific product and the intended use. Understanding the distinction is key to navigating the healthcare regulations. We offer guidance in this regard and provide examples in more detail in Case Studies.

The distinction between Wellness and Healthcare

As consumers in developed economies take a more active role in managing their own health, overall lifestyle choices are increasingly identified as a major contributor to health and well-being. As a result, more products are appearing on the market promoting 'wellness' and the determination of whether a product falls within the scope of medical device regulations can be challenging as the boundaries between wellness and healthcare become blurred.

Hardware, Software and the Network

We can only assume that computing power and functionality will continue to increase, becoming more distributed and closer to the point of service. With increasing convergence of the medical and telecommunications industries, the boundaries between all these elements becomes increasingly more difficult to define.

The pace of technological change means that revision and reissue of regulations essentially lags behind, providing challenges for all stakeholders, including regulators themselves. For example, 'downloadable Apps' or iPhones did not exist when the EU medical device regulations were originally published. Regulators are therefore actively seeking to engage in a dialogue with industry to accommodate new developments within the regulations and providing clarity on the regulatory requirements.

2. Context in which medical device regulations might influence mobile platforms

There are a number of ways in which mobile technologies can be utilized in medical devices. The capabilities of off-the-shelf phones are ever increasing, which facilitates development of new products for individuals and healthcare professionals. Connecting external devices (e.g. sensors) and downloading software onto mobile platforms offers new possibilities by virtue of the processing power of the phone and network access. Similarly, gateway devices connected can provide an alternative route to network access for medical devices. Each of those options has different regulatory implications and is illustrated below in Figure 1.

Figure 1. Examples of mobile technologies and medical device combinations

Use of mobile platform for medical communications	Turning a phone into a mobile medical device		Embedding cellular devices into medical devices
Phone or tablet	Smart phone with App	Smart phone with App and new sensor	Embedded cellular device

Technological combinations

Communicating with a healthcare professional **For example**: sending photos to your GP.	**Extended use of new hardware or software adding new medical or clinical usage options.** Covers a large range of possibilities. **For example**: connecting to a medical image server, controlling a blood-pressure cuff connected to a mobile platform or collecting blood glucose reading and caloric intake to help manage diabetes.		**Extend a medical device by adding wireless cellular network connectivity** **For example**: sending hospital bed records to an online database.

Possible uses

Source: PA Consulting

Defining whether a product is a medical device is the first step in identifying the impact of medical device regulations may have for new products, as depicted in Figure 2 below.

In the US, a medical device is defined[1] as "… an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is … [either] 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] intended to affect the structure or any function of the body of man or other animals."

In Europe a Medical Device is defined as[2] "any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, investigation, replacement or modification of the anatomy or of a physiological process, control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted by such means."

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1   Section 201 (h) of the Federal Food, Drug and Cosmetic Act

2   According to Directive 2007/47/EC (21 March 2010) amendment to the Directive 93/42/EEC

In both cases what defines whether a product is a medical device is its 'intended use' or 'indication for use'. This includes all claims made by the device manufacturer or brand owner advertising the properties of the device. If a product's intended use is found to be medical it must comply with medical device regulations.

Figure 2. Guidance on medical device definition

Results in a low level regulatory burden:
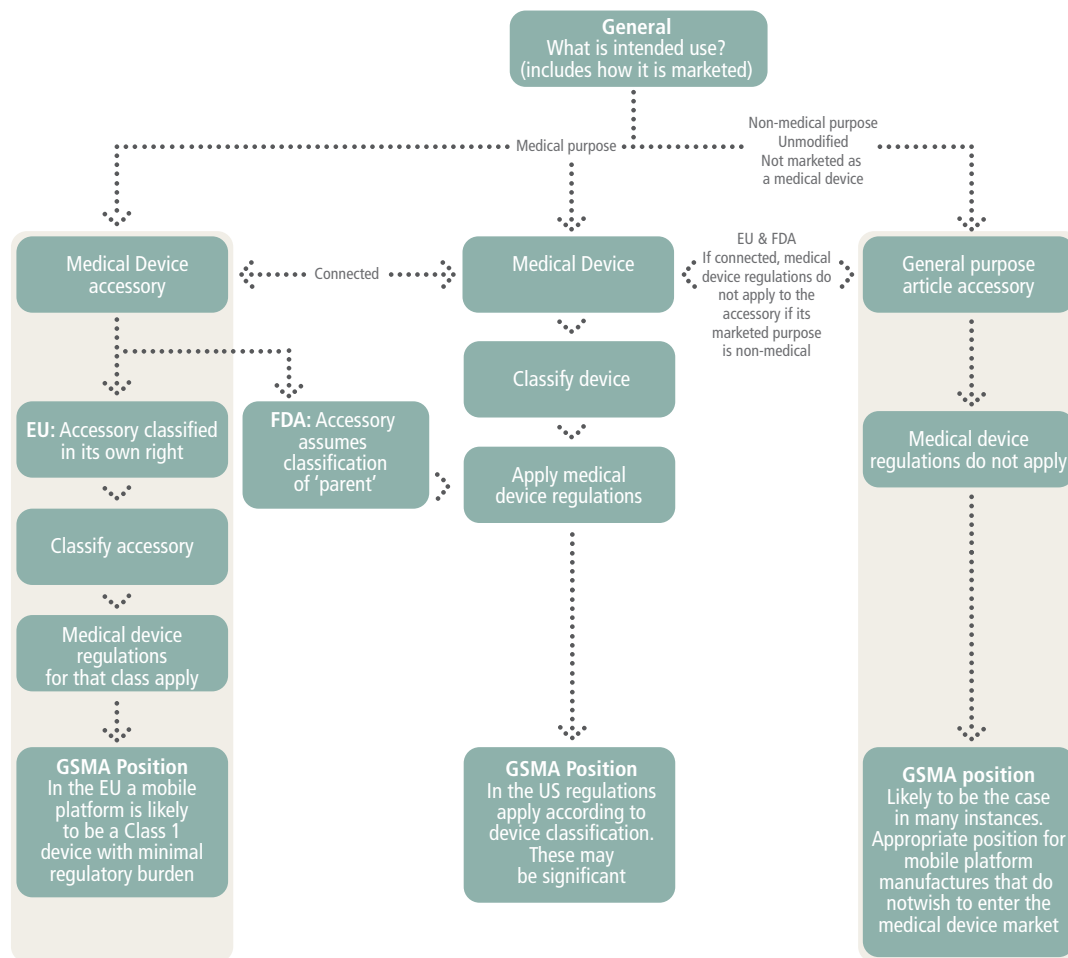
Source: PA Consulting

2.1 Using a mobile platform for medical communications

Sensors are already integrated into many mobile phones. These may be capable of not only connecting people but displaying high quality, colour images, capturing and storing images and using microphones and speakers to record and re-play audio messages and music. More advanced smart phones possess live teleconference options, GPS trackers and accelerometers. Currently, mobile platforms are generally not sold or promoted for any medical purpose, and hence are outside the scope of current medical device regulations.

However, the proliferation in enabling technologies together with both government and public interest in potential benefits of direct interactions between patients and medical professionals, means that mobile telecommunications platforms may be increasingly promoted for this purpose. Questions have thus been raised around the possibility of devices ultimately becoming sufficiently sophisticated to warrant re-classification as medical devices.

As indicated above, under the current definitions, phones marketed as communication devices are clearly not intended as medical devices, notwithstanding the potential impact on patient health in facilitating effective communication of medical information.

However, given the pace of change, more products are likely to be developed in this space and medical professionals and patients may be ever more likely to adopt mobile technologies (for health, wellness or medical purposes). Ultimately, the regulatory landscape may have to develop also and it would be prudent for manufacturers to keep uppermost in mind the concepts of 'intended use' and 'potential to cause harm'.

2.2 Transforming a phone into a mobile medical device

General use versus medical intended use

In recent years, the increasing computing capabilities of phones have made it possible to bridge the gap between personal digital assistants (PDAs) (is this a smart phone? may want consistent terminology) and phones. Existing phones and their sensors can be used for medical purposes thanks to new software or Apps downloaded from distributor sites. Moreover, new medical functionality can be added to phones with development of new sensors for connection to them. Such extensions can enable display and recording of physiological factors such as blood pressure or temperature, ECG (Electrocardiogram), EEG (Electroencephalogram), or blood glucose concentration, to name a few. Such combinations can further be used to analyse and share data with health practitioners.

As phones, software or sensors are integrated into a system, mobile platforms could potentially become classified as accessories to medical devices. However, recognising this as a potential issue, the FDA states[3] that: "the fact that a mobile platform could be used to run a mobile medical app identified by this guidance does not mean that the mobile platform manufacturer is considered a medical device manufacturer. For example, if it is possible to run mobile medical apps on BrandNamePhone but BrandNamePhone is not marketed by BrandNameCompany with a medical device intended use, then BrandNameCompany would not be a medical device manufacturer".

Such an approach is reasonable and facilitates innovation and flexibility among suppliers, manufacturers and distributors. In this instance, the FDA recognises that the intended use of the mobile platform is not for a medical purpose and therefore does not fall within the medical devices regulations. However, it is incumbent on the medical device manufacturer (in this case the App writer or sensor manufacturer) utilizing the mobile platform to verify and validate the suitability and safety of the system utilizing the mobile platform for the intended medical purpose.

For the purposes of this document, sensor hardware is not discussed further as it is assumed that these would only be developed by existing medical device companies with appropriate experience and not phone manufacturers.

Components and Accessories

One area of potential confusion is the distinction between 'components' and 'accessories'. In general the constituent parts comprising medical devices can be generally defined as 'components' if they are provided to the manufacturer by a supplier to enable fabrication of a device. Examples of components include electronic components, moulded or mechanical parts that may be off-the-shelf or custom parts. Components in themselves are typically, not sold for medical use and hence are not subject to medical device regulations. However, it is the regulatory responsibility of the medical device manufacturer to ensure that components are of appropriate quality and suitability for the purpose to which they are being put. 'Accessories', in contrast, are purchased on the open market by the end user for use with an existing product to enable the assembly device to function as intended.

Software can be considered a component if it is part of an embedded program in a device, and could be either off-the-shelf or custom designed. However, an App for sale on a distributor site would be an accessory, or even a medical device in its own right, as it is sold to users to provide new functionality for a device. Custom software, whether a component, an accessory or a medical device, must be written and developed in accordance with IEC 62304, which has been adopted by the EU and FDA as a harmonised standard for software design in medical products.

Risk based approach

The purpose of medical device regulations is to ensure that products are safe and effective in use. All medical devices require adoption of a risk based approach to product and system development in

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3   Draft guidance for industry and FDA administration staff, Mobile Medical Applications" Issued on July 21,
     2011, page 10 Chapter 3 "Definitions" section E "Mobile Medical App Manufacturer"

accordance with *ISO 14971:2007 Medical devices -- Application of risk management to medical devices.*
In support of this, the regulatory process evaluates each device on a case-by-case basis to
discriminate between high, medium and low risk devices. This evaluation is based on the risk of
harm posed to the users and not technological complexity. It is this risk based approach that ensures
regulatory controls are applied in a proportionate and appropriate way, avoiding over-regulation
of low risk devices. Risk assessment forms the basis of the medical regulatory approval process and
thus must be embraced by GSMA stakeholders as a factor in entry to the medical device world.

**Figure 3. Increasing levels of risk of harm to users is mitigated by applying an incremental level
of scrutiny**

Intended use

Wellness
Intended use has to be clearly
stated as wellness. The product
might contain a disclaimer.

Clinical or medical
Falls under medical device regulations.
Depending on the classification identified
during the safety assessment, the degree of
action necessary for certification will vary.

Increasing level of
safety risk

Source: PA Consulting

This approach is referred to by the FDA as the 'least burdensome approach'. In the USA and EU,
devices are classified from class I (lowest risk) to class III (highest risk) which then drives the scale
of the development activities and the burden of proof of safety and efficacy. There is much guidance
and support available for manufactures in navigating the regulations, and the authorities encourage
manufacturers to engage and discuss applications in advance.

App classification

As clearly stated in its Mobile Medical App guidance document[4] the FDA proposes that the
following Apps are NOT to be regulated: *"Mobile apps that […] are solely used to provide clinicians
with training or reinforce training previously received; Mobile apps that are solely used to log, record, track,
evaluate, or make decisions or suggestions related to developing or maintaining general health and wellness;
Mobile apps that only automate general office operations with functionalities that include billing, inventory,
appointments, or insurance transactions; Mobile apps that are generic aids that assist users but are not
commercially marketed for a specific medical indication".*

In other words, Apps that allow medical professionals and patients to access already publicly
available material, or perform administrative tasks are not to be regulated. This is a positive step,
as it indicates that the intent of the regulators is not to enforce blanket compliance, which could
inhibit useful, low risk technological improvements from reaching patients. However, it also implies
that other types of mobile medical Apps are to be regulated which means that those Apps must be
developed, manufactured and supported in compliance with the regulations.

There are three categories of apps identified:

Apps *"for the purpose of displaying, storing, analyzing, or transmitting patient specific medical device data"*

Apps that *"transform or make a mobile platform into a regulated medical device […] or [performs] similar
medical device functions"*

Apps that *"allow the user to input patient-specific information and - using formulae or a processing
algorithm - output a patient-specific result, diagnosis, or treatment recommendation that is used in clinical
practice or to assist in making clinical decisions"*

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4   Draft guidance for industry and FDA administration staff, Mobile Medical Applications" Issued on July 21, 2011, pages 10
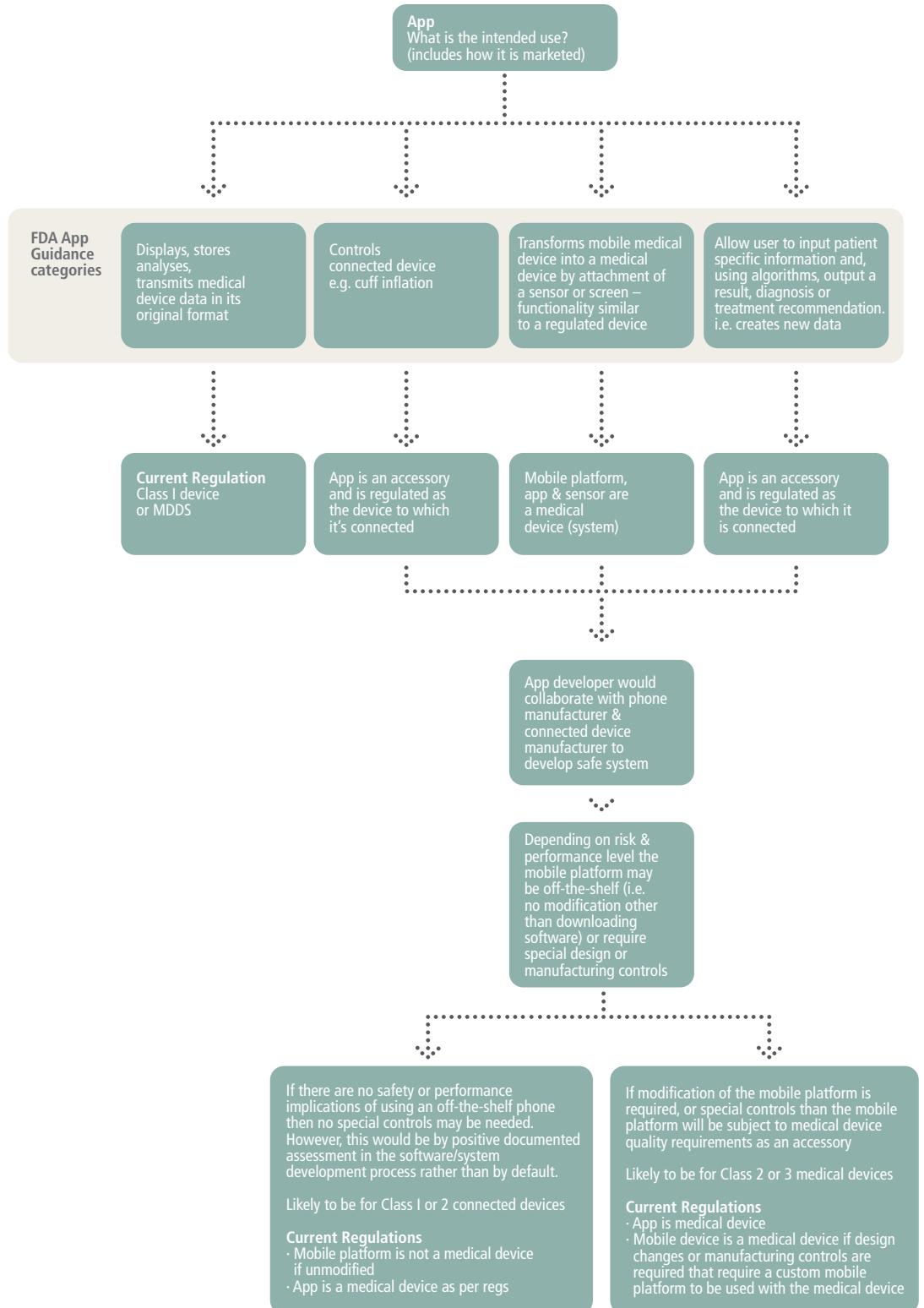   and 11 Chapter 4 "Scope"

In its response to this guidance document, GSMA has suggested further clarification by the regulators would be useful for App manufacturers. Nevertheless, it is clear that the FDA's basis for the application of the regulations and product classification is based logically on the intended use of the App and the potential risk to patient and users as illustrated in figure 4 below. The FDA's suggested approach to classification of Apps is shown in Figure 5.

Figure 4. Examples illustrating the FDA's proposition to classify connected devices and Apps according to their potential risks to users

Examples of connected devices and Apps	Intended use	Potential regulation	Potential Classification
Apps that use the mobile platform as a magnifying glass (but not specifically for medical purposes), recording audio, note-taking, replaying audio with amplification, and other similar functionalities.	Non-Medical	None	None
Apps that control a blood-pressure cuff connected to a mobile platform to inflate the cuff and measure a person's blood pressure.	Medical	Medical device	Lower risk
Apps that act as a glucose meter using an attachment to a mobile platform.	Medical	Medical device	Medium risk
Apps that collect blood glucose readings and caloric intake to help manage diabetes by calculating pre-meal insulin dose (Bolus) or Basal adjustments.	Medical	Medical device	Higher risk

Source: Mobile Medical Applications draft guidance

Figure 5. Current FDA proposition for mobile medical App classifications and implications for GSMA members

App
What is the intended use?
(includes how it is marketed)

FDA App Guidance categories

Displays, stores analyses, transmits medical device data in its original format

Controls connected device e.g. cuff inflation

Transforms mobile medical device into a medical device by attachment of a sensor or screen – functionality similar to a regulated device

Allow user to input patient specific information and, using algorithms, output a result, diagnosis or treatment recommendation. i.e. creates new data

Current Regulation
Class I device or MDDS

App is an accessory and is regulated as the device to which it's connected

Mobile platform, app & sensor are a medical device (system)

App is an accessory and is regulated as the device to which it is connected

App developer would collaborate with phone manufacturer & connected device manufacturer to develop safe system

Depending on risk & performance level the mobile platform may be off-the-shelf (i.e. no modification other than downloading software) or require special design or manufacturing controls

If there are no safety or performance implications of using an off-the-shelf phone then no special controls may be needed. However, this would be by positive documented assessment in the software/system development process rather than by default.

Likely to be for Class I or 2 connected devices

Current Regulations
· Mobile platform is not a medical device if unmodified
· App is a medical device as per regs

If modification of the mobile platform is required, or special controls than the mobile platform will be subject to medical device quality requirements as an accessory

Likely to be for Class 2 or 3 medical devices

Current Regulations
· App is medical device
· Mobile device is a medical device if design changes or manufacturing controls are required that require a custom mobile platform to be used with the medical device

Source: PA Consulting

2.3 Embedding communication technologies into medical devices

Whilst connecting a medical device to a standard phone may be acceptable for lower risk devices, there are instances where the risk level warrants the use of a more controlled means of accessing the network.

In this case a custom mobile device or 'gateway' device is developed that is specific to the needs and risks associated with use of the particular device. This approach is particularly suited to high risk applications where it may not be appropriate to integrate a general purpose phone to the medical device that is performing a vital clinical task. To ensure safety only the minimum necessary functions are incorporated into the gateway design, as all the other functionality that a general purpose phone provides is an unnecessary complication to the design.

In the case where bespoke, embedded communication technology is integrated into a medical device then the full regulatory requirements apply to the system.

3. Medical devices regulations provide a framework for stakeholders

3.1 General principles of medical device regulations

Medical device regulations clearly define the responsibilities of stakeholders in various guidance documents available on the regulatory web pages. Nevertheless, they also acknowledge that regulations must be capable of supporting introduction of new technology without constraining innovation, whilst protecting public safety. There has been a shift by the regulatory authorities in recent years to a more collaborative interaction, with regulators actively encouraging a consultative approach.

Regulations and standards provide a generic framework for proper design, development and manufacturing, with some product specific guidance; including responsibilities for managing partner relationships. The rules applied by regulators on both side of the Atlantic are similar, but evolutionary differences have led to differences in emphasis of these principles. Manufacturers placing products on the market therefore need to be cognisant of these differences and shape their regulatory strategy accordingly.

Although the overall responsibility of placing medical devices on the market lies with the manufacturer, other stakeholders have their part to play. In general, stakeholders can be divided into manufacturers, specification developers and component suppliers. Their regulatory responsibilities are summarised below in Figure 6.

Figure 6. Regulations and standards applying to medical device manufacturers, specification developers and components suppliers in Europe and in the US.

		Regulations						Standards
Stakeholders		Establishment Registration & MD Listing (21CFR part 807)	Premarket Notification 510(k) - 21 CFR part 807 Subpart E	PMA-21 CFR Part 814 and IDE 21 CFR Part 812	Quality System Regulation 21 CFR Part 820	Medical Device Reporting 21 CFR Part 803	Medical Device Directive	ISO13485, ISO14971
Medical Device Manufacturers		●	●	●	●	●	●	●
Specification Developers	Manufacturer	●	●	●	●	●	●	●
	Not Manufacturer				●			●
Component Suppliers					*			*

*By quality agreement with manufacturer

Source: PA Consulting

Manufacturers

Manufacturers are responsible for defining the intended use of the device, determining the regulatory classification and route for complying with the Medical Devices Directive or the relevant FDA Code of Federal Regulations. Consequently, they are also responsible for developing the specification for the device.

Manufacturers are responsible for the safety of the device in the market and for post marketing vigilance of the device, reporting adverse events and for establishing a system for corrective and preventative actions (CAPA) based on adverse reports or complaints from the field. They are also responsible for registering the establishment with the authorities as a medical device manufacturer. This would also apply to software houses that write Apps classified as medical devices.

Specification developer

Specification development may be contracted out to an organisation that will not manufacture the device; however the manufacturer remains accountable under the regulations. In this case the manufacturer will specify to the specification developer the quality standards that must be applied such as ISO 13485, ISO 14971 and software standards, and is accountable for ensuring and verifying that the standards have been complied with.

Component supplier

As discussed earlier, component suppliers are not subject to medical device regulations. It is the responsibility of the manufacturer to ensure that components are suitable for the medical use to which they are being put as defined in the specification. The manufacturer must put in place quality and service level agreements to ensure that components are supplied to an appropriate quality standard and they must verify and provide evidence that this is the case.

App distributor

Another stakeholder in the medical device supply chain is the App distributor. Currently distributors (e.g. i-Tunes) are exempt from medical device regulation. In general, App authors are required to follow limited template development rules and some distributors undertake a perfunctory peer review to check performance of the App.

Mobile medical Apps will have undergone a more rigorous development and approval process; and as indicated above, the regulations require post market maintenance, version control, surveillance, reporting of adverse events and CAPA. The App author therefore needs to give due consideration as to how these requirements will be complied with.

Customers purchasing mobile medical Apps in a particular country will rightly expect that the products are safe and approved for use. It should therefore be clear to customers that these products have been assessed, given that there may not be any physical packaging and instruction leaflet to place a CE mark on. It is a requirement that there must be a clear process for reporting adverse events or complaints to the manufacturer by the user.

An example regulatory flowchart is given in Figure 7 below.

Application Programming Interface (API) development

An API developer can, in theory, aim at being "medical use ready": This claim does not sufficiently define its intended use or identify a complete test programme; therefore it cannot yet be classified or approved as a medical device. The analogy would be the same as any component that meets a certain recognised standard (for example a polymer meeting USP Class 6, or an accessory / component meeting Continua), but is not an approvable product in its own right. These components would be marketed as potentially suitable for use in medical products and then evaluated within the context of the product into which they have been incorporated. Being "continua ready" should therefore not impact the certification of a device with no specific medical intended use. However for the API to be useful for medical devices, any software should be developed with medical regulations in mind (e.g. ISO 13485 and 21CFR820) as it's often harder to retrospectively validate software for medical applications, should this become the intended use.

On the other hand, an API can be marketed with a (or multiple) specific medical intended use (for example, being an accessory of a specific medical App):

Then the development process is impacted by med device regulations which involves supporting specification, testing and documentation according to ISO 13485 / CFR 820.

Figure 7: Medical device regulation Application example
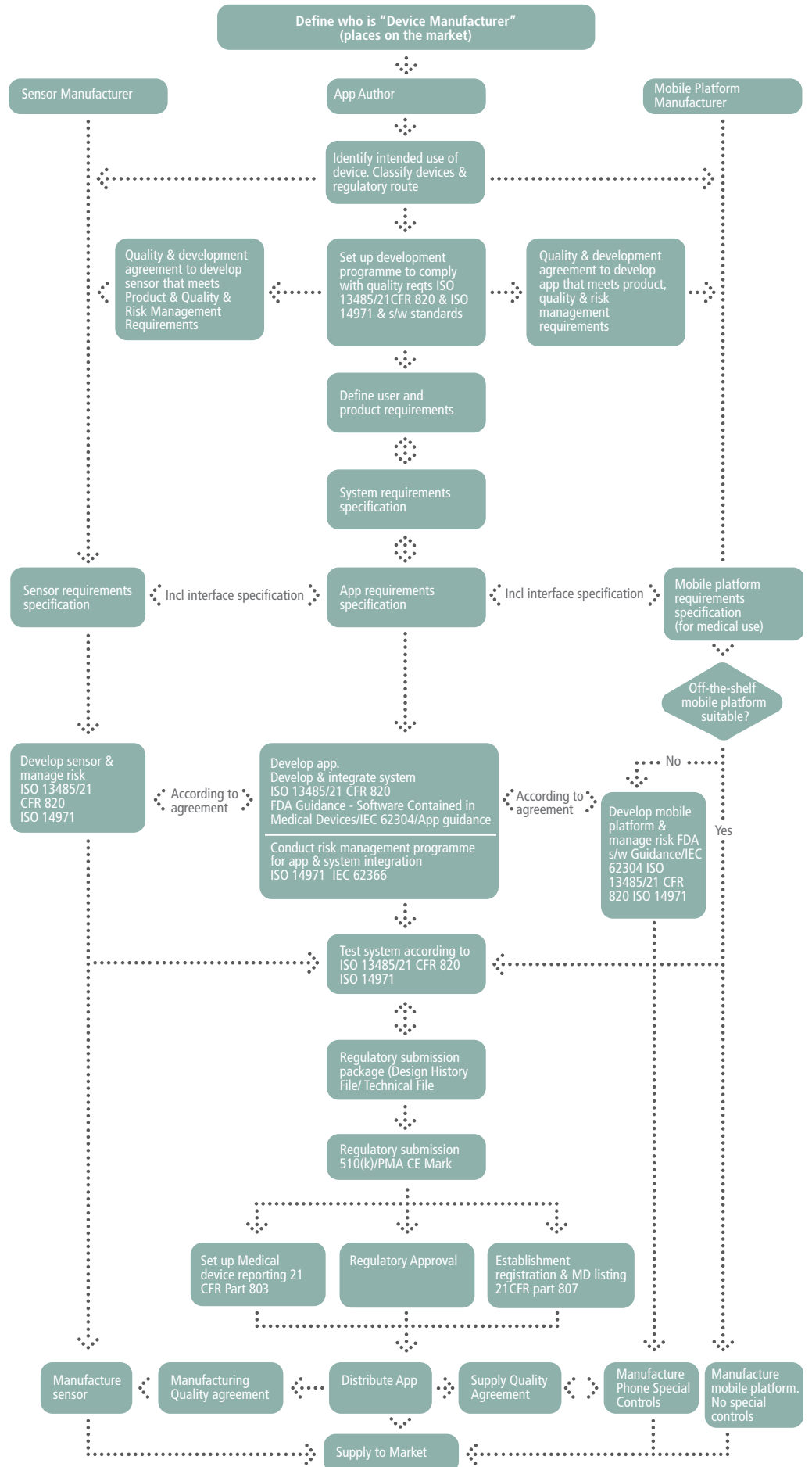
Source: PA Consulting

3.2 Applications in the US

Products need to be defined as medical devices

The first step is to determine whether the envisaged product will be classed as a medical device. This assessment should take place early during product concept design as it will have significant implications for design, development and manufacturing of the product.

Medical devices are products, which include software. that is intended to directly influence people's health. Medical devices can function independently, or be used in conjunction with accessories. In the US, accessories assume the class of the parent device they are connected to. For example, a blood glucose meter is a medical device using individual strips as accessories.

Once it has been determined that your device is a medical device, it is recommended to approach the regulators, using a regulatory affairs advisor as appropriate, to confirm and engage with the regulatory bodies.

Medical devices are classified into regulatory classes

The Food and Drug Administration has established classifications for approximately 1,700 different types of devices and grouped them into 16 medical specialties referred to as 'panels'. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. The three classes and the requirements which apply to them are:

Device Class and Regulatory Controls:

Class I General Controls (controls relating to general device safety)
Class II General Controls and Special Controls (controls specific to the device type)
Class III General Controls and Premarket Approval (more rigorous controls including clinical data)

The class to which a device is assigned determines the type of premarketing submission / application required for FDA clearance to market the product. If the device is classified as Class I or II, and it is not exempt, a 510(k) will be required for marketing. For Class III devices, a PreMarket Approval application (PMA) will be required.

It is important to note that devices are classified into panels according to their intended use, rather than by technology. Therefore mobile technology could in theory fall into any one of the 16 panels and attract different controls depending on the classification.

510(k) application is based on the existence of a predicate device

The FDA provides several pathways for product registration, which are different from the EU. For class I and II devices, the route to market is a 510(k) application. This application is based on the fact that a legally marketed predicate medical device exists which is 'substantially equivalent' to the one for which approval is sought. Essentially the 510(k) allows manufacturers to piggy-back off the efforts of other products that are considered as 'substantially equivalent predicates'. Manufacturers must provide documented evidence of substantial equivalence through design control, testing and risk management. Most medical device manufacturers aim to find predicates and use the 510(k) route as this reduces the regulatory burden of proof. If predicates cannot be found or if the device is high risk (class III), then the PMA route must be followed with implications of substantially more safety testing and documentation.

In general the FDA has made concessions to manufacturers via the 'least burdensome approach' which it applies to software. The challenge for mobile medical apps is that it is difficult to derive clear rules / decision trees for assessing predicates, which is an area that GSMA can engage with regulators to shape the discussion.

Pre-Market Approval (PMA) is the route if no predicate device exists and for Class III devices

Products requiring PMAs are devices that pose a significant risk of harm (Class III), or devices found not substantially equivalent to Class I and II predicates through the 510(k) process. The PMA process is more rigorous and includes the submission of pre-clinical and clinical data to support claims made for the device.

Hence for Class III mobile medical devices, the development and market launch is likely to be led by a medical device company rather than a mobile telecoms company.

Quality system regulation sets the rules for medical device quality control

The US codifies rules for the quality control of medical devices within the Code of Federal Regulations Title 21 part 820 (21CFR 820) often known as the Quality System Regulation (QSR). The QSR sets out the rules for good design and manufacturing practice (GMP). It is important for GSMA members to recognize that it is not only the manufacture of medical devices that is regulated, but also the design and development process prior to manufacture. Design Controls require that design development is documented through requirements specifications that are traceable through the design verification and validation work that follows. This provides evidence that user requirements (of safety, efficacy and performance) were correctly specified and then met through device design. Design Controls tighten up the development process; impose discipline and generation of formal documented evidence of all activities. The QSR also requires that products are supported in the market place and that manufacturers are vigilant in monitoring and addressing any post marketing issues relating to safety.

Whilst it is likely that mobile products developed by GSMA stakeholders are appropriately designed and verified   we cannot assume that the design processes employed will comply with the requirements of the medical device regulations.

Post-marketing considerations

The FDA states[5] that "Medical device manufacturers as well as other firms involved in the distribution of devices must follow certain requirements and regulations once devices are on the market. These include such things as tracking systems, reporting of device malfunctions, serious injuries or deaths, and registering the establishments where devices are produced or distributed."

Medical device reporting is another key area where mobile medical devices differ from conventional mobile devices. The medical device regulation provides a mechanism for FDA and manufacturers to identify and monitor significant adverse events involving medical devices. The goals of the regulation are to detect and correct problems in a timely manner.

Distributors/manufacturers must report device-related deaths, serious injuries and reportable malfunctions. In addition the FDA requires distributors and manufacturers to certify to FDA the number of MDR reports filed or that no reports have been filed. In order to do this, manufacturers must put in place the appropriate systems to enable reporting of problems.

Medical Device Data Systems or MDDSs are medical devices in the eyes of regulators

The FDA defines an MDDS[6] as "[…] a device that is intended to transfer, store, convert from one format to another according to preset specifications, or display medical device data. An MDDS may include software, electronic or electrical hardware such as a physical communications medium (including wireless hardware), modems, interfaces, and a communications protocol. [However] an MDDS acts only as the mechanism by which medical device data can be transferred, stored, converted, or displayed. An MDDS does not modify the data or modify the display of the data, [and] […] by itself, does not control the functions or parameters of any other medical device. [It] […] can only control its own functionality. This device is not intended to provide or be used in connection with active patient monitoring. Any product that is intended for a use beyond the uses (or functions) identified in this […] classification rule is not an MDDS […]".

5   http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/default.htm

6   http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/MedicalDevice
      DataSystems/ucm251906.htm

Interestingly risks associated with MDDS were found by the authority[7] to "include the potential for inaccurate, incomplete, or untimely data transfer, storage, conversion, or display of medical device data. In some cases, this can lead to incorrect patient diagnosis or treatment. Based on evaluation of these risks, the FDA has determined that general controls such as the Quality System Regulation (21 CFR part 820), will provide a reasonable assurance of safety and effectiveness. Therefore, special controls and premarket approval are not necessary".

This is why the FDA has been "exempting MDDSs from the premarket notification requirements" and did issue "[…] a final rule to reclassify Medical Device Data Systems (MDDSs) from class III (premarket approval) into class I (general controls)" on February 15, 2011[8].

7   http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/MedicalDeviceDataSys
     tems/ucm251897.htm

8   http://edocket.access.gpo.gov/2011/pdf/2011-3321.pdf

3.3 Applications in Europe

General principles and definitions

The EU differs from the US in that it is not one country with one regulator, but an economic union of different countries that have gone through a lengthy process of harmonizing national law. A single EU regulatory group does exist (the European Medicines Agency), but the member states retain their own regulatory bodies, known as competent authorities. However the process to regulate and approve medical devices is now harmonised into three EU directives, of which the Medical Devices Directive (MDD 93/42/EEC) (or MDD) is one. There are two further directives with specific requirements for specific medical devices. The In Vitro Diagnostic Device Directive (IVDD 98/79/EC) applies to in-vitro diagnostic devices and the Active Implantable Medical Device Directive (AIMDD 90/385/EEC) applies to devices such as pacemakers or implantable infusion pumps. The member countries of the EU are required to pass laws to implement these directives. It is possible that mobile medical devices may fall into any of these three directives.

Unlike the US, the approval of medical devices is not through national authorities but through organisations known as Notified Bodies (NBs). NBs are commercial organizations registered by the competent authorities for licensing new medical devices.

NBs act on behalf of the regulators and carry out much of the auditing of the Quality Management systems (QMS) of companies and approvals of their products. In most cases it is the NBs that assess and accredit companies for ISO standards, of which ISO 13485 is the relevant one for medical device specification developers and manufacturers. NBs generally operate in a consultative manner and prefer early and active engagement with manufacturers, perhaps more so than the FDA. NBs are heavily involved with the approval of higher risk devices from class II and above, much less so with Class I medical devices, where most can have a CE mark assigned by self-declaration.

During product approval, the NBs determine if a product complies with the directive by assessing the design and documentation. There are various routes that the manufacturer can take (defined in the various annexes of the MDD) and which depends on their capability. The annexes allow greater self-determination for experienced medical device companies and routes based on independent testing for those less experienced.

If the NB determines that the new medical device meets the requirements of the MDD then it will issue a CE mark and four-digit identifier when appropriate. This CE mark is not a quality marking aimed at consumers; instead the CE Mark for medical devices is a legally binding statement by the manufacturer that the product meets all requirements applicable to them. The CE mark does not apply outside of the EU, although some territories in emerging markets accept them at face value. Much of the work done for the technical file required to achieve the CE mark is the same for that required for the US market, although the format of the submission is quite different.

As in the US, European routes to approval depend on the medical device classification[9].

In order to comply with the MDD essential requirements (Annex I), manufacturers must provide and demonstrate that they have:

- Technical documentation which must contain full construction details and test data known as design validation and verification for your medical device. The International Organization of Standards (ISO) provides guidance on the selection of standards in support of recognized essential principles of safety and performance of medical devices (ISO/TR 16142).
- Performed a safety risk assessment which must include a construction evaluation, materials used, bio-compatibility analysis, infection and cross-infection risks, and potential risks during use.
- A quality system, which can be achieved by conforming to ISO 13485 (harmonized standard in the EU)

9   Note that the full classification rules are given in Annex IX of the Medical Devices Directive

Standards

The various standards for medical devices that have been developed in Europe are not mandatory, but they are almost universally applied in design, development and manufacturing of medical devices. There are many standards that are applicable to medical devices and they provide a framework for proper design and development and manufacturing. General standards that are likely to apply to mobile medical device manufacturers include[10]:

ISO 13485:2003 Medical devices – Quality management systems – Requirements for regulatory purposes

ISO 13485 Quality management systems or QMS (derived from ISO9001) is roughly equivalent to the QSR in the US. This standard specifies requirements for a quality management system where an organization needs to demonstrate its ability to provide medical devices and related services that consistently meet customer requirements and regulatory requirements applicable to medical devices and related services.

ISO 14971:2007 Medical devices – Application of risk management to medical devices

This standard establishes the requirements for risk management to determine the safety of a medical device by the manufacturer during the product life cycle. This standard is also recognized by the US authorities. It specifies a process for a manufacturer to identify the hazards associated with medical devices, including in vitro diagnostic (IVD) medical devices, to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls. The requirements of ISO 14971:2007 are applicable to all stages of the life-cycle of a medical device.

IEC 62366:2007 Medical devices – Application of usability engineering to medical devices

This specifies a process for a manufacturer to analyse, specify, design, verify and validate usability, as it relates to safety of a medical device. The usability engineering process assesses and mitigates risks caused by usability problems associated with correct use and use errors, i.e. normal use. If the usability engineering process detailed in this International Standard has been complied with and the acceptance criteria documented in the usability validation plan have been met, then the residual risks, as defined in ISO 14971, associated with usability of a medical device are presumed to be acceptable.

IEC 60601 – Series Medical electrical equipment

IEC 60601-1 is applicable to medical devices and is sub-divided in sub-sections which include: safety requirements for medical electrical systems, electromagnetic compatibility - requirement and tests, programmable electrical medical systems, usability, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems.

IEC 62304 – Medical device software life cycle processes

The IEC standard for medical device software defines a software life cycle processes which specifies life cycle requirements for the development of medical software and software within medical devices. It is harmonized by the European Union and the United States, and therefore can be used as a benchmark to comply with regulatory requirements from both these markets.

The essential requirements of the MDD has a requirement that medical devices incorporating electronic programmable systems must be designed to ensure the repeatability, reliability and performance of these systems according to the intended use. In the event of a single fault condition (in the system) appropriate means should be adopted to eliminate or reduce as far as possible consequent risks.

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10   http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_tc_browse.htm?commid=54892

The implications for software products are:

Software products that are a single piece of software with an intended purpose that fits the medical device definition will be regulated as medical devices

A system that is a combination of software applications assembled for a purpose that fits the medical device definition may be regulated, although this is not yet clear

For devices which incorporate software or which are medical software in themselves, the software must be validated according to the state of the art taking into account the principles of development lifecycle, risk management, validation and verification.

For developers of mobile medical Apps, this means that a systematic process is required for software development which is likely to be more rigorous that currently used.

IEC 80001-1 – risk management for IT networks incorporating a medical device

The ISO standard website states[11] that " recognizing that medical devices are incorporated into IT-networks to achieve desirable benefits (for example, interoperability), defines the roles, responsibilities and activities that are necessary for risk management of IT-networks incorporating medical devices to address safety, effectiveness and data and system security (the key properties). IEC 80001-1:2010 does not specify acceptable risk levels. IEC 80001-1:2010 applies after a medical device has been acquired by a responsible organization and is a candidate for incorporation into an IT-network. It applies throughout the life cycle of IT-networks incorporating medical devices. IEC 80001-1:2010 applies where there is no single medical device manufacturer assuming responsibility for addressing the key properties of the IT-network incorporating a medical device. IEC 80001-1:2010 applies to responsible organizations, medical device manufacturers and providers of other information technology for the purpose of risk management of an IT-network incorporating medical devices as specified by the responsible organization. It does not apply to personal use applications where the patient, operator and responsible organization are one and the same person"

This standard takes a more holistic approach recognising that implementing a medical device in a crowded environment has its own risks (e.g. a hospital, with potentially many electronic medical devices competing for frequencies or networks). To fully assess these risks a system approach is needed considering the device in the working environment. The responsibility falls to the 'responsible organisation' incorporating the medical device into the IT- network, which in most cases will be the hospital but calls for medical device manufacturers to engage in the risk assessments. This is a complex area of telecoms and it is likely that GSMA members will play a vital supporting role.

Note: in the US , this is being interpreted that medical device manufacturers which connect to a network will be required to divulge any and all networking behaviour associated with the medical device and risks associated with that networkability as well as interoperability with other components on the network - in the mobile example, if a mobile application will be using a VPN or some other mechanism for information retrieval/measurement or transfer, uni or bi-directionally might be required to divulge the information regarding this behaviour and risk mitigation to the healthcare provider so that they may be able to meet the IEC 80001 requirements.

11   http://www.iso.org/iso/catalogue_detail.htm?csnumber=44863

4. Case studies

4.1 Implications for medical device manufacturers seeking to link with mobile platforms

iPhone connected blood pressure cuffs from Withings®

After starting its business with WiFi-connected scales for which it received venture capital funding of US$ 3.8 million from Ventech, Withings announced in February 2011 the production of a blood pressure monitor and cuff retailing at 129 euros which plugs into an iPhone and an iPad. The mobile platform is used to control the cuff, save and analyse the data, and optionally share the results with a physician or another party.

Intended to be used by the general public, the different Withings® products (scale, baby monitor and blood pressure monitor) are at the border between wellness/self-monitoring products and medical devices. However, this particular product is clearly defined as a medical device according to the regulations. Just like other automatic blood pressure monitors, the blood pressure cuff from Withings® has to comply with medical device regulations.

Withings® obtained European approval for the device by complying with the essential requirements of the Medical Device Directive 93/42/EEC, and is currently in the process of obtaining FDA 510(k) clearance on the principle that it is not significantly different from blood pressure monitors connecting to PDAs.

Despite being connectable to an Apple product, complying with the regulation and therefore ensuring product safety is the sole responsibility of Withings®. The recent mobile medical app guidance[12] re-iterates the fact that off-the-shelf phones, although part of medical device systems, are not to be regulated. Making such a distinction between the 'mobile' and the 'medical' parts of a medical system has a big impact on possible innovation in the field. By allowing medical devices to access the cellular network via an unregulated mobile handset, the regulators are introducing further flexibility into the application of the regulations.

ECG monitor case for iPhone from AliveCor®

AliveCor® is a snap-on ECG wireless case for the iPhone 4 with two electrodes to be put in contact with the patient's skin. It allows the diagnosis and monitoring of cardiac rhythm disturbances and is targeted at physicians and other healthcare professionals who may need fast access to an ECG in the field, and should retail at under US$100.

This device is in the process of obtaining regulatory approval. Going through CE marking at first the company is planning on subsequently filing a 510(k) in order to start production in Q4 2011.

Qualcomm Ventures, Burrill & company and the Oklahoma Life Sciences Fund have invested a total of US$3 million in the company. This was following the suggestion made during last January Consumer Electronics Show that combining geo-tracking data to ECG data could further the understanding of environmental factors on cardiovascular diseases.

This clip-on ECG case is considered by the FDA as transforming a phone into a medical device as it is intended to support the diagnosis of cardiovascular diseases. Such a definition directly impacts the development of this product as a risk assessment of the entire system (including the mobile phone) has to be done. It is not however the responsibility of the handset company (in this case Apple) to comply with medical device regulation as it is not providing its phone with the intended use of having them clipped to AliveCor® cases. Such repartitions of the responsibilities, as described by the FDA, are again, in our view, sensible.

In both cases, the medical device manufacturers (Withings and AliveCor) did seek (or are probably seeking) regulatory approval independently from the mobile handset they intended to connect to.

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12   http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm263280.htm

This was possible as mobile handsets can be recognised by regulators as off-the-shelf 'tools' that are not directly intended for medical usage and therefore not falling under medical device regulation per see. However both manufacturers need to demonstrate that such handsets are fit for purpose. By restricting the range of mobile handsets intended to be used with their products, both companies limited the scope of the risk assessment to be performed and possibly the number of safety mitigation strategies they had to put in place, possibly speeding the (potential) approval process.

Wireless connected insulin pump from CellNovo®

Cellnovo, a UK-based company, has developed a mobile diabetes management system, including an insulin patch pump and a dedicated wireless touch screen handset/tablet with a built-in blood glucose monitor. The system transmits real-time data to a web-based portal, freeing patients and carers from the burden of keeping meticulous journals and ensuring optimal monitoring and treatment of the disease.

This system is composed of multiple entities interactively connected with one another: an insulin pump, which according to the FDA classification database[13] is a Class II medical device, a mobile tablet, a firmware, which according to the recent FDA mobile app guidance[14] is to be regulated, and a web-based database linked through a network service. As they are connected to a medical device, all parts of this system are potentially impacted by medical device regulations.

As the tablet is used not only for receiving data but also for wirelessly controlling the insulin pump and updating medical professionals of current status (leading to a possible diagnosis), serious risks can be envisaged by improper use or malfunctions. Requirements needed to guarantee user safety can therefore most conveniently be achieved by developing a custom made tablet and software. It is therefore understandable that CellNovo created its own tablet, fully designed for and dedicated to this system. This removes any concerns of compatibility and reliability potentially associated with using off-the-shelf tablets. From a regulatory point of view, this strategy also implies that this platform is defined as a component of this system; it cannot be purchased separately or interchanged by the user. Therefore CellNovo is responsible for ensuring that the tablet, even if sourced from third party, fulfills safety and usability requirements.

Once recorded, medical data are then transferred to a dedicated database accessible through a web portal. Such a database is regarded by the FDA as a Medical Device Data System (MDDS). The FDA defines[15] "risks associated with MDDS [to] include the potential for inaccurate, incomplete, or untimely data transfer, storage, conversion, or display of medical device data. In some cases, this can lead to incorrect patient diagnosis or treatment." Recently, "the FDA has determined that general controls such as the Quality System Regulation (21 CFR part 820), will provide a reasonable assurance of safety and effectiveness, […] [and that] special controls and premarket approval are not necessary" hereby reducing the regulatory burden on MDDS from Class III to Class I.

Network and connectivity services are in this case not affected by medical regulations as they are not marketed with a medical intended use and are considered as generic commodities.

Altogether such a system can bring high value to patients and healthcare professionals, and while regulatory approval for such a complex systems can seem daunting, it can be achieved by systematic identification of the risks associated to each part composing the system.

After receiving regulatory approval for a CE Mark, Cellnovo has just been announced by Frost & Sullivan to be the winner of its 2011 European Technology Innovation Award in Diabetes Care[16] therefore proving the high value of such innovations and paving the way for subsequent similar products.

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13   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/PCDSimpleSearch.cfm

14   Draft guidance for industry and FDA administration staff, Mobile Medical Applications" Issued on July 21, 2011,

15   http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/MedicalDevice DataSystems/ucm251897.htm

16   http://www.pressdispensary.co.uk/releases/c993180/Cellnovo%20Receives%202011%20European%20Technology%20 Innovation%20Award%20in%20Diabetes%20Care.html

4.2 Implications for software and App writers creating medical software devices

Radiology viewing app called Mobile MIM®

Mobile MIM is a diagnostic imaging app produced by MIM Software Inc. It is intended for the viewing of diagnostic radiology scans by medical professionals when accessing a workstation is not possible and is available for various types of medical imaging (such as PET scans, X-rays or MRIs). Not intended for public use, Mobile MIM interacts with MIM's cloud, into which doctors or hospitals can upload a scan for a fee of US$1. While the App is free to download, accessing the securely encrypted imaging data and downloading it to the mobile device costs another fee of US$1-2. (comment - it is very difficult to control the intended use of this product by clinicians - it is very clearly stated in the regulatory assessment by the FDA that it is intended for use *only* when an appropriate quality workstation is unavailable - I'm fairly sure that it is used more broadly than that intended by the manufacturer due to the accessibility of the end product - the manufacturer will need to be diligent regarding this if there is some type of future litigation or hazard incident)

The risks incurred by the use of such a product might seem low if one considers it as a simple portable version of medical image displays as it does not provide any diagnostic information. But as medical images are usually analyzed in a controlled environment in low-light conditions, the opportunity to inspect images 'on-the-go' introduces the risk of inadequate luminosity for diagnostic work. In addition to showing that screen resolution on Apple's products (or any other it might intend to be used onto) is adequate for diagnostic applications, Mobile MIM had to integrate dynamic visual tests into the software to determine that the ambient lighting was not too bright for diagnostic work.

This meant that Mobile MIM only received FDA 510(k) clearance in February 2011 after several years of working with the regulators and two rejected 510(k) applications. It has since obtained approval to affix the CE marking by providing evidence to its notifying body of having met all the essential requirements of the Medical Device Directive 93/42/EEC. It was one of the first mobile apps developed with an intended medical use that has been given regulatory approval and it received the Apple Design Award for Best iPhone Healthcare & Fitness Application.

Such an App belongs to a rather grey area in international regulations as it is stand-alone software with a clear medical intended use. The FDA's opinion has been evolving on the matter as it was at first believed to be a new medical device without predicate, and as such a Class III medical device. This opinion later changed as this App has since been granted 510(k) clearance. This is almost certainly due to active engagement between the App developers and the regulatory bodies who are still developing a better understanding of each other's constraints and requirements. It is therefore demonstrated here that an early involvement of the regulators can only be beneficial to stakeholders wishing to enter the mobile medical device market.

Chemotherapy dose calculation app called iCHEMO®

iCHEMO® is an oncology app developed and distributed by Medsync Research, Inc. It is intended to be used by medical professionals to calculate a patient's body surface area and chemotherapy dose and is available from Apple's App Store for US$6.99.

Despite being located in the Medical category of the Apple AppStore, no regulatory approval can be found for this app. Whereas it clearly enters the definition of medical device as it is intended for treatment of disease, this App also belongs to a rather grey area of international regulations as it is stand-alone software providing support in making clinical decisions.

In their last "Regulating medical software" presentation[17] the FDA clearly states that they are looking for feedback on such applications. Their current approach would be to further assess such tools based on the level of impact on patient health but also the degree of acceptance in clinical practice, the ability of users to easily identify erroneous output (deriving from either erroneous input or computation). Such an approach, not only based on the risks to patients, and not impacted by the platform being a mobile phone seems very sensible. Nevertheless, it raises fundamental cultural differences between App writers and medical device manufacturers. From the point of view of an App author such an App can be considered an automated calculator which therefore does not need regulatory approval. (please see comment above regarding calculations) The responsibility in using such a tool would therefore lie with the physician trusting it. In contrast, from a medical device manufacturer's point of view, this tool involves high risks to patient safety as erroneous chemotherapy doses calculated by this app would potentially be life threatening.

Both points of view being valid, the FDA's approach in potentially requesting mitigating actions to help enhance the user's ability to identify erroneous output seems reasonable. Such mitigating actions have not been clearly identified yet and could, just like in the case of Mobile MIM, allow this category of Apps to gain faster regulatory approval.

The fact that a regulated App such as Mobile MIM can be found side by side with an unregulated one such as iChemo can lower the degree of confidence users have with such products. GSMA members seeking to expand their activity in this area would therefore benefit from a much clearer classification system in order to be able to price their product accordingly. It would be prudent for an App writer targeting healthcare professionals to ensure their product satisfies a recognized unmet need, such that it will be used by enough users to justify the cost and effort in meeting the regulations.

17   http://www.amiando.com/eventResources/3/Y/vbaDboTDGMSDrX/1400_Bakul_Patel_Overview_In_The_USA.pdf

4.3 Implications for mobile network providers and other stakeholders entering the medical device market

Telecom Italia® - MyDoctor@Home®

Telecom Italia runs MyDoctor@home, a remote diagnostics service, which allows patients suffering from various chronic ailments to measure their clinical parameters at home, either alone or with nurse support. The results are then automatically uploaded from the connected medical device to the eHealth Connecting Platform over any available fixed line or mobile network. A portal to the platform can be accessed by patients and medical staff via a smartphone, PC or television.

The MyDoctor@home solution is already run on a commercial basis in the Italian market and a pilot has been launched in Brazil.

The service can be considered to be composed of three distinct parts: the medical devices used by the patients, the medical data storage system, and the network services between these two. All the end-user medical devices used in the service have EU regulatory approval, and are monitoring devices for chronic conditions only – not emergency medical devices intended for critical or acute situations. The data storage systems are considered Class I medical devices and have to comply with medical device regulations.

Telecom Italia provides numerous network related services linking multiple medical devices and associated data systems. There is lack of clarity how these services and products may be impacted by medical device regulations as they could be defined as devices, accessory or components. According to the FDA[18] 'an accessory' is a finished device that is "distributed separately but intended to be attached to or used in conjunction with another finished device" often referred to as a 'parent device'. Moreover the FDA stipulates that[19] "accessories to classified devices take on the same classification as the "parent" device. An accessory such as software that accepts input from multiple devices usually takes on the classification of the "parent" device with the highest risk, i.e., class." Therefore if connecting to a Class III device such as an ECG monitor, such a service could be defined as being a Class III medical device. As the manufacturer of such a system, if directly applying previous medical device regulation, Telecom Italia® would be responsible for the system's continuous functionality and safety.

Nevertheless, network services do not fall under medical device regulations, as they are not solely intended to be used for medical purposes. Just like mobile handsets, network services are considered as generic commodities and are not impacted by medical device regulations. However they do have to comply with the appropriate data protection legislation (such as HIPAA in the US, or the data protection act in the UK). Such legislation is aimed at ensuring safe and secure patient data handling and includes requirements such as data encryption.

Microsoft® HealthVault®

Microsoft® HealthVault® is a web-based platform launched in 2007 for storing, maintaining and sharing health and medical information aimed at both patients and healthcare professionals. HealthVault provides a way for individuals to store details of their medical consultations, prescriptions and results of home-based medical monitoring in the "cloud" so it can be easily read, transferred and analysed. In June 2010, Microsoft® HealthVault® was launched in the UK and is addressed to both healthcare professionals and individuals. As this system supports medical device functions, it is impacted by medical device regulations, whereas if it were a generic web database, it would fall beyond the scope of the regulations.

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18   CTR. FOR DEVICES & RADIOLOGICAL HEALTH, FOOD & DRUG ADMIN., HHS PUB. NO FDA 97-4179, Medical Device
     Quality Systems Manual: A Small entity Compliance Guide (Dec 1996), available at http://www.fda.gov/MedicalDevices/
     DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/MedicalDeviceQualitySystems
     Manual/default.htm

19   Final Rule, Medical Devices, Medical Device Data Systems, 76 Fed. Reg. 8637, 8643-8644 (Feb. 15, 2011)

5. Glossary

Intended use

As defined by the FDA[20], for a product to be a medical device it must be intended to be used for medical purposes.

Medical Device

In the US
A medical device is defined[21] in the USA as "… an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is … [either] 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] intended to affect the structure or any function of the body of man or other animals."

In Europe
In Europe a Medical Device is defined as[22] "any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and / or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, investigation, replacement or modification of the anatomy or of a physiological process, control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted by such means."

Accessories

In the US
According to the FDA[23] an accessory is a finished device that is "distributed separately but intended to be attached to or used in conjunction with another finished device" often referred to as a 'parent device'.

In Europe
According to the European regulators[24] an "accessory means an article which whilst not being a device is intended specifically by its manufacturer to be used together with a device to enable it to be used in accordance with the use of the device intended by the manufacturer of the device"

Components

Components are defined by the FDA[25] as " […] any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device"

Components are assembly parts to a medical device sourced by the manufacturer. Component suppliers are not directly subject to regulations but need to fulfill the manufacturer's quality requirements. This might mean keeping complete audit trails and comply with specific quality standards.

Component supplier

A component supplier is defined as a person or entity supplying parts to a medical device manufacturer. Very often component suppliers are not the manufacturer of the medical device. They therefore have no legal obligation to comply with the various regulatory bodies. Nevertheless, medical device manufacturers need to ensure that their component suppliers deliver parts of a satisfactory quality, and will require them to follow quality standards.

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20 21 USC 301-399a
21 Section 201 (h) of the Federal Food, Drug and Cosmetic Act
22 According to Directive 2007/47/EC (21 March 2010) amendment to the Directive 93/42/EEC
23 CTR. FOR DEVICES & RADIOLOGICAL HEALTH, FOOD & DRUG ADMIN., HHS PUB. NO FDA 97-4179, Medical Device
    Quality Systems Manual: A Small entity Compliance Guide (Dec 1996), available at http://www.fda.gov/MedicalDevices/
    DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/MedicalDeviceQualitySystems
    Manual/default.htm
24 COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993
25 According to 21CFR820 Sec. 820.3(c)

Risk management

Risk management is defined by the FDA[26] as "the systematic application of management policies, procedures, and practices to the tasks of identifying, analyzing, controlling, and monitoring risk. It is intended to be a framework within which experience, insight, and judgment are applied to successfully manage risk. It is included in this guidance because of its effect on the design process. Risk management begins with the development of the design input requirements. As the design evolves, new risks may become evident. To systematically identify and, when necessary, reduce these risks, the risk management process is integrated into the design process. In this way, unacceptable risks can be identified and managed earlier in the design process when changes are easier to make and less costly."

Quality systems

As defined in Design Control Guidance For Medical Device Manufacturers § 820.3 (v) Quality system means "the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management"

Design controls

Design controls are defined by the FDA[27] as "an interrelated set of practices and procedures that are incorporated into the design and development process, i.e., a system of checks and balances. Design controls make systematic assessment of the design an integral part of development. […] Design controls increase the likelihood that the design transferred to production will translate into a device that is appropriate for its intended use."

Design verification

According to the FDA[28] design verification means the "confirmation by examination and provision of objective evidence that specified requirements have been fulfilled"

Design validation

While Design Validation means "establishing by objective evidence that device specifications conform to user needs and intended use(s)."

Technical file

Technical file also called electronic common technical documents (eCTDs) by the FDA is the standard format for electronic regulatory submissions. General descriptions and content of a technical file can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

CFR - Code of Federal Regulations

Code of Federal Regulations is the collection of rules and regulations related to multiple departments and agencies of the American federal government. Title 21 is related to Food and Drugs and contains 1499 parts covering specific regulatory areas.

Manufacturer

The FDA[29] defines manufacturers as "any person who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking, or specification development, and initial distributors of foreign entities performing these functions".

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26   Design Control Guidance For Medical Device Manufacturers Relating To Relates To Fda 21 Cfr 820.30 And Sub-Clause 4.4 Of Iso 9001. It Can Be Found At Http://Www.Fda.Gov/Medicaldevices/Deviceregulationandguidance/Guidancedocuments/Ucm070627.Htm

27   Design Control Guidance For Medical Device Manufacturers relating to relates to FDA 21 CFR 820.30 and Sub-clause 4.4 of ISO 9001. It can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070627.htm

28   Design Control Guidance For Medical Device Manufacturers relating to relates to FDA 21 CFR 820.30 and Sub-clause 4.4 of ISO 9001. It can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070627.htm

29   Quality System Regulation 21 CFR 820 - Basic Introduction available at http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm126252.htm

Mobile medical apps manufacturer

Mobile medical apps manufacturer is further defined in the Mobile App guidance draft document[30] to "include anyone who initiates specifications, designs, labels, or creates a software system or application in whole or from multiple software components. […] [It includes] a person or entity that creates a mobile medical app by using commercial off the shelf (COTS) software components and markets the product to perform as a mobile medical app, [someone that] provides mobile medical app functionality through a "web service" or "web support" for use on a mobile platform. For example, a manufacturer of a mobile medical app that allows users to access the application's medical device functionality over the web is considered a mobile medical app manufacturer. [It also includes a person or entity that] initiates specifications or requirements for mobile medical apps or procures product development/manufacturing services from other individuals or entities (second party) for subsequent commercial distribution. For example, when a "developer" (i.e., an entity that provides engineering, design, and development services) creates a mobile medical app from the specifications that were initiated by the "author," the "author" who initiated and developed specifications for the mobile medical app is considered a "manufacturer" of the mobile medical app under 21 CFR 803.3. […] [In other worlds] manufacturers of a mobile medical app would include persons or entities who are the creators of the original idea (initial specifications) for a mobile medical app, unless another entity assumes all responsibility for manufacturing and distributing the mobile medical app, in which case that other entity would be the "manufacturer." Software "developers" of a mobile medical app that are only responsible for performing design and development activities to transform the author's specifications into a mobile medical app would not constitute manufacturers, and instead the author would be considered the manufacturer"

Specification developers

The FDA defines specification developers as "person or entity creating the initial specifications for a product. The specification developer may or may not be the manufacturer". Some clarifications are to be highlighted in the case of:

Mobile medical apps[31]: "The author is defined as the person or entity that initiated and developed specifications for the mobile medical app while the developers are only responsible for performing design and development activities to transform the author's specifications into a mobile medical app".

ISO standards

International Organization for Standardization is a non-governmental organization having members mandated by local governments as well as, private sector national partners and industry associations, therefore forming a bridge between the public and private sectors. Its mission is to develop and publish international standards enabling a consensus to be reached on solutions that meet both the requirements of business and the broader needs of society.

GMP - Good manufacturing practice

Good manufacturing practices are policies and systems needed to manufacture and test aspects of production that can impact the quality of an active pharmaceutical product, diagnostic tool, food, and medical device. They include the establishment of quality controls and quality systems and are, in some countries, required by law in order to safeguard the health of the public.

EU directive[32]

Directives are used to bring different national laws into line with each other, and are particularly common in matters affecting the operation of the single market (e.g. product safety standards). They lay down certain end results that must be achieved in every Member State. National authorities have to adapt their laws to meet these goals, but are free to decide how to do so. Directives may concern one or more Member States, or all of them. Each directive specifies the date by which the national laws must be adapted - giving national authorities the room for manoeuvre within the deadlines necessary to take account of differing national situations.

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30   Draft guidance for industry and FDA administration staff, Mobile Medical Applications" Issued on July 21, 2011

31   Draft guidance for industry and FDA administration staff, Mobile Medical Applications" Issued on July 21, 2011

32   http://ec.europa.eu/eu_law/introduction/what_directive_en.htm

Wellness

The definition of wellness is still something that has not been fully defined by international regulators.

In general it can refer to related but slightly different concepts depending on the context this term is used. The term has been defined by the Wisconsin-based National Wellness Institute as "an active process of becoming aware of and making choices toward a more successful existence".

The New York Times[33] has recently traced the historical changes in the meaning of this word as follow:

Though the Oxford English Dictionary traces wellness (meaning the opposite of illness) to the 1650s, the story of the wellness movement really begins in the 1950s. New approaches to healthful living were emerging then, inspired in part by the preamble to the World Health Organization's 1948 constitution: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." Halbert L. Dunn, chief of the National Office of Vital Statistics, was looking for new terminology to convey the positive aspects of health that people could achieve, beyond simply avoiding sickness. In a series of papers and lectures in the late '50s, Dunn sketched out his concept of "high-level wellness," defined as "an integrated method of functioning, which is oriented toward maximizing the potential of which the individual is capable."

EMA - European Medicines Agency

According to their website the European Medicines Agency[34] is "a decentralised agency of the European Union, located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union."

MDDS - Medical Device Data System

The FDA[35] defines an MDDS as "a device that is intended to provide one or more of the following uses, without controlling or altering the functions or parameters of any connected medical devices:

The electronic transfer of medical device data;

The electronic storage of medical device data;

The electronic conversion of medical device data from one format to another format in accordance with a preset specification; or

The electronic display of medical device data.

An MDDS may include software, electronic or electrical hardware such as a physical communications medium (including wireless hardware), modems, interfaces, and a communications protocol. This identification does not include devices intended to be used in connection with active patient monitoring".

The FDA clarified further that an MDDS[36] is NOT "general-purpose IT infrastructure used in health care facilities that is not altered or reconfigured outside of its manufactured specifications. Modifications within the off-the-shelf parameters of operation are still considered general IT infrastructure and not MDDS. For example, components with the following functions by themselves are NOT considered MDDS if they are used as part of general IT infrastructure even though they may transfer, store, display or convert medical device data, in addition to other information: The electronic transfer of medical device data [such as] Network Router, Network Hub, [or] Wireless access point; The electronic storage of medical device data [such as] Network Attached Storage (NAS) [or] Storage area network (SAN); The electronic conversion of medical device data from one format to another in accordance with a preset specification [such as] Virtualization System (ex: VM Ware) [or] PDF software."

33   http://www.nytimes.com/2010/04/18/magazine/18FOB-onlanguage-t.html

34   http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000235.jsp&mid=

35   FDA guidance on Identifying an MDDS that can be found on http://www.fda.gov/MedicalDevices/Productsand

36   MedicalProcedures/GeneralHospitalDevicesandSupplies/MedicalDeviceDataSystems/ucm251906.htm
       http://edocket.access.gpo.gov/2011/pdf/2011-3321.pdf

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