



REGULATORY PROFILE

GLUCOSE SELF-MONITORING TOOLS

OCTOBER 2021

Regulatory Profile for Glucose Self-monitoring Tools

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Abbreviations, definitions and descriptions

| | |
|------------------|---|
| AHWP | Asian Harmonization Working Party |
| AIMD | Active implantable medical device |
| AMDF | African Medical Device Forum |
| ANVISA | Agência Nacional de Vigilância Sanitária or ANVISA is the regulator of devices for Brazil. |
| CAB | Conformity Assessment Body. They are the bodies that undertake conformity assessment against requirements. For medical devices, they can be government agencies, national standards bodies, or private or publicly owned companies. |
| CE | Conformité Européenne |
| CEG | Consensus error grid. The consensus error grid (also known as the Parkes error grid) was developed as a tool for evaluating the accuracy of a blood glucose meter. |
| CE marking | CE marking is a mandatory administrative marking that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area (EEA). The CE marking is also found on products sold outside the EEA that have been manufactured to EEA standards. |
| CMDE | Center for Medical Device Evaluation, part of the Chinese regulatory agency, the NMPA |
| CGM | Continuous glucose monitoring systems, that measure glucose in interstitial fluid via a device implanted under the skin. Different from SMBGs, that measure blood glucose levels from (usually) a fingerstick collection. |
| CLSI | Clinical and Laboratory Standards Institute https://clsi.org/ |
| Devices | For this report, encompasses medical devices and IVD medical devices |
| EC | European Commission |
| EU | European Union |
| FDA | Food and Drug Administration of the United States of America |
| FDA OTC Guidance | This abbreviation is used in this document to describe the FDA guidance, "Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use" of September 2020. It can be found at the following link: |

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/self-monitoring-blood-glucose-test-systems-over-counter-use>

| | |
|-----------|---|
| GHTF | Global Harmonization Task Force |
| HbA1c | Glycated haemoglobin |
| HIV | Human immunodeficiency virus |
| iCGM | Intermittently viewed Continuous Glucose Monitoring System |
| IDF | The International Diabetes Federation |
| IEC | International Electrotechnical Commission |
| IFCC | International Federation of Clinical Chemistry and Laboratory Medicine |
| IMDRF | International Medical Device Regulators Forum |
| IMDRF ToC | IMDRF Device Market Authorization Table of Contents |
| Interpol | International Criminal Police Organization |
| ISO | International Organization for Standardization |
| IVD | In vitro diagnostic |
| IVDD | In Vitro Diagnostic Medical Device Directive 98/78/EC of the European Union |
| IVDR | In Vitro Diagnostic Medical Device Regulation (EU) 2017/746 of the European Union |
| LMIC | Low- and middle-income country |
| MARD | Mean absolute relative difference, currently the most common metric used to assess the performance of CGMs. |
| MAUDE | Medical Device Adverse Event Reports |
| MDSAP | Medical Device Single Audit Program |
| MDD | Medical Device Directive 93/42/EEC of the European Union |
| MDR | Medical Device Regulation (EU) 2017/745 of the European Union |
| | |
| NMPA | National Medical Product Administration of China |
| NRA | National Regulatory Authority |
| PAHO | Pan American Health Organization |
| QMS | Quality management system |
| rtCGM | Real-time Continuous Glucose Monitoring System |
| SI | Système Internationale |
| SKUP | Scandinavian evaluation of laboratory equipment for point of care testing. The purpose of SKUP is to improve the quality of near patient testing in Scandinavia by providing objective and supplier-independent information |

| | |
|-------|---|
| | about analytical quality and user-friendliness of laboratory equipment. This information is generated by organizing SKUP evaluations. |
| SMBG | A system for self-monitoring of blood glucose. For this report, it refers to those systems where a person living with diabetes self-collects capillary blood and measures it with a glucose monitor. |
| STED | GHTF Summary Technical Documentation for demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices |
| TMDA | Tanzania Medicines & Medical Devices Authority |
| TPLC | Total Product Life Cycle is a database of events reported to the US FDA for a particular product type. The TPLC database combines data from various FDA databases (data sources) to present an integrated record of pre-market and post-marketing activity for medical devices. |
| UDI | Unique Device Identifier |
| US(A) | United States (of America) |
| WHO | World Health Organization |

1. INTRODUCTION

According to the International Diabetes Federation (IDF), 463 million people worldwide were living with diabetes in 2019, many from low- and middle-income countries (LMICs) where inequalities in access to quality healthcare persist. Diabetes is often undiagnosed or inadequately treated, with people unable to access the essential medicines and devices they need. Over the next 25 years, diabetes prevalence is expected to increase in all countries, with the greatest increase expected in middle-income countries (Figure 1).¹

Figure 1. Top 10 countries or territories for number of adults (20–79 years) with diabetes (IDF Diabetes Atlas¹)

| Rank | 2019 | | 2030 | | 2045 | |
|------|--------------------------|-------------------------------------|--------------------------|-------------------------------------|--------------------------|-------------------------------------|
| | Country or territory | No. of people w diabetes (millions) | Country or territory | No. of people w diabetes (millions) | Country or territory | No. of people w diabetes (millions) |
| 1 | China | 116.4 | China | 140.5 | China | 147.2 |
| 2 | India | 77.0 | India | 101.0 | India | 134.2 |
| 3 | United States of America | 31.0 | United States of America | 34.4 | Pakistan | 37.1 |
| 4 | Pakistan | 19.4 | Pakistan | 26.2 | United States of America | 36.0 |
| 5 | Brazil | 16.8 | Brazil | 21.5 | Brazil | 26.0 |
| 6 | Mexico | 12.8 | Mexico | 17.2 | Mexico | 22.3 |
| 7 | Indonesia | 10.7 | Indonesia | 13.7 | Egypt | 16.9 |
| 8 | Germany | 9.5 | Egypt | 11.9 | Indonesia | 16.6 |
| 9 | Egypt | 8.9 | Bangladesh | 11.4 | Bangladesh | 15.0 |
| 10 | Bangladesh | 8.4 | Germany | 10.1 | Turkey | 10.4 |

For confidence intervals, see full IDF Diabetes Atlas, Table 3.5.

In 1989, the 42nd World Health Assembly (WHA) recognised that diabetes mellitus is a chronic, debilitating and costly condition, and that it represents a significant burden on the public health services of Member States. It also acknowledged that the problem is growing, especially in developing countries. The Assembly called on Member States to assess the national importance of diabetes and to *implement population-based measures, appropriate to the local situation, to prevent and control diabetes*.

Controlling diabetes requires management of glucose levels in people living with diabetes. Accurate measurement of glycaemic levels enables many people to self-manage to avoid the dire consequences of uncontrolled disease. One way that the Assembly’s call for action can be realised, therefore, is through enabling greater access to accurate, affordable, quality diagnostic tools for the self-management of diabetes.

Self-monitoring has become a vital part of the solution for many people living with type 1 diabetes and for certain individuals living with type 2 diabetes. Along with self-monitoring blood glucose test systems (SMBGs), which require fingerstick-collected capillary blood, alternatives to testing, such as continuous glucose monitoring systems (CGMs), are enabling the individual to better achieve glycaemic targets with less inconvenience. The advent of insulin pens and pumps has also provided empowering self-management. The technology landscape is evolving quickly, and now CGMs can be linked with appropriate software and other hardware to automatically deliver appropriate doses of insulin. Standalone software applications are also providing the person with diabetes with improved self-management support. These technologies, when applied appropriately, can improve the lives and health of people with diabetes; however, there remains inequity as to who benefits from these technological innovations.

¹IDF Diabetes Atlas. <https://diabetesatlas.org/en/sections/demographic-and-geographic-outline.html> (Accessed 01 March 2021)

An important aspect of access is the regulation of the technologies used for self-monitoring of this condition. This document has been created to review the current regulatory practices in place for market authorisations of glucose self-monitoring tools (SMBGs and CGMs) used by individuals. It also reviews the assessment mechanisms employed at an international level to ensure access to safe, effective and quality devices for the self-monitoring of diabetes in LMICs. The aim is to gain an overall understanding of these mechanisms and identify opportunities for improvement.

The focus of the report is an evaluation of the regulatory assessment mechanisms employed by European Union (EU) and the United States of America (US). These two jurisdictions represent mature regulatory systems for such technologies, which in both are considered as medical devices and in vitro diagnostic (IVD) medical devices. Approvals of these devices from the EU and US are recognised in various manners to expedite market access in many jurisdictions, regardless of a jurisdiction's economic status. Countries as diverse as Australia, Ghana, Malaysia, Switzerland and South Africa all use reliance mechanisms that include the recognition of Conformité Européenne (CE) mark (EU approval) or Food and Drug Administration (FDA) authorisation.

Understanding the regulatory assessment processes provides a means to understand the level of assurance that can be placed in the clinical safety and performance profile of a self-monitoring device. To provide context, the framework for regulation of devices is reviewed. To provide comparison, a high-level overview of the regulation of glucose self-monitoring devices in Tanzania and China is provided, as examples of countries with regulatory bodies that have committed to regulatory harmonisation efforts.

The report aims to identify some of the challenges and opportunities that arise due to the current state of regulation of these technologies. An emphasis is placed on identifying measures to help secure equitable access to quality devices for people living with diabetes, regardless of the location of their use. The scope of this report is limited to those devices that allow self-monitoring of glucose levels, i.e., SMBGs and CGMs.

2. DEVICES FOR SELF-MONITORING OF DIABETES

2.1. Self-monitoring blood glucose systems - SMBGs

Self-monitoring blood glucose systems are the most broadly available tools for self-testing of glucose levels. These systems typically use capillary whole blood collected from a fingertip or alternative anatomical sites. The systems are generally composed of:

- Blood glucose meter (henceforth referred to as the meter), for use on multiple occasions;
- Blood glucose meter strips (henceforth referred to as strips), used only once for testing of a specimen. The strips are provided by the manufacturer of the meter.
- Lancets, to aid collection of capillary blood for testing. Lancets are single-use.

According to the internationally agreed terminologies, the meter and strips are, for regulatory purposes, considered IVD medical devices. Lancets are medical devices.

An international standard, International Organization for Standardization (ISO) 15197² exists to assist manufacturers of SMBGs in developing accurate devices. The US FDA provides specific guidance³ which also guides manufacturers in the expectations of the US regulator. These documents have been created to reduce the incidence of problems identified with a SMBG. The design of any device for self-testing must take into account the abilities of a broad range of users and the need for robust and safe design. The meters need to be simple to use and maintain, and the user needs to ensure that: the strips are appropriate for the meter; the strips are stored as indicated; and the blood sample is applied to the strip as indicated. These are tasks that need to be simplified or explained sufficiently so that a result is accurate and will truly reflect the glycaemic status of the individual.

2.2. Continuous glucose monitoring systems - CGMs

A continuous glucose monitoring system monitors glucose levels in more or less real time. In high-income countries, the market for continuous glucose monitoring systems is growing. Although the uptake of these devices has been limited in low-income settings, this is not the case in many middle-income settings, where their use is gaining in popularity, especially as they become more simple, robust, and affordable.⁴ There is strong consensus that the use of CGMs reduces hypoglycaemic risk and increases the amount of time a person with diabetes can stay in the target glucose range.⁵

CGMs are recommended for certain subsets of people with diabetes.⁶ They are available in several formats. The system uses a replaceable sensor, worn just under the skin, measuring glucose levels in interstitial fluid continuously throughout the day and night. A display unit, receives the results from the sensor (via a transmitter), using Bluetooth. The results are interpreted, and information relayed to the user. The sensor is usually for short term use and is usually replaced every seven to fourteen days, however new versions may remain in place for several months. In addition, some models are designed to be used with automated insulin dosing systems.

²ISO 15197:2013 In vitro diagnostic test systems – requirements for blood-glucose monitoring for self-testing in managing diabetes mellitus

³<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/self-monitoring-blood-glucose-test-systems-over-counter-use>

⁴<https://www.globenewswire.com/news-release/2020/11/12/2125254/0/en/Continuous-Glucose-Monitoring-Device-Market-size-to-surpass-USD-12-billion-by-2026.html> (Accessed 02 March 2021)

⁵Bruttomesso et al. The use of real time continuous glucose monitoring or flash glucose monitoring in the management of diabetes: A consensus view of Italian diabetes experts using the Delphi method. *Nutrition Metabolism and Cardiovascular Diseases* 2019;29 (5):421–31

⁶Type 1 diabetes in adults: diagnosis and management NICE guideline. Published 26 August 2015. www.nice.org.uk/guidance/ng17

CGMs uniformly track the glucose concentrations in the body’s interstitial fluid, providing near real-time glucose levels. The glucose detected by CGMs is that which has left the blood and has moved into the tissues. As such, there is a lag time for CGM readings of approximately 5–15 minutes, compared with readings from capillary blood. Thus, CGM results do not always match blood glucose readings.

There are two classes of CGM (**Table 1**):

- Real-time CGM (rtCGM) have a transmitter attached to the sensor to continuously send glucose results to a display unit. The display unit can provide alerts when the glucose level reaches certain limits or changes too quickly. Fingerstick testing is needed to calibrate rtCGMs at least twice daily on many devices.
- Intermittently Viewed CGM (iCGM) has no transmitter piece. Instead, the user manually scans the iCGM sensor with a handheld reader (display unit) to see current and stored results. Some devices can have optional automated alarms for when glucose levels reach certain limits. The latest versions do not need calibrating with fingerstick testing and comparison with readings from a SMBG device. This is primarily due to innovations in software algorithms, although also in part to new sensor technology and improved manufacturing techniques.

Table 1. The two types of CGM

| | |
|---------------------------|--|
| Real-time CGM | CGMs that measure glucose levels continuously and send results automatically to a display unit, providing the user with automated alarms and alerts at specific glucose levels and/or for changing glucose levels. |
| Intermittently viewed CGM | CGMs that measure glucose levels continuously but only display glucose values when swiped by a reader (display unit) or a smart phone that reveals the glucose levels. |

These technologies facilitate daily management decisions and reduce the need for fingerstick testing. CGMs address many of the limitations inherent in SMBG, as they provide a means to more easily identify glucose patterns. Both rtCGM and iCGM facilitate monitoring of time spent in the target glucose range (“time in range”). The readings from certain CGM can be used to calculate insulin doses, again reducing the need for fingerstick testing. Challenges for their use include cost, user alarm fatigue, skin irritations, the lag time, and that regardless of the brand, fingerstick glucose testing is still required in certain circumstances. Furthermore, accuracy of the glucose measurements is not constant, and varies depending on the blood glucose concentration and the rate of blood glucose exchange.⁵

In high-income countries, the current trend towards more personal ownership of a patient’s medical journey has become a driver for increased use of CGMs. Although the uptake of these devices has been limited in low-income settings, in many middle-income settings, they are gaining in popularity, especially as they become simpler and more robust.

According to internationally agreed regulatory definitions, the sensor, the transmitter, the display unit and associated software are medical devices. A specific standard exists to assist manufacturers in defining performance metrics for CGMs (Clinical and Laboratory Standards Institute [CLSI] POCT05).⁷ This guideline covers how CGM data should be assessed for accuracy,

⁷Clinical and Laboratory Standards Institute. Performance Metrics for Continuous Interstitial Glucose Monitoring. 2nd ed. POCT05. 2020

how CGMs should be assessed for factors that can decrease accuracy, and how CGMs should be operated for optimal performance. In addition, the CEN/ISO/IEEE 11073⁸ family of standards for device communication provides guidance that enables communication between medical, health care and wellness devices, and external computer systems. These standards also provide guidance on automatic and detailed electronic data capture of client-related and vital signs information, and of device operational data.

⁸CEN ISO/IEEE 11073 Health informatics – Medical / health device communication standards

3. AN OVERVIEW OF THE REGULATION OF MEDICAL DEVICES

The purpose of this section is to provide an overview of how medical devices and diagnostic tests (known as IVDs) are regulated in certain jurisdictions.

To provide context and a better understanding of the regulations, this section describes important regulatory harmonisation efforts that are undertaken, including the efforts by international regulatory bodies and the World Health Organization (WHO) to ensure best regulatory practice is adopted globally. These efforts should help democratise access to quality self-monitoring tools for diabetes.

International efforts towards harmonising regulation of medical devices were originally initiated by a group comprised of regulators and industry from the US, Australia, Canada, the EU and Japan—jurisdictions with established and mature regulatory systems for medical devices in the 1990's. This group was called the Global Harmonization Taskforce (GHTF). The purpose of the GHTF was to encourage the convergence in regulatory practices related to ensuring the safety, effectiveness, performance and quality of medical devices, promoting technological innovation and facilitating international trade. The primary way in which this is accomplished was via the publication and dissemination of harmonised guidance documents on basic regulatory practices, which can be adopted/implemented by member national regulatory authorities. GHTF recognised the need to create agreed definitions, an important starting point in ensuring common regulatory pathways. This group no longer exists but has been replaced by a regulators-only group, the International Medical Device Regulators Forum (IMDRF). The expanded membership encompasses other jurisdictions, such as Brazil, China, Singapore, South Korea and Russia. Low-income countries can attain observer status under the umbrella of the Pan American Health Organization (PAHO) and the Asian Harmonization Working Party (AHWP).⁹ IMDRF has adopted the definitions and many of the working documents created by GHTF. These have now become fundamental starting points for many jurisdictions implementing regulation of both IVDs and medical devices.

3.1. Definitions of medical devices and IVDs

The tools used for monitoring diabetes are generally acknowledged to fall into two types of health product categories: IVDs or medical devices. As the name proposes, IVDs are regarded in most jurisdictions as a specific subset of medical devices. It is important to know the differences, to understand the approaches to their regulation.

The following definitions were created by GHTF and have been adopted in their entirety or with slight modifications in legislation in many countries.¹⁰

3.1.1. Medical device

'Medical device' means any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
- investigation, replacement, modification, or support of the anatomy or of a physiological process;
- supporting or sustaining life;
- control of conception;
- disinfection of medical devices;

⁹<http://www.ahwp.info/>

¹⁰GHTF/SG1/N071:2012 Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'

- providing information by means of in vitro examination of specimens derived from the human body

and

- does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means.

3.1.2. IVD medical device

‘IVD medical device’ means a medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.

IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction or determination of physiological status.

Of importance to note in these definitions are the following aspects:

- A medical device does not achieve its “primary intended action by pharmacological, immunological or metabolic means”. Such means would render it a medicine.
- For regulatory purposes, an IVD is distinguished from other medical devices, primarily because it is used with “specimens derived from the human body”. It is not applied to the body, therefore according to GHTF definitions, a continuous glucose meter, which is placed transcutaneously to measure glucose levels, is NOT an IVD but a medical device, even though it measures glucose from a bodily specimen (interstitial fluid). The purpose of this separation is to change the types of controls a manufacturer needs to ensure the product is safe to use, as an IVD is not invasive and cannot directly harm a patient, whereas an invasive device can cause direct harm.

3.1.3. Devices

For the purposes of this report, the term “devices” will be used in a generic manner, to refer to both medical devices and IVDs.

3.2. Internationally agreed regulatory framework

3.2.1. Evolution of regulation of medical devices and IVDs compared with medicines

Medicines have been regulated since the first half of the last century and most WHO Member States have established agencies to regulate this class of essential health products. The regulation of medical devices and IVDs as separate entities only occurred much later, evolving from innovation in the device sector as well as the differences in risk profiles seen with the diversity of medical devices. Hence, the concept of quality systems for medical devices (in place of emphasis on purely good manufacturing practice) arose not only in response to serious problems associated with the manufacturing of both medicines and medical devices, but also from the variety of products, the fact devices have multiple components sourced from many different sites, a magnitude of principles of operations and various modes of action, and that the quality systems approach provided a more principle-based means to accommodate this variety and improve quality.

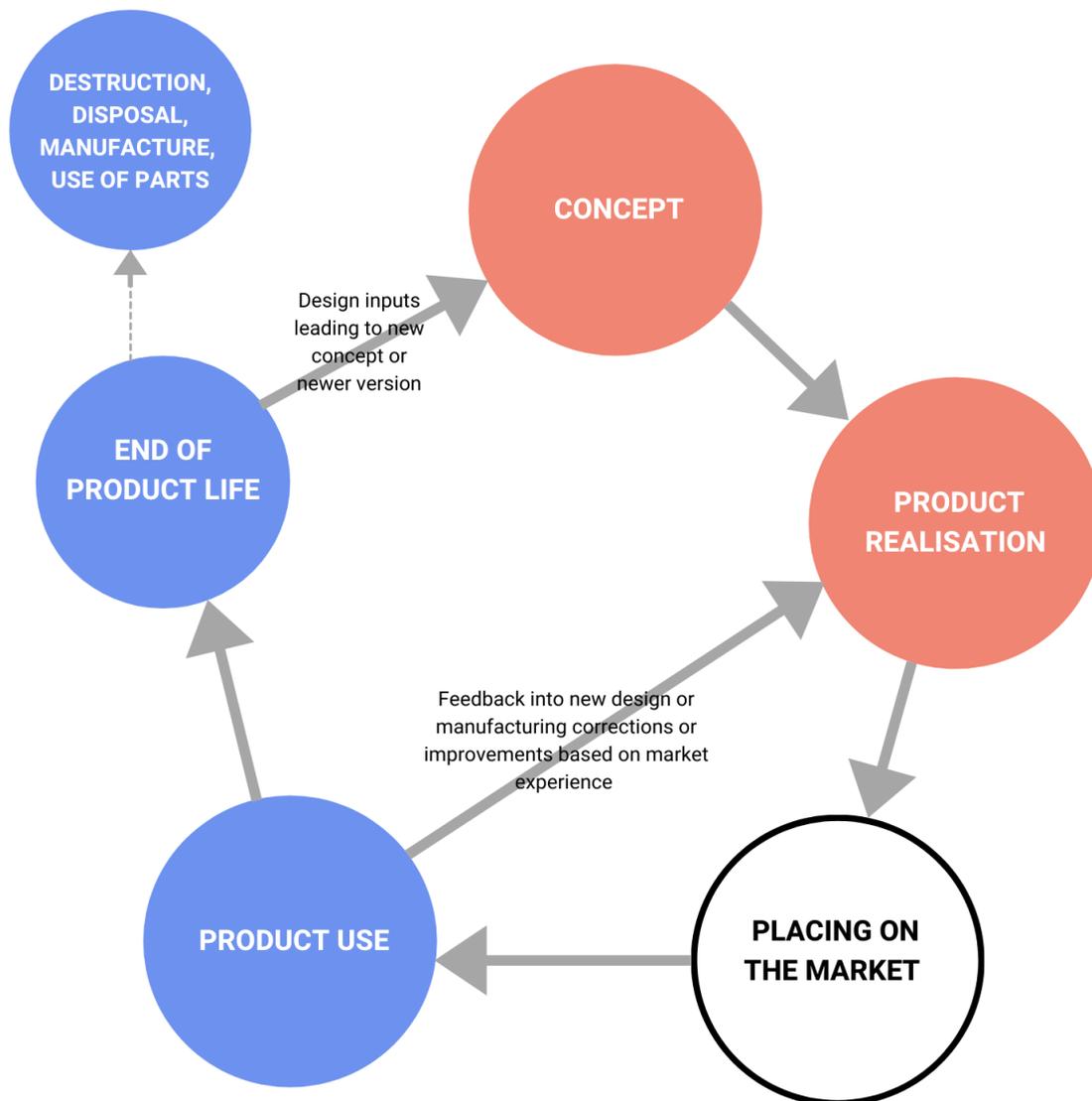
GHTF has proposed that regulation of devices should be risk-based, with regulatory controls (pre- and post-market), commensurate to the risk to the individual or to public health. Given that IVDs will almost always pose an indirect risk to patients, GHTF proposed that they are as regulated as a subset of medical devices, and that special rules should apply, to account for this shift in regulatory risk profile.

Although this framework has been agreed at an international level, its implementation is not universal, with many established regulatory regimes bringing in harmonised requirements over time.

3.2.2. The GHTF model for regulation of medical devices and IVDs¹¹

The fundamental life cycle of a medical device (and IVD) demonstrates that medical device development is a continuous process with interdependencies at various stages of the development cycle (Figure 2).

Figure 2. Medical device lifecycle

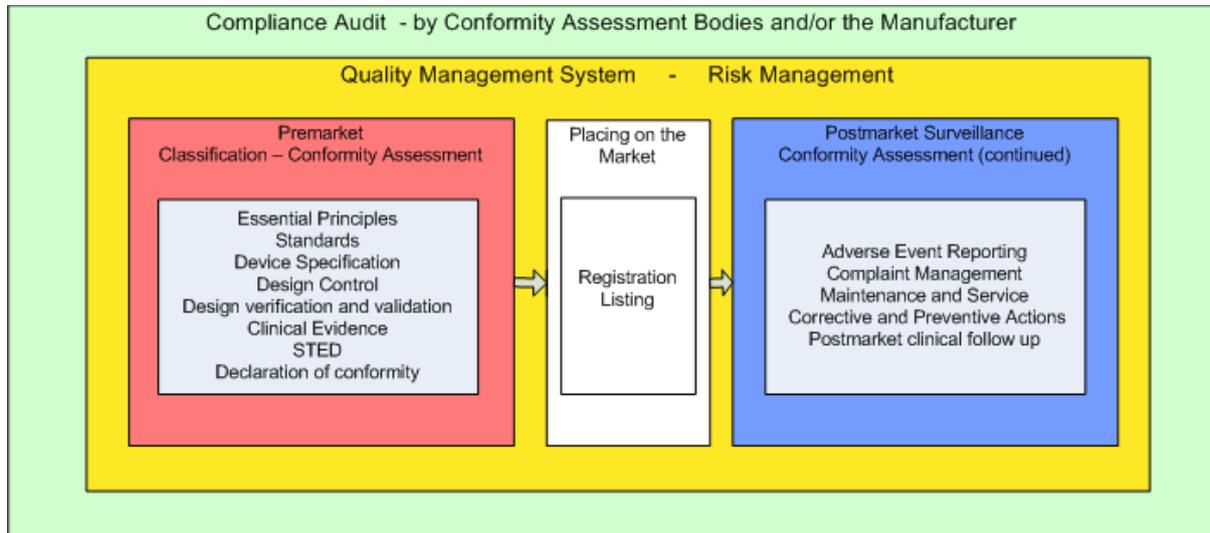


Regulatory controls can be placed at all or any of these phases of the lifecycle. GHTF proposed a risk-based model to regulation of devices, simplified by breaking the lifecycle into the three major

¹¹GHTF/AHWG-GRM/N1R13:2011 The GHTF Regulatory Model

regulatory phases: pre-market, placing on the market and post market. **Figure 3** schematically describes the different regulatory points of interaction.

Figure 3. Product life cycle: linear representation with applied processes



3.3. Critical elements of the GHTF regulatory model

The key subsystems of the GHTF regulatory model are:

- risk-based pre-market controls, of which the requirement for technical documentation forms a major control;
- a system for post-marketing vigilance and surveillance;
- a quality management system (QMS) and risk management process encompassing the lifecycle; and
- a regulatory audit process to periodically assess conformity throughout the lifecycle of the device.

These elements are interrelated and mutually interdependent. Fundamental to this model is the understanding that the level of regulatory control will be decided based on risk to the patient or public health, which is determined by the stated intended use and classified according to a set of risk classification rules. Constants within the model are: the requirements that determine quality (an effective QMS), safety and performance (technical documentation to demonstrate the fulfilment of the essential principles of safety and performance through appropriate design, and verification and validation activities). How these latter aspects are executed is dependent on the risk profile of the device, the intended use, and its novelty.

Important concepts in the regulation of devices are as follows:

3.3.1. Conformity Assessment

The manufacturer has to establish the compliance of their product and of their QMS when placing a new product on the market. Conformity assessment is undertaken by the regulator or conformity assessment body (CAB) for most products as a pre-market activity, to enable market authorisation. The manufacturer must review the compliance of their product and QMS constantly throughout the device lifecycle. This provides the means to demonstrate that the product remains in conformity with essential requirements over its lifecycle.

Device regulations should specify the manner in which the manufacturer demonstrates to the regulatory authority that its medical devices comply with the legislation. The necessary conformity assessment elements are:

- technical documentation;
- establishment of safety and performance (if needed through clinical trial / performance evaluation);
- a QMS;
- a system for post-marketing surveillance;
- a declaration of conformity;
- the registration of manufacturers and their medical devices by the regulatory authority.

3.3.2. Risk classification

The risk profile of a device, according to the GHTF model, will determine the level of regulatory control placed on a device, such as if a device requires pre-market assessment by a CAB. It is determined by a series of principle-based rules. The lower the risk a device poses for the patient, the user or others, the less controls are needed to ensure safety and performance. Lessons have been learnt from the adoption in Europe of classification based on a list of named devices or diseases, albeit that these were listed because they have a higher risk. With the arrival of newly discovered pathogens and new technologies, the weakness of such lists was quickly evident. GHTF realised that classifying a device based on a set of principles, including the risk level, provides for more regulatory flexibility based on science.

A different set of rules is used to classify IVDs to those used for other medical devices. Regardless of which set of rules is used (according to the type of device), by applying the risk classification rules to the intended use of a device, the rules will determine which of four risk classes a device will be categorised as. Class A are devices deemed to be the lowest risk class, and Class D the highest. Pre-market controls for Class A are generally minimal, although a manufacturer must declare, and therefore is legally obliged, to follow the regulatory conditions to assure safety, quality and performance. Conversely, a Class D device will be subjected to the most stringent pre- and post-marketing controls. With the GHTF model, conformity assessment is usually required for all classes except Class A, to achieve approval for placing on the market. The level of evidence required to be submitted for assessment increases with the risk class.

3.3.3. Technical documentation

A manufacturer is obliged under the GHTF model to prepare and hold technical documentation that shows how each medical device was developed, designed and manufactured together with the descriptions and explanations necessary to understand the manufacturer's determination with respect to such conformity with a regulation. This technical documentation is updated as necessary to reflect the current status, specification and configuration of the device. Depending on the regulatory system, the full technical documentation or summaries or excerpts of these documents are submitted to the regulator as part of conformity assessment. GHTF proposed a harmonised set of documents to be submitted for regulatory review. This is known as the GHTF *Summary Technical Documentation for demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices*,¹² or STED. The extent of evidence in a STED is likely to increase with the class of the device, its complexity, and the extent to which it incorporates new technology. WHO prequalification and a number of jurisdictions have adopted the STED as the format for submitting the documentation for review.

¹²<http://www.imdrf.org/docs/ghrf/archived/sg1/technical-docs/ghrf-sg1-n063-2011-summary-technical-documentation-ivd-safety-conformity-110317.pdf> and <http://www.imdrf.org/docs/ghrf/archived/sg1/technical-docs/ghrf-sg1-n011r17-conformity-to-safety-principles-medical-devices-021025.pdf>

However, IMDRF has now replaced the STED with the IMDRF Device Market Authorization Table of Contents (IMDRF ToC).¹³ Although designed primarily to assist in enabling electronic submissions of technical documentation, it also provides more transparency around the requirements for technical documentation. The IMDRF ToC is used in conjunction with a classification matrix that describes the level of detail to be submitted for each requirement (if any) dependent on the risk class. At time of publication, Health Canada and the Chinese NMPA have adopted the IMDRF ToC as the mandatory format for device applications.

3.3.4. Use of standards

This GHTF generic model for regulation of such a diversity of devices adapts to product specificities by reference to use of standards. International consensus standards are based upon science, technology and experience and generally reflect the best experience of industry, researchers, consumers, regulators and other experts worldwide.¹⁴ As such, these standards can be a means of demonstrating internationally acknowledged best practice or state of the art. Where international consensus standards are used, harmonisation efforts are enhanced. These standards provide a benchmark for both manufacturers and regulators to assess product quality and performance.

For IVDs, the use of standards extends from consensus papers or written standards to include material standards. WHO provides international biological reference preparations which serve as reference sources of defined biological activity expressed in an internationally agreed unit (the “Système Internationale [SI] Unit”). Use of these material standards, where they exist and are applicable, offer a manufacturer a means of demonstrating that a product meets quality and performance standards and provides a harmonised system for comparison.

3.3.5. Unique Device Identifier (UDI)

A powerful tool for post-marketing surveillance, the unique device identifier or UDI, was proposed by the GHTF, and continues to be a pivotal subject supported by IMDRF. When adopted by a jurisdiction, the “label of most devices will include a UDI in human—and machine—readable form, which will ultimately improve patient safety, modernise device post-marketing surveillance, and facilitate medical device innovation”.¹⁵ According to IMDRF, the UDI system is intended to provide a single, globally harmonised system for positive identification of medical devices.¹⁶

In the most basic format, the UDI would be a coded number registered with standards organisations, and would incorporate a variety of information, including (but not limited to) the manufacturer of the device, expiry dates, the make and model of the device, and any special attributes that the device may possess.

The UDI is composed of two parts: Device Identifier (UDI-DI) + Production Identifier (UDI-PI) = Unique Device Identifier (UDI). UDI-DI + UDI-PI = UDI.

- **Unique Device Identifier - Device Identifier (UDI-DI):** The Device Identifier of the UDI is a unique numeric or alphanumeric code specific to a model of medical device and that is also used as the “access key” to information stored in a UDI database. This mandatory, fixed portion of a UDI identifies a manufacturer’s specific product and package configuration.
- **Unique Device Identifier - Production Identifier (UDI-PI):** The Production Identifier of the UDI is a numeric or alphanumeric code that identifies the unit of device production

¹³ <http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-190321-nivd-dma-toc-n9.pdf> and <http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-190321-ivd-mdma-toc-n13.pdf>

¹⁴ IMDRF/Standards WG/N51 FINAL 2018 Optimizing Standards for Regulatory Use

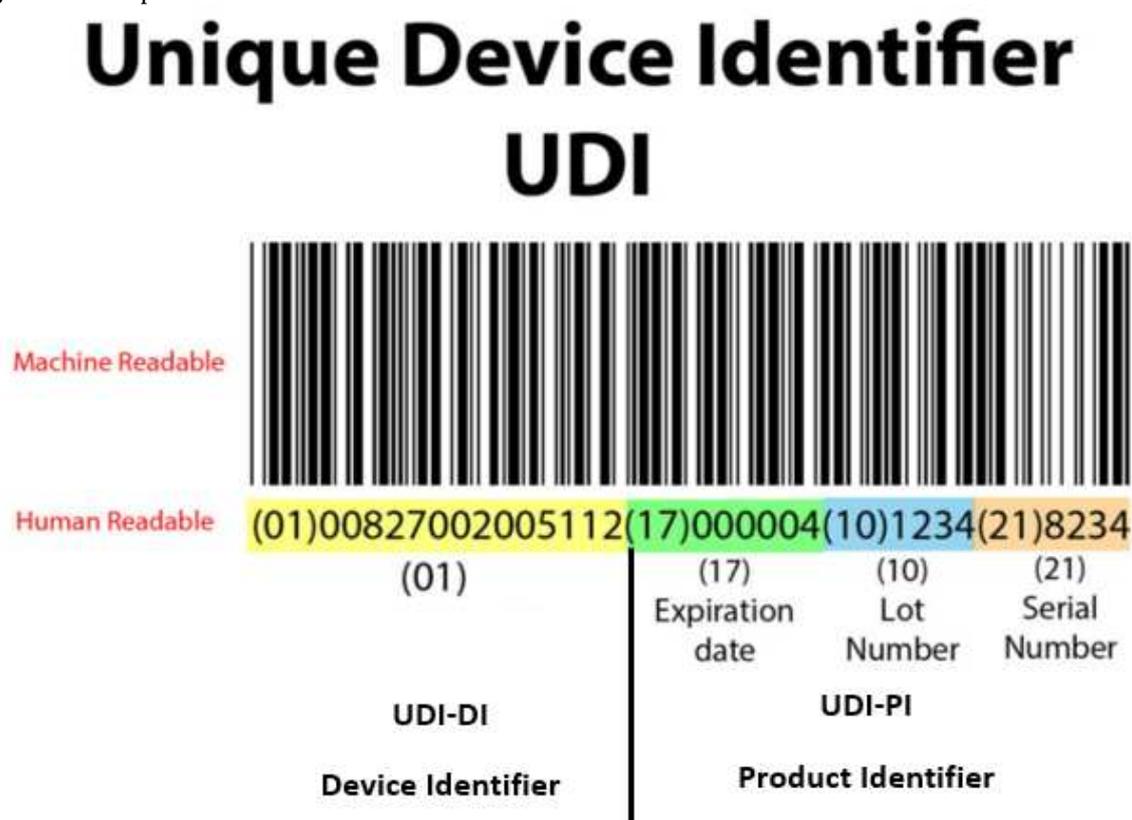
¹⁵ <https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-system-udi-system> (Accessed 10 February 2021)

¹⁶ UDI Guidance. Unique Device Identification (UDI) of Medical Devices IMDRF/UDI WG/N7FINAL:2013

when one or more of the following is included on the package label of the device. The different types of Production Identifier(s) may include:

- a) The Lot or Batch within which a device was manufactured;
- b) The Serial Number of a specific device;
- c) The Expiration Date of a specific device;
- d) The date of manufacture (may not be required if other Production Identifiers are on the label);
- e) the Version

Figure 4: Composition of a UDI label¹⁷



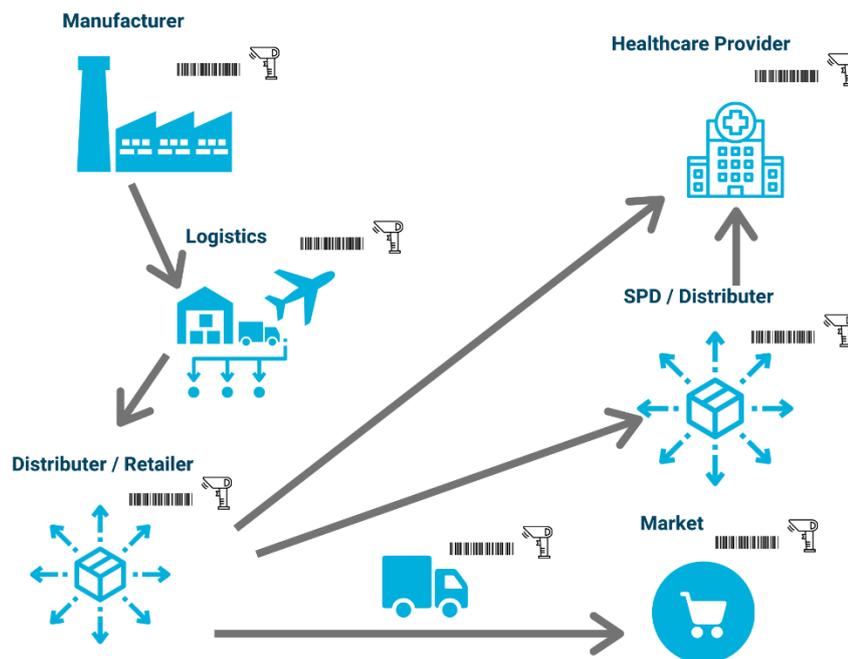
The requirement for a label to include a UDI has now been implemented in a number of jurisdictions, notably the US, China, South Korea. The EU is transitioning to inclusion of a UDI on labelling as part of its role out of the new regulations for medical devices and IVDs.

The following figure provides a very high-level perspective of the linkages that are achieved from the application of a UDI.¹⁸ Across those systems, the different aspects of the UDI (UDI-Dis, UDI-PIs and data from UDI databases) are used to link device identification data across separated systems and to use the results of that linkage to improve the quality of healthcare delivery or healthcare research or market surveillance.

¹⁷ Adapted from <https://easymedicaldevice.com/udi/> (Accessed 15 April 2021)

¹⁸ System requirements related to use of UDI in healthcare including selected use cases IMDRF/UDI WG/N54 FINAL:2019 (Accessed 15 April 2021)

Figure 5: Linkages via the UDI



3.4. Global adoption of the GHTF regulatory model

The GHTF model has been designed so that it can be adopted in a progressive manner, allowing jurisdictions with no prior experience in the regulation of devices to incrementally and logically adopt aspects of regulatory activity as expertise and capacity is increased. Meanwhile, the adoption of the GHTF model, principles and guidance in a jurisdiction’s regulatory practice can provide the possibility for reliance on the work of other jurisdictions. For a WHO Member State, this is perhaps one of the greatest strengths of the work of harmonisation. For a manufacturer, it also means fewer unique regulatory requirements to meet, keeping down costs associated with regulatory compliance.

It is important to note that this initiative for regulatory harmonisation of medical devices is no longer only undertaken by IMDRF. There are several other similar initiatives, including the AHWP and the African Medical Device Forum (AMDF). All, however, are building on the formative work of GHTF. As such, this initial work of GHTF will act as the benchmark or reference point for this report.

3.5. Implementation of medical devices and IVD regulation

Effective regulatory systems are seen as the basic building block of a well-functioning health system. According to WHO,¹⁹ many countries still lack effective regulatory systems for any type of health product. Among its 194 Member States, only 50 countries (26%) have what are considered mature regulatory agencies, whilst the remaining countries have suboptimal regulatory systems. Just over half are at the lowest level of maturity. A recent report warned that “when manufacturers of medical products want to bring their products to market, they face a landscape of disparate regulations, unclear regulatory pathways, frequent delays in accessing essential medicines and limited transparency. This suppresses innovation, drives up medicine prices and opens the door for substandard and falsified medical products. It also leaves regulators ill-prepared to deal with public health emergencies, where, for example, a vaccine or medicine may need to be fast-tracked through the regulation process”.²⁰

¹⁹https://www.who.int/medicines/technical_briefing/tbs/TBS2019_WHO_RSS_Capacity_Building_GBT.pdf

²⁰<https://doi.org/10.3389/fmed.2020.00457> (Accessed 21 March 2021)

In 2015/2016, WHO conducted a desktop survey to determine the status of a legal framework for medical devices in Member States.⁵ Unlike the previous report, this survey did not include an analysis of the effectiveness of implementation. However, the numbers indicated that regulatory systems for devices are in many cases non-existent or, if present, unlikely to be effective (**Figure 6**). Of the 194 participating Member States, 113 responded positively to having a legal framework for medical devices in place, and 53 indicated no legal framework. In total, 121 Member States claimed to have a national regulatory authority responsible for implementing and enforcing medical device regulations.

Figure 6. Number of countries with established basic regulatory elements based on the 113 countries that have a legal framework for medical devices, analysed by World Bank Income group²¹

| Basic Elements | Low income | Lower middle income | Upper middle income | High income | Total |
|--------------------------------|------------|---------------------|---------------------|-------------|-------|
| Pre-market | | | | | |
| Definition | 7 | 26 | 27 | 45 | 105 |
| Risk classes | 3 | 15 | 22 | 43 | 83 |
| Essential principles | 4 | 11 | 23 | 40 | 78 |
| On the Market | | | | | |
| Listing of Medical Devices | 7 | 22 | 27 | 41 | 97 |
| Registration of Establishments | 7 | 16 | 23 | 42 | 88 |
| Import Controls | 7 | 21 | 21 | 25 | 74 |
| Post-market | | | | | |
| Adverse Event Reporting | 4 | 12 | 18 | 44 | 78 |

Further analysis by WHO (personal communication) indicated that of the approximate 60% of Member States with medical device regulation, only approximately 50% of these included the regulation of IVDs. Thus, for many jurisdictions there is no or very limited regulatory oversight of technologies for self-monitoring of diabetes.

Prior to this survey, in 2014, Member States of the United Nations voted at the 67th WHA in favour of the following mandate:

WHA Resolution 60.29: “to encourage Member States to draw up national or regional guidelines for good manufacturing and regulatory practices, to establish surveillance systems and other measures to ensure the quality, safety and efficacy of medical devices and, where appropriate, to participate in international harmonisation”.

As with medicines, harmonisation of technical requirements for device regulation is a desirable goal for many reasons:

- Companies have to generate only one data set for all regions thereby reducing the cost of development of regulatory documentation; this can lead to lower prices
- Common regulatory standards for scientific evaluation and inspection facilitate regulatory communication and information sharing
- Local products are more likely to be acceptable for export to other countries
- Faster access to devices of high public health value
- Increased competitiveness resulting from newly developed common markets²²

²¹Regulation of medical devices. https://www.who.int/medical_devices/safety/3_2.pdf?ua=1

²²https://www.who.int/medicines/areas/quality_safety/regulation_legislation/harmonization/en/

There have been considerable efforts by WHO, its donors and other bodies to implement or improve the number of regulations for devices as a result of this resolution, coupled with the findings of the WHO survey. However, progress is slow, and funding for such activities has not been as consistent as it is for strengthening regulation for medicines.

Probably most successful has been the effort made by the AHWP. Using the fundamental regulatory principles defined by GHTF, AHWP has supported the implementation of regulation of medical devices, including of IVDs, in a number of Asian jurisdictions.

Yet despite efforts by IMDRF, AHWP and WHO (see next section) to strongly support the introduction of harmonised regulation, some of the jurisdictions recently implementing device regulation have introduced regulations that vary from the recommendations for a harmonised framework. These potentially can block good products getting to market due to the complexity that the additional requirements introduce.

3.6. WHO model regulatory framework for medical devices including IVDs²³

Realising that many countries were struggling with the adoption of effective regulation of devices, WHO produced a guidance on developing a regulatory framework. This guidance builds on the work of GHTF, IMDRF and AHWP. It recommends a two- or a three-step approach and is now being used as the basis for implementation. An emphasis is placed on leveraging the work of trusted regulatory assessments through regulatory decision-making recognition and reliance. A number of African Member States are using this model to introduce regulation and a new initiative, the Africa Medical Devices Forum (AMDF), has arisen to support it. AMDF is supported both by WHO and the Africa Union.

3.7. Global progress in implementing medical device regulation

In summary, a significant number of LMIC WHO Member States lack effective regulation of medical devices and IVDs, with the African region having the most significant gaps. Although efforts are ongoing, progress is sporadic and not all efforts have resulted in a system based on the principle of harmonisation that enables recognition and reliance, which are essential concepts of effective regulation.²⁴

The lack of (1) adoption and (2) uniformity, results in difficulties in access in many WHO Member States. It also results in a lack of desire by manufacturers to place their devices on the market in some jurisdictions. Often, medical devices and especially IVDs are low value, low-income commodities. The effort required to navigate the regulatory pathway in some LMICs can well outweigh potential financial rewards for many manufacturers. This is usually due to unclear and shifting requirements. A recent report authored by several WHO employees also warned that the lack of a robust regulatory system leaves a jurisdiction vulnerable to substandard and falsified medical products.²⁵

In high-income WHO Member States, the influence of IMDRF is apparent. New regulations are often modelled on IMDRF guidance. The benefits are clear. As many of these jurisdictions import a large proportion of their devices, the ability to use reliance mechanisms means limited regulatory agency resources can be placed into post-marketing monitoring rather than pre-market conformity assessment.

²³http://www.who.int/medical_devices/publications/global_model_regulatory_framework_meddev/en/

²⁴https://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodRegulatory_PracticesPublicConsult.pdf

²⁵<https://doi.org/10.3389/fmed.2020.00457> (Accessed 21 March 2021)

3.8.Roles and responsibilities within a regulatory system: manufacturers, national regulatory authorities (NRAs) and Conformity Assessment Bodies (CABs)

GHTF identified the basic roles and responsibilities of the various actors within a regulatory system. **Tables 2–4** illustrate some of the most important aspects. National regulatory authorities (NRAs) have legal authority to oversee the enactment of the medical device legislation. They are often responsible for ensuring that products released for public use are evaluated appropriately and meet national standards of quality and safety. The NRA may engage certain conformity assessment bodies (CABs) to undertake some of the assessment activities on their behalf (for instance, QMS certification, or in the case of Europe, all pre-market assessment activities) or they may undertake the conformity assessment activity themselves. A CAB is the legal entity that performs a conformity assessment against regulations and relevant standards, the output of which is a conformity assessment report which carries a judgement of conformity or non-conformity. A CAB may be a certification body for a QMS, an inspection body, a certification body for a product or process, a testing laboratory or a validation/verification body.

Table 2. NRA roles and responsibilities^a

| General | Pre-market | Post-market | QMS | QMS audit | Clinical safety |
|---|---|--|---|---|---|
| <ul style="list-style-type: none"> • Link government policies and priorities to regulatory system^b • Consult stakeholders^b • Draft and adopt laws and regulations^b • Appoint and oversee CABs • Maintain adequate resources • Enforce laws and regulations • Import/export controls | <ul style="list-style-type: none"> • Define 'medical device' • Registration of manufacturers importers, and distributors and device listing • Establish medical device classification rules • Establish 'essential principles' of safety and performance • Recognise standards • Pre-market conformity assessment | <ul style="list-style-type: none"> • Establish adverse event report requirements • Establish and maintain national vigilance database • Evaluate adverse event reports received • Monitor manufacturer investigation and field safety corrective actions • Handle information concerning adverse event reports • Exchange information with other authorities | <ul style="list-style-type: none"> • Establish QMS requirement • Recognise ISO 13485 standard | <ul style="list-style-type: none"> • Establish audit requirements, including frequency • Oversee CAB audits • Conduct audits | <ul style="list-style-type: none"> • Enforce human subject protections and ethical framework • Establish and oversee ethics committees • Oversee clinical investigations • Enforce laws and regulations • Evaluate adverse event reports |

^aNot exhaustive. Requirements and roles vary depending on class of devices.

^bThese activities may be the responsibility of the Ministry of Health, depending whether the NRA is an independent executive agency or fully part of the Ministry of Health.

Table 3. Roles and responsibilities of a CAB^a

| General | Pre-market | Post-market | QMS | QMS audit | Clinical safety |
|--|--|---|-----|--|--|
| <ul style="list-style-type: none"> Comply with CAB designation criteria (of NRA) Maintain accreditation, if required Maintain appropriate qualified resources | <ul style="list-style-type: none"> Verify manufacturer determination of device class^b Conformity assessment (review summary technical documentation, including labelling)^b Verify standards appropriately applied by manufacturer^b | <ul style="list-style-type: none"> Assess manufacturer post-marketing surveillance and vigilance reporting systems during QMS audits^b Assess manufacturer field safety corrective action systems during QMS audits^b | N/A | <ul style="list-style-type: none"> Conduct and report manufacturer QMS audits^b Assess manufacturer corrective actions from audit findings | <ul style="list-style-type: none"> Audit/assess manufacturer's clinical evaluation process^b Assess clinical evaluation and clinical evidence during conformity assessment^b |

^aSome or all of the roles of the CAB may be performed by the NRA.

^bThe level of assessment is related to the risk class of the device.

Table 4. Roles and responsibilities of a manufacturer

| General | Pre-market | Post-market | QMS | QMS audit | Clinical safety |
|---|--|--|--|---|---|
| <ul style="list-style-type: none"> Comply with national requirements Investigate and evaluate complaints and product experience information | <ul style="list-style-type: none"> Determine whether product is 'medical device' Register, list Determine appropriate essential principles Apply appropriate standards Prepare, hold and maintain technical file (QMS) Submit STED Prepare and hold declaration of conformity | <ul style="list-style-type: none"> Establish and maintain post-marketing surveillance system (part of QMS) Prepare and submit vigilance reports As appropriate, conduct field safety corrective actions | <ul style="list-style-type: none"> Establish and maintain appropriate and effective QMS, including risk management (e.g., ISO13485, ISO14971) | <ul style="list-style-type: none"> Subject of periodic audits Respond to audit findings | <ul style="list-style-type: none"> Conduct clinical evaluation (ongoing) As needed conduct, monitor, report clinical investigations (per ISO 14155/20916) |

4. REGULATION OF SELF-MONITORING DEVICES FOR DIABETES

Self-monitoring enables people living with diabetes to achieve appropriate metabolic control, avoiding hypoglycaemia and reducing the likelihood of developing long term complications of hyperglycaemia, such as blindness or renal failure. CGMs further facilitate diabetes care in such a way as to maximise user care whilst minimising discomfort. However, the proper functioning of these devices is absolutely essential for people with diabetes; malfunctions can have serious consequences and, in some cases, could result in death.²⁶ In addition to the impact of incorrect dosage due to malfunctions, there are harms associated with an implanted device. As such, regulatory requirements and associated conformity assessment mechanisms should be risk-based and fit for purpose.

This section will review regulatory frameworks for SMBGs and CGMs in the US, the EU, the Republic of Tanzania and the People's Republic of China. Both, the EU and the US, have been regulating devices for several decades and thus have evolved systems. Because of this, many jurisdictions use reliance mechanisms and accept CE marking and FDA market authorisation in place of undertaking comprehensive pre-market assessment. Thus, the assessment of the frameworks for these two jurisdictions in this report will be detailed. In addition, both the EU and US represent jurisdictions where considerable manufacturing occurs.

To provide contrast, a high-level overview of the regulation of self-monitoring devices in China and Tanzania will be examined, to demonstrate how the WHO and GHTF models are being adopted in a recent member of IMDRF and in a lower middle-income country that almost exclusively imports all devices.

4.1. The regulation of devices in the USA and the EU

4.1.1. Comparison of US and EU regulation

By comparing the regulatory scrutiny mechanisms for self-monitoring devices, this section endeavours to understand the impact of those mechanisms on device safety and performance. Comprehensive details of the US and EU regulations with respect to devices for self-monitoring of glucose levels can be found in **Appendices 1 and 2**.

4.1.1.1. Important similarities in approach

It is important to understand that some fundamental regulatory requirements for devices within US and EU law are basically aligned, with requirements for manufacturing under an appropriate QMS aligned to ISO 13485, which incorporates risk management, essential requirements for safety and performance, use of standards, design specification and design control, validation and verification of design, clinical evidence, a summary of safety and performance, the need for suitable labelling, registration and or listing for market access, and a system for post-marketing surveillance. The details differ in certain particular sub-requirements (for instance, which standards are recognised, reporting requirements, labelling including use of a UDI), and in how they are assessed for conformity.

4.1.1.2. Important differences in approach

Although the EU and the US have been regulating devices for several decades, the origins of device regulation in each jurisdiction have arisen due to specific challenges, resulting in some fundamental differences in the approach to how each jurisdiction regulates devices. For example:

- For the US, device regulation relies on a strictly centralised process through the FDA, thus has the advantages of centralisation and common rules. This contrasts with the EU, which

²⁶Adapted from "Medical Devices in Diabetes Care: A statement on behalf of the European Association for the Study of Diabetes" 2013

regulates medical devices utilising not only each Member State's regulators, known as competent authorities, but also with a network of decentralised, private CABs known as notified bodies. Notified bodies are responsible for the pre-market assessment of devices in Europe. The competent authorities of each EU Member State are responsible for clinical trial authorisation, market vigilance and for oversight of the notified bodies. The EU approach is intended in part to provide greater choice and faster time to market for device manufacturers needing pre-market conformity assessment. There is much debate regarding the benefits and weaknesses of these two approaches. The FDA provides a consistent and rigorous approach, whereas the strength of the EU approach with respect to use of notified bodies lies in its agility and efficiency of pre-market regulatory evaluation. The jury is still out as to which is better for patients.^{27,28}

- For the FDA regulations, where market authorisation is via the so called 510(k) pathway (see Appendix), the authorisations are valid without any time limits. The EU requires renewal of the QMS certificate and of the product certificate in regular intervals of three to five years.
- New regulations (IVD regulation [IVDR] and medical device regulation [MDR]) currently under transition in the EU are bringing many changes. Some of the significant items that may have an impact on assuring quality devices for diabetes are as follows:
 - The use of a UDI. This is already an FDA requirement but is being phased in for the IVDR and the MDR.
 - IVD clinical evidence under the IVDR must include evidence of the clinical association of the marker being detected and the clinical conditions as claimed. This is known in the IVDR as scientific validity and is not an FDA requirement. However, the relationship of glucose with diabetes is well established and as such, does not represent any new risk for current devices on the market.
- For implanted medical devices, there will be a requirement under the MDR that each implant has an implant card. This will apply to CGMs and is not a requirement under the current EU Directive, nor for the FDA. These cards will (i) enable the patient to identify the implanted devices and to get access to other information related to the implanted device (e.g., via the medical device database EUDAMED, and other websites); (ii) enable patients to identify themselves as persons requiring special care in relevant situations e.g., security checks; (iii) enable, for instance, emergency clinical staff or first responder to be informed about special care/needs for relevant patients in case of emergency situations.
- Both the EU IVDR and MDR have increased requirements for post-marketing activities and reporting. These activities are in addition to those for FDA and for the EU Directives.
- Finally, all certificates issued by a notified body, informing of conformity with the new Regulations, must be included in the new medical device database EUDAMED. The public will be able to identify devices with CE marking due to these certificates. Such transparency of market authorisation already exists for the FDA, but has not existed with the EU Directives.

4.1.2. Comparison of the US and EU regulation of self-monitoring blood glucose devices (SMBGs)

For the FDA, SMBGs are classified as Class II devices (moderate risk) and are regulated by the 510(k) notification, which requires product developers to present data demonstrating that the device functions similarly to a previously approved device. Under the outgoing IVD Directive of the EU, where a list-based classification system was in place, SMBGs qualified as part of list B of Annex II of the IVD Directive. This list represents moderate risk, requiring notified body conformity assessment. Under the forthcoming EU IVD Regulation, SMBGs will be Class C, the

²⁷ "Regulation of Medical Devices in the United States and European Union" Kramer D, Shuai X and Kesselheim M. N Engl J Med 2012; 366:848-855

²⁸ Drugs and Devices Comparison of European and U.S. Approval Processes Van Norman, G. JACC: Basic to Translational Science 2016; Vol 1 No399-412

second highest risk category, also requiring notified body conformity assessment. **Table 5** provides a high-level overview of the similarities and differences in regulatory scrutiny of SMBGs.

Table 5. Comparison of conformity assessment activities by the CAB for SMBGs

- General alignment in assessment criteria
- Potential source of difference in assessment criteria
- Significant difference in assessment criteria

| CAB procedures | US FDA | EU CE IVDD (outgoing IVD Directive) | EU CE IVDR (new IVD Regulation) | Potential impact of the difference on safety and performance |
|---|--|---|---------------------------------------|--|
| Classification | Class II, 510 (k) | Annex II List B | Class C | Focus of assessment |
| Pre-market assessment required | Y | Y | Y | |
| QMS required | Y | Y | Y | FDA and IVD Directive requirements similar. IVDR requirements enhanced |
| CAB assessment team | FDA technical unit at Center for Devices and Radiological Health | Notified bodies IVD directive | Notified bodies IVDR | FDA approach more consistent (one CAB) |
| Comprehensive CAB assessment activities (Note: + indicates mandatory assessment action, +/- indicates an optional activity at time of product assessment) | Technical + clinical +/- quality | Technical +/- quality | Technical + clinical +/- quality | <ul style="list-style-type: none"> FDA inspection of QMS may not coincide with technical file assessment, but later. FDA inspects all Class II manufacturers on a 2-year cycle. The EU IVDD requires a technical documentation review of each product, but the QMS aspects related to that product may not be reviewed until later if the manufacturer has already been inspected under the IVDD. For the EU IVDR, a manufacturer can submit several similar self-tests, and only one will receive an in-depth technical assessment at point of application. The remaining technical documentation files will be assessed over the life of the certificate. As with the IVDD, the QMS may be audited simultaneously, or later if the system has already been audited. |

| | | | | |
|---|------------------------------|-------------------------------------|---|---|
| Recognition of standards for conformity assessment? | Y FDA consensus standards | Y EN harmonized standards | Y EN harmonized standards; none harmonised at time of publication | The difference in the performance standards is addressed in Section 7, Analysis of effectiveness of current assessment tools (part 1) |
| Official recognition of ISO 15197:2013 | N | Y | Assumption this will be harmonised | |
| Regional specific guidance for performance of SMBGs | Y | N | N | |
| Technical documentation content for assessment | | | | |
| Risk management report and risk benefit ratio discussion submitted | Y | Y | Y | |
| Scientific validity/clinical association | N | N | Y | Likely to have little impact as the association of glucose measurements with diabetes is well established |
| Analytical performance studies | Y | Y | Y | |
| Clinical performance studies (using device in question) | Y | N | Y | The IVDR will rectify some of the problems associated with the IVD Directive's lack of specific requirements in this area |
| Specific requirements for lay user studies | Y | Y | Y | |
| Testing population requirements for clinical performance studies | Equivalent to US population | Equivalent to a European Population | Equivalent to a European Population | Unlikely to have a high level of impact, if any |

| | | | | |
|---|--------------------|---------------------|----------------------|--|
| Clinical evaluation report | Y | Y | Y | |
| Software/firmware assessment including cybersecurity | Y | Y | Y | |
| Electrical safety | Y | Y | Y | |
| Post-marketing performance plan and report | N | N | Y (updated yearly) | <ul style="list-style-type: none"> • May be required by FDA in individual circumstances. • IVDR requirements ensure performance is monitored |
| Post-marketing surveillance plan and report | N | N | Y (updated yearly) | IVDR requirements ensure safety and performance are monitored |
| Adverse event reporting | Y | Y | Y | |
| Notification of significant changes | Y | Y | Y | |
| QMS audit | | | | |
| Mandatory QMS audit by CAB required before application? | N | Y | Y | FDA prioritises inspections by risk (e.g., new manufacturer) and gives higher risk devices/situations a higher priority, including Class II devices. An ISO 13485 certificate is sufficient for application. |
| Surveillance audit of QMS by CAB | Y Every 2 years | Y (every 1–2 years) | Y (yearly) | |
| Mandatory unannounced audits of QMS by CAB | N | N | Y (once per 5 years) | |
| Subject matter expert review of lot release procedures during review of STED | Y | N | Not mandatory | This obligation is considered a strength of the FDA review process. |
| QMS auditor review of lot release procedures | optional | optional | optional | QMS audit will look at a selection of technical documents associated with the device. |

| Other requirements | | | | |
|--|---|---|-------------------|--|
| Independent performance evaluation a pre-requisite | N | N | N | |
| UDI requirements | Y | N | Y (in transition) | UDI provides traceability in supply chain. Potential to improve adverse event reporting and discourage counterfeiting |
| Public databases to inform of market authorization, adverse events | Y | N | Y (in transition) | Greater transparency for end users where this is implemented |

4.1.3. Comparison of the US and EU regulation of Continuous Glucose Monitoring systems (CGMs)

For the FDA, most CGMs have recently been down-classified to Class II devices (moderate risk) and are thus regulated by the 510(k) notification, which requires product developers to present data demonstrating that the device functions similarly to a previously approved device. For the EU, the classification is similar. For those that are not associated with delivery of insulin, they are Class IIb, the second highest classification for medical devices, making them moderate to high risk. **Table 6** provides a high-level overview of the similarities and differences in regulatory scrutiny of CGMs.

Table 6. Comparison of conformity assessment activities by the CAB for CGMs

- General alignment in assessment criteria
- Potential source of difference in assessment criteria
- Significant difference in assessment criteria

| CAB Procedures | US FDA | EU CE MDD (outgoing medical device directive) | EU CE MDR (new medical device regulation) | Potential impact of the difference on safety and performance |
|--|--|--|--|--|
| Classification | Class II, 510 (k) | Class IIb | Class IIb/III | For the EU, the class can alter depending on specific attributes. |
| Pre-market Assessment required | Y | Y | Y | |
| QMS required | Y | Y | Y | FDA and MDD requirements similar. MDR requirements enhanced. |
| CAB assessment team | FDA technical unit at Center for Devices and Radiological Health | Notified bodies MDD | Notified bodies MDR | FDA approach more consistent (one CAB) |
| Comprehensive CAB assessment activities (Note: + indicates mandatory assessment action, +/- indicates an optional activity at time of product assessment) | Technical + clinical +/- quality | Quality +/- technical + clinical on a risk- based approach | Quality +/- technical + clinical on a risk- based approach | <ul style="list-style-type: none"> FDA inspection may not coincide with technical file assessment. FDA inspects all Class II manufacturers on a 2-year cycle. For both the EUMDD and MDR, the assessment of the technical documentation of at least one representative device is obligatory for CE marking (of an application of a number of similar devices is made to the NB), with review of remaining similar devices to occur over the certification cycle, unless the device is Class III. If Class III, the technical documentation must be reviewed. |

| | | | | |
|---|------------------------------|------------------------------|---|---|
| Recognition of standards for conformity assessment? | Y FDA consensus standards | Y EN harmonised standards | Y EN harmonised standards; none harmonised at time of publication | |
| Recognition of CLSI POCT05 performance metrics | Y | N | N | The difference in the performance standards is addressed in Section 7. Analysis of effectiveness of current assessment tools (part 1) |
| Special controls | Y | N | N | May have potential to impact safety and performance |
| Technical documentation for assessment | | | | |
| Risk management report and risk benefit ratio discussion | Y | Y | Y | |
| Biocompatibility studies | Y | Y | Y | |
| Analytical performance studies | Y | Y | Y | |
| Clinical performance studies (using device in question) | Y | Y | Y | |
| Specific requirements for lay user studies | Y | Y | Y | |
| Clinical evaluation report | Y | Y | Y | |
| Software/firmware Assessment | Y | Y | Y | |
| Sterility | Y | Y | Y | |

| | | | | |
|--|--------------------|------------------------|--------------------|--|
| Electromagnetic Compatibility | Y | Y | Y | |
| Electrical safety | Y | Y | Y | |
| Environmental testing | Y | Y | Y | |
| Interoperability | Y | Y | Y | |
| Calibration | Y | N | Y | The MDR will rectify some of the problems associated with the MDD's lack of mandatory requirements in this area |
| Environmental testing | Y | Y | Y | |
| Sensor life and stability | Y | Y | Y | |
| Human factors | Y | Y | Y | |
| Cybersecurity | Y | N | Y | The MDR will rectify some of the problems associated with the MDD's lack of mandatory requirements in this area |
| Post-marketing clinical performance plan and report | N | Plan only | Y | May be required by FDA in individual circumstances. |
| Post-marketing surveillance plan and report | N | N | Y (updated yearly) | |
| Adverse event reporting | Y | Y | Y | |
| Notification of significant changes | Y | Y | Y | |
| QMS audit | | | | |
| Mandatory QMS audit by CAB required before application? | N | Y | Y | FDA prioritises inspections by risk (e.g., new manufacturer) and gives higher risk devices/situations a higher priority, including Class II devices. |
| Surveillance audit of QMS by CAB | Y Every 2 years | Y (every 1–2 years) | Y (yearly) | |

| | | | | |
|---|-----------------------------|-------------------------------------|-------------------------------------|--|
| Mandatory unannounced audits by CAB | N | N | Y (once per 5 years) | |
| Other requirements | | | | |
| Testing population requirements for clinical performance studies | Equivalent to US population | Equivalent to a European population | Equivalent to a European population | Unlikely to have a high level of impact, if any. |
| UDI requirements | Y | N | Y (in transition) | UDI provides traceability in supply chain. Potential to improve adverse event reporting and discourage counterfeiting |
| Implant card | N | N | Y | Potential to improve patient safety following field safety correction actions |
| Public databases to inform of market authorization, adverse events | Y | N | Y | Greater transparency for end users where this is implemented |

4.1.4. Comparison of the regulatory mechanisms

Tables 5 and 6 demonstrate that the regulation of self-monitoring devices is not uniform. This variability may impact on the quality, safety and accuracy of these devices.

4.1.4.1. Analysis of the FDA oversight

New FDA guidance for SMBGs, “Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use”, released in September 2020, requires that a manufacturer submit their procedures for lot release. These must be approved by the FDA. A lot release procedure describes how the manufacturer will assure that each new batch (or lot) of product will deliver the same performance of the lot before. This requirement represents best practice for these products.

The US FDA has recently down-classified most CGMs to that of Class II, the same as for SMBGs. The FDA has made the change due to approximately 20 years of experience with these products and considered that they do not have a Class III risk profile. A Class II device in the US is subject to a 510(k) pre-market clearance. The evidence provided for a 510(k) submission for performance relies on establishing substantial equivalence with a preceding device that is already on the market. Typically, this is done in a laboratory setting and human testing is rarely required. The principle of substantial equivalence therefore also runs the risk of compounding bias (creating greater inaccuracy) if the comparator device has a systematic bias in reporting.

However, even for a 510 (k), the FDA provides greater transparency in its requirements for self-monitoring devices than do the EU Directives or Regulations. It lists for each type of device (SMBG or CGM), the consensus standards that may be utilised; in the case of CGMs, special controls; and in addition, provides many FDA guidance documents that clarify requirements. Such transparency not only assists the manufacturer in understanding the requirements, but also ensures that the assessors from the agency are consistent in how they assess. The staff undertaking these assessments for the FDA all rest in one centre (CDRH) providing the opportunity for a standardised assessment procedure. In addition, the fact that the requirements are clearly enunciated, means that suboptimal studies by a manufacturer are more likely to be identified than in the case of the EU, where under the Directives there were many different notified bodies, thus greater variety in the staff undertaking the assessment and resultant variability in assessment standards, as well as less clarity in requirements.

Finally, the FDA now requires all devices to include a UDI. This identifier will greatly assist in investigations of problems associated with the device.

4.1.4.2. Analysis of the EU oversight

Of significance, under the new EU Regulations, the requirements for quality systems and their inspection are strengthened, as are the requirements for documentation of processes and procedures for the manufacturer. Manufacturers must have a plan and reports for post-market clinical performance follow-up that includes reactive and proactive measures. These will be challenging to develop for these devices for self-testing. The manufacturer must update their clinical evaluation report on a yearly basis with the information from the clinical performance follow-up, as well as other post-marketing measures. These new requirements will be investigated during the QMS audit. Also, during the five-year cycle of a QMS certificate, the notified body is expected to undertake one unannounced audit. These have the potential to identify poor quality practices.

For SMBGs, a major change under the new Regulations with potential to impact on performance is the enhanced emphasis on clinical performance. Under the EU IVD Directive, the emphasis was on analytical performance data. This no longer suffices.

Perhaps one of the biggest weaknesses of the Directives that is being rectified with the introduction of the new regulations is the extremely strict requirement by the European

authorities that, with the new requirements, the notified body assessment staff are highly qualified to undertake the assessments. This should indeed raise the bar for quality clinical evidence.

A weakness of the EU system compared to that of the FDA is the relative lack of good guidance documents. For SMBGs, EN ISO 15197 is noted as a harmonised standard, and obviously applies to these devices, but few other harmonised standards are as explicitly applicable to these devices. The FDA recognises the CLSI standard series, and these are acknowledged as state of the art for many aspects of IVD validation and verification. Unfortunately, the CLSI standards are not recognised in the EU. This, however, does not prevent a manufacturer from using them. With time, more standards will be available for IVDs in the EU.

Although the EU IVD Regulation is in many ways a superior tool for regulation than the IVD Directive, when it comes to SMBGs, there is one weakness. A manufacturer may apply for a group of SMBGs to be assessed by a notified body. The notified body is only obliged to comprehensively assess, in the first instance, one of these products. It must have a plan to review remaining technical files within the certificate lifecycle. The documentation chosen at time of application should be that representing the highest risk. The notified body must justify its choice.

A strength of the Regulations compared to the Directives is that a summary of safety and performance for each self-monitoring device must be made available on the medical device database, Eudamed. This summary, akin to that of the FDA summary of safety and effectiveness, will also be publicly available. It is hoped that this will provide greater transparency to the assessment process to which the application was subjected.

As is in the US, under the new Regulations, all devices will eventually be required to have a UDI on the label, the benefits of which have already been described. For CGMs, it is also required under the new EU regulation that everyone with a sensor has an implant card. Implant cards are intended for patients to be able to identify information about devices that is published elsewhere, for example in Eudamed. It is also intended for the patient to identify themselves in case of field safety corrective action or other issue. It is hoped that such initiatives will improve knowledge of any ongoing safety issues associated with these devices.

4.2. High level overview of regulation of self-monitoring devices by China and Tanzania

4.2.1. China

China has one of the highest numbers of adults with diabetes in the world. This statistic is unlikely to change in the next decade. The national regulator of medical devices and IVDs in China is the NMPA. China has become a member of the IMDRF and its processes are aligning more with time. Since becoming a member, China has fully adopted 14 IMDRF guidelines and partially implemented another 14.²⁹ In 2020, China was revising its prime medical device legislation. The outputs of this activity were not available at the time of publication, but it is certain that there will be changes. This bodes well for more harmonised international requirements.

The approval process for imported goods in China depends on the class of the medical device. The class is determined by the “product panel”, which in turn groups devices with similar applications and product codes together. For low risk, Class I devices the NMPA will make a direct decision for market approval, but a technical review is required for Class II and III medical devices. SMBG strips are Class II. The CAB for imported products is the Center for Medical Device Evaluation (CMDE), part of the NMPA. Type testing by an NMPA-certified tester or testing laboratory is often necessary. Approval is valid for five years. It should be noted that requirements differ for local production, which is regulated on a provincial basis. These requirements are not the subject of this review.

²⁹<http://www.imdrf.org/docs/imdrf/final/meetings/imdrf-meet-200921-singapore-webconference-05.pdf>

4.2.1.1. Product classification

According to *Provisions for In-vitro Diagnostic Reagent Registration* (Decree No.5 of China's Food and Drug Administration), SMBGs will be Class II IVDs. Similar guidance identifies CGMs as Class II devices.

Locally manufactured Class II medical devices and IVDs are reviewed by the food and drug regulatory department of the provinces, autonomous regions and municipalities directly under the central government. Class III domestic medical devices and IVDs are reviewed by NMPA, and imported class II and class III medical devices are reviewed by NMPA. For all of the above, the medical device registration certificate is issued after approval.³⁰ Hence the standards of assessment may differ for Class II devices because locally produced Class II devices are assessed by provincial regulators, whereas imported Class II devices are subject to assessment by the NMPA.

4.2.1.2. Clinical trials for SMBGs

Pre-market approvals for Class II and Class III medical devices and IVDs in China will, by default, require clinical trials in support of the application, unless the applicant can:

- Identify its product on the clinical trial exemption list;
- Provide sufficient information about a predicate device that is NMPA-approved; or
- Provide sufficient overseas clinical trial data.

These requirements are largely the same whether a company is a domestic or foreign applicant.

4.2.1.3. Standards

China insists on national standards. These are often identical, or at least similar, to international standards. A significant outlier, however, is that the NMPA does not accept International Electrotechnical Commission (IEC) 60601-X test report forms for the testing of electromagnetic compatibility and electrical safety. IEC 60601 is a series of technical standards for the safety and essential performance of medical electrical equipment. The NMPA insists on a device complying to national specifications for electrical safety.

4.2.1.4. QMS requirements

Although China has its own QMS requirements, there is high alignment with ISO 13485. Therefore, an ISO 13485 certificate can be used to support a market application. The NMPA may request review of the audit report associated with an ISO 13485 certificate to ensure China-specific requirements have also been met.

4.2.1.5. UDI

China has issued rules on the adoption of the UDI (2019, No 66). This initiative is being piloted with high-risk implants, such as brain and heart implants. Its final rollout will greatly assist in post-marketing investigations.

4.2.1.6. Clinical evaluation

A clinical evaluation is mandatory for imported Class II and III medical devices (SMBGs and CGMs are class II). This evaluation is based on the results of clinical investigations/studies (e.g., published in specialist literature) and on non-clinical data. A comparator device can be used for this. Clinical investigations are required if no equivalent devices can be found, and safety and

³⁰NMPA Provisions for In-vitro Diagnostic Reagent Registration. Updated 2019-07-25; Provisions for Medical Device Registration. Updated 2019-07-25

efficacy cannot be proven with other clinical and non-clinical data. The NMPA has published its own guidelines (“Medical device clinical evaluation technical guidance”). This is similar to MEDDEV 2.7/1, but has different priorities.

The requirements for clinical investigation are still different, but recent changes are making China an increasingly attractive option for clinical trials for IVDs and medical devices.

4.2.2. Tanzania

The regulator of IVDs in Tanzania is the Tanzania Medicines and Medical Devices Authority (TMDA). Tanzania has been one of the first African nations to adopt the WHO regulatory model framework, undertaking a stepwise approach to build up its capacity to regulate devices. As such, Tanzania has been chosen to highlight a jurisdiction maximising the benefits of harmonised regulation.

All medical devices, including IVDs, must have marketing authorisation by TMDA unless given special approval by the TMDA. A list of all registered medical devices and IVDs is available on the TMDA website. The agency has implemented regulations that, in general, adopt the GHTF definitions that consider the class based on the GHTF classification scheme, which determines which products require registration (classes B to D are evaluated for quality, safety and performance; notification is required for class A devices). Guidance documents exist to assist in the process of registration and notification. A registration is valid for five years.

4.2.2.1. Classification

According to the TMDA website, SMBGs are Class C IVDs and CGM devices may be either class B or C. No definitions have been provided to define duration of use. If the use of a CGM is considered long term usage, it will be Class C, if not it will be a Class B. The guidance provides no clear difference in the expectations of the regulator between submissions for a class B and a class C device.

Thus, SMBGs and CGM devices must be registered with the TMDA. This requires submission of a STED and QMS documents, for evaluation of acceptability. The TMDA website states the following:

“In the course of evaluation of applications, reference will routinely be made to ISO standards and other internationally accepted guidelines to include those published by WHO and IMDRF to ensure that IVDs of good quality, safe and performing are authorised for marketing. An abridged assessment procedure will be adopted for IVDs which have been prequalified by WHO to avoid duplications and hasten registration of such products.”

Similar wording regarding assessment standards is also provided for medical devices.

Internal procedures allow for a comprehensive abridged assessment of a device with proven market authorisation in the US, Canada, EU, Australia or Japan (personal communications with staff at the TMDA, 27 January 2021). This demonstrates that Tanzania is implementing reliance mechanisms and can do so due to the harmonisation of their legal framework with international best practice. SMBGs and CGMs in Tanzania are primarily on the market via the route of this regulatory reliance mechanism.

4.2.2.2. QMS

Evidence to demonstrate an effective QMS that will be accepted by the TMDA includes a CE certificate issued by a notified body designated in Europe. ISO 13485 certificates issued by notified bodies designated in Europe for the purposes of the IVD directive will also be accepted.

4.2.2.3. UDI

At this point of time there is no indication that Tanzania will require labelling including a UDI.

4.2.2.4. Post-marketing requirements

The TMDA website states:

“Applicants should also note that they will now be required to conduct post marketing surveillance of IVDs in countries that mimic Tanzania conditions to accrue information on their quality, safety and performance to testify whether they still meet registration requirements post approval. Such information should be prepared and submitted after every two years (biennial) as indicated in these guidelines and pursuant to the Tanzania Medicines and Medical Devices (Control of Medical Devices) Regulations, 2015.”

As such, there are mechanisms in place whereby the regulator can ensure ongoing compliance with the Tanzanian regulations.

4.3. WHO Prequalification

Although WHO is not a regulatory body, it undertakes assessments of safety and performance of certain health products, e.g., medicines and devices for malaria, to inform procurement and to support its programmes. In 2019, WHO announced that the WHO Prequalification (PQ) of IVDs programme will prequalify SMBGs. The timing of this activity was planned for 2020, but PQ has experienced significant time shifts in implementation forced by the COVID-19 pandemic. It is unknown when it will be implemented.

4.3.1. The PQ Procedure

In its current incarnation, WHO PQ for IVDs is modelled on the GHTF model for high risk IVDs, in that the assessment includes a comprehensive evaluation of a product, with the following steps being undertaken. The WHO Prequalification procedure consists of the following assessment steps:

- Technical documentation assessment. The product dossier, submitted according to internationally recognised practices, is reviewed with the purpose of gaining an understanding of the product, its safety and performance, design and manufacture; and determining if the manufacturer’s QMS is of an adequate standard to warrant an inspection.
- QMS assessment. The manufacturing site inspection is carried out to assess compliance with the quality management standard ISO 13485, with focus on the suitability of the implemented processes and procedures for the reliable supply of products in LMICs.
- Performance evaluation. Laboratory evaluation of the product using specimens, often sourced globally, to verify performance and to assess the operational and characteristics of the product. WHO has approved certain laboratories to undertake this activity, using a WHO approved protocol.
- Instructions for Use Review. If a product has been deemed to meet minimum standards of quality, safety and performance via the three steps noted above, WHO will review the instructions for use to ensure that the contents are appropriate for the end users (including their usability) and any claims are supported by the evidence.

When a product is successfully prequalified by WHO, it will be added to the list of WHO Prequalified products and be eligible for procurement with United Nations funding. The Global Fund also acknowledges the PQ status as a means of being eligible for purchase with Global Fund donations.

The programme has evolved with time and now includes evaluation of important post-market responsibilities of the manufacturer, including for instance, reporting of adverse events and of significant changes. Countries with weak or non-existent regulatory systems in place put high emphasis in the findings of WHO PQ, at times, preferring this reliance mechanism than others offered by recognition of decisions made by a single regulatory authority.

4.3.2. Abridge PQ procedure

Some products undergoing PQ will already have had comprehensive conformity assessment by a mature regulatory agency as part of market authorisation. WHO leverages this assessment and focuses its efforts on aspects that may be of less relevance to a high-income countries. For instance, the importance of performance of a test using specimens sourced from Africa and other such jurisdictions will be investigated by PQ, as will the ability of the manufacturer to support users in these countries.

5. CHALLENGES ASSOCIATED WITH THE USE OF SMBGS AND CGMS

5.1. Access to accurate devices

SMBGs are the most affordable option for self-management for many people living with diabetes. The tests are simple but require collection of fingerstick blood using an uncomfortable procedure. To ensure good performance, the design of any device for self-testing must consider the abilities of a broad range of users and the need for robust and safe design. The meters need to be simple to use and maintain, and the user needs to ensure that the strips are appropriate for the meter, the strips must be stored as indicated, and the blood sample applied to the strip as indicated. These are tasks that need to be simplified or explained sufficiently so that a result is accurate and will truly reflect the glycaemic status of the individual.

The availability of the international standard, ISO 15179 (current version 2013) “IVD test systems – requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus” has led to improved accuracy with these devices, as the standard specifies design verification procedures and requires the validation of performance by the intended users. With this standard, and the requirement in a number of jurisdictions for pre-market assessment by the regulator for conformance with this standard, there has been a general trend to better, more accurate SMBG devices on the market in high-income countries.

Despite this, there are still SMBGs with variable performance. Lack of effective regulation in many LMICs means that there is a real potential in some settings for access to unregulated, poor-quality SMBGs, made more affordable as they bypass stringent regulatory assessment processes. Anecdotal evidence (personal communication) informs that some manufacturers offload batches of test strips that do not meet accuracy criteria for stringent regulators to less regulated markets. Furthermore, reports from the International Criminal Police Organization (Interpol) indicate all jurisdictions are vulnerable to receipt of counterfeit and substandard devices, thus this issue is a global concern.

It has been almost two decades since the first CGM was marketed, and in that time accuracy, as measured by the mean absolute relative difference (MARD) reading between the CGM and a laboratory-based state of the art blood glucose system, has fallen from around 25% to 9–11% with the latest generation (factory calibrated) systems.³¹ This equates to a large improvement in accuracy. The relative inaccuracies between the two measurements (CGM versus laboratory-based blood glucose result) are in part due to the difficulty in accurately measuring glucose levels in interstitial fluids compared to the relative ease in measuring a blood sample (volume of specimen, variable glucose lag time), as well as the inherent inaccuracies in the comparator assay itself. Device inaccuracy is still not optimal and can lead to harm to the user. Unlike SMBGs, there is no internationally accepted standard guiding the design of verification procedures or assay validation for CGM performance comparable with the ISO 15197 standard. Although SMBGs can be directly compared with laboratory methods to analyse differences and accuracy in measuring glucose levels, no consensus has been developed for comparing CGM devices to reference methods. This is because there is no reference measurement procedure for glucose in interstitial fluid.

5.2. Adverse events reported for the use of self-monitoring devices

5.2.1. Adverse event reporting

Major regulators have requirements for adverse event reporting associated with the use of their device contributing to death or serious injury. Manufacturers may also report when they become aware that their device has malfunctioned and would be likely to cause or contribute to a death

³¹Forlenza et al. Factory-calibrated continuous glucose monitoring: how and why it works, and the dangers of reuse beyond approved duration of wear. *Diabetes Technology & Therapeutics* 2019;21(4):222–229

or serious injury if the malfunction were to recur. Such malfunctions or device deficiencies may include any inadequacy in the identity, quality, durability, reliability, safety or performance of a device, user errors or inadequacy in information supplied with the device.

It is important to note that device deficiencies of IVDs are often hard to monitor, and even more so when the IVD is used for self-testing. This is due to the indirect nature of harm with an IVD, whereby it is not the device itself, rather it is the impact of a false result, that directly causes harm. If a SMBG is not accurate, and there is no warning indicating this, it may only be when a serious adverse event occurs as a result of the failure, that the problem is recognised.

The FDA maintains a publicly accessible database (Total Product Life Cycle [TPLC] database) of adverse events covering both pre-marketing and post-marketing data concerning medical devices. It includes information about device classification product codes, pre-market approvals, pre-market notifications (510[K]), Medical Device Adverse Event Reports (MAUDE), and Center for Devices and Radiological Health medical device recalls.

The following information was obtained from the FDA TPLC database, using the product codes NBW (code for SMBG) and QBJ (code for CGM). A review of TPLC for SMBGs identified the following issues:

5.2.1.1. FDA Adverse event reporting for SMBG

From a total of 167,778 events reported since 2016, **Tables 7 and 8** describe the top 10 adverse events for SMBGs and their consequences reported to the FDA. Of note, although device deficiencies did not result in patient harm in a large proportion of these events (142,954 or 86.3% claimed), 5,828 users (3.7%) did report a significant finding (either hyper- or hypoglycaemia).

Table 7. Top 10 device deficiencies reported to the FDA associated with SMBGs (11 March 2021)

| Device problem | Number of events | Percentage of total reported events |
|---|------------------|-------------------------------------|
| Failure to power up | 38,751 | 23.1 |
| Device displays incorrect message | 38,691 | 23.1 |
| Incorrect, inadequate or imprecise result or readings | 13,738 | 8.2 |
| Incorrect or inadequate test results | 13,486 | 8.0 |
| Loss of power | 7,609 | 4.5 |
| High test results | 7,140 | 4.3 |
| Device operates differently than expected | 5,074 | 3.0 |
| Device alarm system | 3,436 | 2.0 |
| Gauges/meters | 2,663 | 1.6 |
| Low test results | 2,161 | 1.3 |

Table 8. Top 10 clinical outcomes reported to the FDA associated with SMBG adverse events (11 March 2021)

| Clinical problem | Number of events | Percentage of total reported events |
|---|------------------|-------------------------------------|
| No known impact or consequence to patient | 79,760 | 47.7 |
| No consequences or impact to patient | 63,194 | 37.8 |
| Hyperglycaemia | 3,084 | 1.8 |
| Hypoglycaemia | 2,744 | 1.6 |
| Shaking/tremors | 2,354 | 1.4 |
| Sweating | 2,081 | 1.2 |
| Dizziness | 1,986 | 1.2 |

| Clinical problem | Number of events | Percentage of total reported events |
|---|------------------|-------------------------------------|
| No clinical signs, symptoms or conditions | 1,276 | 0.8 |
| Loss of consciousness | 799 | 0.5 |
| Weakness | 777 | 0.5 |

5.2.1.2. FDA adverse event reporting for CGMs

From a total of 351,058 clinical problems reported since 2018, **Tables 9 and 10** describe the top 10 adverse events for CGMs and their consequences reported to the FDA. Of note, although device deficiencies did not result in patient harm in a large proportion of these events (346,327 or 98.7% claimed), 1,496 users (0.4%) did report a significant finding (being hyper- or hypoglycaemia, loss of consciousness or diabetic ketoacidosis, the latter of which there were 119 reports).

Table 9. Top 10 device deficiencies reported to the FDA associated with CGMs (11 March 2021)

| Device problem | Number of events | Percentage of total reported events |
|--|------------------|-------------------------------------|
| Wireless communication problem | 126,308 | 34.4 |
| No device output | 97,790 | 26.6 |
| Imprecision | 56,546 | 15.4 |
| Premature end-of-life indicator | 19,566 | 5.3 |
| Device displays incorrect message | 18,547 | 5.0 |
| Communication or transmission problem | 11,211 | 3.1 |
| Appropriate term/code not available | 7,786 | 2.1 |
| Detachment of device or device component | 4,578 | 1.2 |
| Unintended application program shut down | 3,847 | 1.0 |
| Retraction problem | 3,729 | 1.0 |

Table 10. Top 10 clinical outcomes reported to the FDA associated with CGM adverse events (11 March 2021)

| Clinical problem | Number of events | Percentage of total reported events |
|---|------------------|-------------------------------------|
| No consequences or impact to patient | 244,264 | 66.5 |
| No known impact or consequence to patient | 6,8125 | 18.5 |
| No clinical signs, symptoms or conditions | 5,6723 | 15.4 |
| Hypoglycaemia | 899 | 0.2 |
| Reaction | 538 | 0.1 |
| Loss of consciousness | 283 | 0.1 |
| Erythema | 275 | 0.1 |
| Hyperglycaemia | 255 | 0.1 |
| Foreign body in patient | 242 | 0.1 |
| Itching sensation | 223 | 0.1 |

5.2.1.3. Observations from the findings

It is not possible to draw strong conclusions from the results of these searches. Databases such as these are limited when it comes to providing information about the severity of the adverse events. The search results have limited use for determining the incidence of an adverse event (that is, how often the adverse event has occurred in users of a particular medical device), or the likelihood of

a user experiencing that adverse event. This is because the search results do not include critical information such as the total number of users of a medical device, the number of medical devices supplied in the country of reporting, or the incidence of adverse events prior to the reporting timeline. Additionally, caution must be made when using the search results to make accurate numerical comparisons between adverse events associated with different medical devices. As such, the following observations are only indicative of where problems with these devices may lie.

Approximately 23% of reported SMBG deficiencies were related to inaccurate results. This finding was obtained by including the following categories of complaints:

- Incorrect, inadequate or imprecise result or readings
- Incorrect or inadequate test results
- High test results
- Low test results
- Missing test results
- False reading from device non-compliance

Meanwhile, 15.6% of device errors for CGMs were identified as being related to inaccuracy. The only relevant category reported associated with inaccuracy was for imprecision. Similarly, problems associated with usability were assessed. For SMBGs, approximately 4.5% of reported deficiencies were due to either the device operating differently than expected, a device operational issue or lack of sufficient information. Only about 0.1% of reported CGM problems were directly attributed to usability issues.

5.2.2. Agência Nacional de Vigilância Sanitária (ANVISA) actions

Although other jurisdictions have databases for adverse event reporting, no others provide the comprehensive data set available on the FDA website. Anecdotal evidence provided via the Brazilian regulator, ANVISA (personal communication, January 2021), revealed that many problems are reported for use of sensors with CGM. The main issue apparently is around clarity of instructions. The need for instructions to be adapted for the intended use population is vital. This must all be done under the control of the manufacturer's quality system, even if third parties are involved to assist. In addition, in 2018, "RESOLUTION-RE NO. 3,161, OF NOVEMBER 16, 2018" published on the official Brazilian government website,³² resulted in the cancellation of 17 registrations of various SMBG and CGM devices. The reason for this cancellation was lack of evidence of conformity with ISO 15197:2013. A number of the products were CE marked and had FDA authorisation. ANVISA had requested the data from manufacturers, however, it had not been forthcoming.

5.3. Substandard and counterfeit devices

In 2020, Interpol reported that in March that year, more than 37,000 unauthorised and counterfeit medical devices were seized, the vast majority of which were surgical masks and self-testing kits (for human immunodeficiency virus [HIV] or glucose), but also various surgical instruments.³³ Rapid test formats are simple to make, if quality is not a consideration, and HIV and glucose self-tests are the most prone to criminal misconduct. With both tests, the impact of an invalid or a false result is serious. As such, the need for unique identifier systems such as the UDI is clear. Also, there is a need for affordable controls so that users can routinely check new batches for efficacy. Regardless of the stringency of regulatory oversight, criminal activity will endure; however, it is hoped that the prevalence is significantly curbed with current regulatory measures to ensure greater traceability and transparency.

³²https://www.in.gov.br/web/guest/materia/-/asset_publisher/Kujrw0TZC2Mb/content/id/50727633/dola-2018-11-19-resolucao-re-n-3-161-de-16-de-novembro-de-2018-50727413 (Accessed 09 February 2021)

³³Global operation sees a rise in fake medical products related to COVID-19. <https://www.interpol.int/en/News-and-Events/News/2020/Global-operation-sees-a-rise-in-fake-medical-products-related-to-COVID-19> (Accessed 08 February 2021)

6. ANALYSIS OF THE EFFECTIVENESS OF CURRENT GUIDANCE FOR DEVICE DEVELOPMENT AND ASSESSMENT

Use of consensus driven standards and guidance provides both manufacturers and regulators with benchmarks for acceptable design and performance features. The implementation of the various iterations of ISO standard ISO 15197, *IVD test systems: requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus*, has resulted in improved performance. The following section will review and compare the various guidance documents currently available and consider their strengths and weaknesses as tools the development for accurate self-monitoring devices. Intentionally highly technical in nature, it is hoped that this analysis will be useful for regulators and will highlight areas for improvement in future revisions.

6.1. Self-monitoring blood glucose devices- SMBGs

This section analyses the differences that may contribute to variability in performance between ISO 15197 and the FDA guidance document *Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use: Guidance for Industry and Food and Drug Administration Staff*, published in September 2020.

The standard ISO 15197 was established in 2003, revised in 2013 and the current version was harmonised with EU regulations in 2015.³⁴ Since its publication in 2003, many manufacturers of SMBGs have used the standard to design their device and validation studies.

In 2016, the FDA released their own guidance document, *Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use*, hence forth referred to as FDA OTC guidance, defining requirements for SMBGs, stating that they believe “that the criteria set forth in the ISO 15197 standard are not sufficient to adequately protect lay-users using SMBGs because, for example, the standard does not adequately address the performance of over-the-counter blood glucose test systems in the hypoglycaemic range (...) or across test strip lots.” This guidance was updated in September 2020.³⁵

A comparison of the current version of ISO 15197 and the FDA OTC guidance reveals that both mainly address the same topics (**Table 11**). Both refer to, for example, robustness regarding environmental and usage variation, the information provided by the manufacturer and analytical performance. The most obvious differences between the two documents relate to the scope and applicable acceptance criteria of the accuracy studies.

³⁴International Organization for Standardization. In vitro diagnostic test systems - Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus. ISO 15197:2013 2013.

³⁵Food and Drug Administration. Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use - Guidance for Industry and Food and Drug Administration Staff 2020 11-Mar-2021. Available from: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM380327.pdf>

Table 11. Differences between ISO 15197 and FDA OTC guidance

| Evaluation | ISO 15197 | | FDA |
|----------------------------|--|--|---|
| | System accuracy | User performance evaluation | Method comparison/user evaluation |
| | Measurements are performed by trained study personnel | Subjects naïve to the respective SMBG | At least 10% of the subjects shall be naïve to self-monitoring of blood glucose |
| | ≥100 different subjects | ≥100 different subjects from the intended use population | ≥350 subjects from the intended use population |
| | Defined distribution of glucose concentrations need to be tested | No defined distribution of glucose concentration need to be tested | No defined distribution of glucose concentration need to be tested |
| | Each sample is measured twice with each of three reagent system lots (600 values, 300 per lot) | Single measurements from one reagent system lot | Single measurements from three strip lots |
| | Altered blood samples allowed to cover extremes of the measuring range | No need to cover complete measuring range | Altered samples proposed to cover extremes of the measuring range |
| | | | 50 altered blood samples at low and high concentrations, respectively |
| Acceptance criteria | Glucose concentrations ≥100 mg/dl (5.55 mmol/l): 95% of measurements shall fall with ±15% of the reference value | | The same as ISO |
| | Glucose concentrations <100 mg/dl (5.55 mmol/l): allowed difference of ±15 mg/dl (0.83 mmol/l) | | Glucose concentrations <100 mg/dl (5.55 mmol/l): maximum deviation of ±15% |
| | All glucose concentrations: 99% of values within zones A and B of the CEG | | All glucose concentrations: minimum of 99% values within ±20% |
| Lots | Each of three reagent lots separately has to fulfil acceptance criteria | Evaluation of one reagent lot | Evaluation of three reagent lots, but results of one lot with insufficient performance may be compensated by two lots with better performance |
| Comparison samples | Perform duplicate measure for each comparison sample | Perform duplicate measure for the comparison sample | Duplicate measures are optional |
| | Take comparison samples before and after sampling for SMBG testing | Only one comparison sample is taken | Only one comparison sample is taken |

ISO 15197 stipulates two types of accuracy evaluations:

- **System accuracy evaluation:** Measurements with the SMBG are performed by trained study personnel. In total, samples of 100 different subjects,^{36,37,38,39} having a defined distribution of glucose concentrations are included. For very low and very high glucose concentration ranges, altered blood samples may be used: Up to all samples ≤ 50 mg/dl (2.77 mmol/l) or >400 mg/dl (22.2 mmol/l) as well as some of the samples ≤ 80 mg/dl (4.44 mmol/l) or >300 mg/dl (16.65 mmol/l). Each sample is measured twice with each of three reagent system lots, resulting in 600 measured values (300 for each reagent system lot). Subject samples must be distributed according to specification, which is helpful when accuracy evaluations of different systems are compared.
- **User performance evaluation:** 100 different subjects, naïve to the respective SMBG, shall be recruited from the intended use population^{40,41,42,43}. Measurements are performed by the subjects with one reagent system lot.

Both studies may be combined with the same 100 subjects, provided that the user performance part is performed first to ensure that subjects are still naïve to the SMBG.

The FDA guidance also requires a combined method comparison/user evaluation, i.e., an evaluation with single measurements being performed by 350 subjects from the intended use population using three test strip lots.⁴⁴ At least 10% of the subjects shall be naïve to self-monitoring of blood glucose (e. g., non-diabetic subjects).

The user samples may not sufficiently cover extremely low or high glucose concentrations. Therefore 50 altered blood samples with glucose concentrations <80 mg/dl (4.44 mmol/l) and 50 altered blood samples >250 mg/dl (13.9 mmol/l) have to be added to the analysis.

It is unclear whether the same subjects may participate both in the user evaluation and provide an additional sample for altering, therefore up to 450 measurements are needed for these accuracy evaluations.

Both ISO 15197 and the FDA guidance for over-the-counter systems require a minimum number of unaltered samples below 80 mg/dl (4.44 mmol/l) and above 300 / 250 mg/dl (16.7 / 13.9 mmol/l), but the number of altered samples differs.

³⁶Freckmann G, Link M, Schmid C, Pleus S, Baumstark A, Haug C. System Accuracy Evaluation of Different Blood Glucose Monitoring Systems Following ISO 15197:2013 by Using Two Different Comparison Methods. *Diabetes Technol Ther.* 2015;17(9):635-48. doi: 10.1089/dia.2015.0085

³⁷Pleus S, Baumstark A, Jendrike N, Mende J, Link M, Zschornack E, et al. System accuracy evaluation of 18 CE-marked current-generation blood glucose monitoring systems based on EN ISO 15197:2015. *BMJ open diabetes research & care.* 2020;8(1). Epub 2020/01/21. doi: 10.1136/bmjdr-2019-001067

³⁸Klonoff DC, Parkes JL, Kovatchev BP, Kerr D, Bevier WC, Brazg RL, et al. Investigation of the Accuracy of 18 Marketed Blood Glucose Monitors. *Diabetes Care.* 2018;41(8):1681-8. Epub 2018/06/15. doi: 10.2337/dc17-1960

³⁹Yu-Fei W, Wei-Ping J, Ming-Hsun W, Miao OC, Ming-Chang H, Chi-Pin W, et al. Accuracy Evaluation of 19 Blood Glucose Monitoring Systems Manufactured in the Asia-Pacific Region: A Multicenter Study. *J Diabetes Sci Technol.* 2017;11(5):953-65. doi: 10.1177/1932296817705143

⁴⁰Bailey TS, Wallace JF, Pardo S, Warchal-Windham ME, Harrison B, Morin R, et al. Accuracy and User Performance Evaluation of a New, Wireless-enabled Blood Glucose Monitoring System That Links to a Smart Mobile Device. *J Diabetes Sci Technol.* 2017;11(4):736-43. doi: 10.1177/1932296816680829

⁴¹Christiansen M, Greene C, Pardo S, Warchal-Windham ME, Harrison B, Morin R, et al. A New, Wireless-enabled Blood Glucose Monitoring System That Links to a Smart Mobile Device: Accuracy and User Performance Evaluation. *J Diabetes Sci Technol.* 2017;11(3):567-73. Epub 2017/07/27. doi: 10.1177/1932296817691301

⁴²Freckmann G, Jendrike N, Baumstark A, Pleus S, Liebing C, Haug C. User Performance Evaluation of Four Blood Glucose Monitoring Systems Applying ISO 15197:2013 Accuracy Criteria and Calculation of Insulin Dosing Errors. *Diabetes therapy : research, treatment and education of diabetes and related disorders.* 2018;9(2):683-97. doi: 10.1007/s13300-018-0392-6

⁴³Jendrike N, Baumstark A, Pleus S, Liebing C, Kamecke U, Haug C, et al. Accuracy of five systems for self-monitoring of blood glucose in the hands of adult lay-users and professionals applying ISO 15197:2013 accuracy criteria and potential insulin dosing errors. *Curr Med Res Opin.* 2019;35(2):301-11. Epub 2018/06/22. doi: 10.1080/03007995.2018.1491832

⁴⁴Katz LB, Smith A, Cameron H, Setford S, Grady M. 10/10 Accuracy Analysis of a Self-Monitoring Blood Glucose System. *J Diabetes Sci Technol.* 2021;1932296821993220. doi: 10.1177/1932296821993220

Altering a sample may change its sample matrix and, subsequently, the reliability of measurement results may be affected. While establishing commutability of samples may be feasible for manufacturers who will likely use similar measurement technology across their products, it is difficult for third parties performing independent verification of performance to do so.⁴⁵

The FDA requirement for the inclusion of subjects who are naïve to self-monitoring of blood glucose is seen as a positive aspect of the guidance. This action may provide additional relevant information about the labelling and/or an intuitively correct handling of the SMBG being investigated.

The acceptance criteria of ISO 15197 and FDA OTC guidance are comparable in that at least 95% of measurements shall fall within $\pm 15\%$ of the reference value for glucose concentrations ≥ 100 mg/dl (5.55 mmol/l). But whereas ISO 15197 allows differences of ± 15 mg/dl (0.83 mmol/l) for glucose concentrations < 100 mg/dl (5.55 mmol/l), FDA also requires a maximum deviation of $\pm 15\%$. These strict criteria set by the FDA are expected to be difficult to fulfil by some SMBG manufacturers. In addition, FDA requirements below 75 mg/dl are stricter for SMBGs than for point-of-care-testing systems.

Both ISO 15197 and FDA have defined additional criteria to limit the allowed deviations for the 5% of values not falling within the 15 mg/dl (0.83-mmol/l) or 15% limits (see Table 11 “Acceptance criteria”). FDA requires in total a minimum of 99% values to be within $\pm 20\%$. For the system accuracy evaluation, ISO 15197 requires at least 99% of values to fall within zones A and B of the consensus error grid (CEG).⁴⁶ This requirement is important because it brings relevance to analytical claims of accuracy. According to Pfützner et al.,⁴⁷ it is possible to assess the clinical accuracy of a blood glucose value measured by a SMBG using an error grid, as “a description of the potential clinical outcome associated with basing a treatment decision on this value”. An error grid maps paired data (results comparing SMBG under investigation with a reference method) and plots these on a grid, known as an error grid. The plotted results then fall into clinical categories (no harm, non-significant harm and significant harm). Thus, this measure of clinical accuracy focuses on the clinical relevance of the meter results in comparison with analytical accuracy.

Whereas ISO 15197 allows for the exclusion of results, e. g., in cases such as obvious handling mistakes or if predefined sample stability criteria are missed, all results have to be included in an evaluation according to the FDA guidance, but results falling outside the defined accuracy limits must be justified from a clinical point of view.

In addition, in a system accuracy evaluation according to ISO 15197, each of the three reagent lots has to fulfil the following criteria: $\geq 95\%$ of values within ± 15 mg/dl (0.83 mmol/l) / $\pm 15\%$ at glucose concentrations < 100 mg/dl / ≥ 100 mg/dl (5.55 mmol/l)). The FDA guidance also requires testing of three different lots, but separate analysis is not stipulated. As the evaluation is performed across all three lots, results of one lot with insufficient performance may be compensated by two lots with better performance. Thus, the requirement of the ISO standard appears to be more robust.

Although ISO 15197 and FDA OTC guidance describe comparable criteria for the reference measurement devices, the procedures to obtain the comparison values for the evaluation have relevant differences. ISO 15197 stipulates that at least duplicate measurements of each comparison sample shall be performed. Moreover, in system accuracy analysis, comparison samples shall be taken before and after sampling for the SMBG measurements, to verify sample stability. Mean values calculated from duplicate measurements of both samples are used as comparison values in the evaluation. According to the FDA OTC guidance, only one comparison sample is taken and

⁴⁵ E.g. for reasons such as post-market surveillance or monitoring.

⁴⁶ Parkes JL, Slatin SL, Pardo S, Ginsberg BH. A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose. *Diabetes Care*. 2000;23(8):1143-8

⁴⁷ Pfützner, A., Klonoff, D. C., Pardo, S., & Parkes, J. L. (2013). Technical aspects of the Parkes error grid. *Journal of diabetes science and technology*, 7(5), 1275-1281. <https://doi.org/10.1177/193229681300700517>

duplicate measurements are optional. The requirement of only one measurement to determine the reference value in accuracy analysis seems inconsistent with the suggestion of at least four replicates to establish the glucose concentration in samples intended for interference evaluation where the specific glucose concentration is not expected to have relevant impact on the study result.

Apart from system accuracy, both ISO 15197 and the FDA OTC guidance require assessment of precision and the influence of endogenous and exogenous substances. Further assessments include mechanical and electrical safety as well as the need for flex studies, although the level of detail with which these assessments are described differs between the standards.

6.2. Continuous glucose monitoring systems - CGMs

Assessment of CGM performance is standardised to a markedly lower degree than that of SMBGs. There are two notable instances, the CLSI POCT05 guideline Performance Metrics for Continuous Interstitial Glucose Monitoring, 2nd Edition⁴⁸, henceforth referred to as POCT05, and the US FDA's CGM special controls as described in the FDA approval letter to Dexcom.⁴⁹

POCT05 covers, for example, point accuracy, trend accuracy and alarm evaluation in addition to technical aspects, like signal availability or sensor life. Point accuracy relates to how well individual CGM results match with results obtained with a comparison method, independent from the current glucose rate of change. One of the recommended metrics is the MARD, which is a commonly used but flawed metric,⁵⁰ as well as concurrence tables. Trend accuracy reflects how well the rate of change in CGM results matches the rate of change in comparison method results. In an alarm evaluation, true and false alerts, as well as confirmed and undetected events of hypo- and hyperglycaemia, are assessed for different alert thresholds.

However, metrological traceability of CGMs covers less than half a page. Metrological traceability is defined by ISO as follows: "Property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty." The concept of such traceability is to be able to understand the level of uncertainty, or in this case, accuracy. Yet the concept of metrological traceability is critical for many devices with a quantitative output. Requirements for traceability are described in the international standard ISO 17511:2020 *In vitro diagnostic medical devices – requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples*.⁵¹ It is currently impossible to obtain sufficiently large volumes of interstitial fluid, making "compare like with like" approaches unfeasible. Nevertheless, metrological traceability could be established, for example, to capillary blood glucose values,⁵² since most CGMs are intended to either supplement or even replace conventional SMBG, which is based on capillary samples.

⁴⁸Clinical and Laboratory Standards Institute. Performance metrics for continuous interstitial glucose monitoring. 2nd ed. CLSI guideline POCT05. Wayne, PA. 2020

⁴⁹http://www.accessdata.fda.gov/cdrh_docs/pdf18/K183206.pdf (Accessed 23 March 2021)

⁵⁰Kirchsteiger H, Heinemann L, Freckmann G, Lodwig V, Schmelzeisen-Redeker G, Schoemaker M, et al. Performance Comparison of CGM Systems: MARD Values Are Not Always a Reliable Indicator of CGM System Accuracy. *J Diabetes Sci Technol*. 2015;9(5):1030-40

⁵¹International Organization for Standardization. *In Vitro Diagnostic Medical Devices – Requirements For Establishing Metrological Traceability Of Values Assigned To Calibrators, Trueness Control Materials And Human Samples*. EN ISO 17511:2020. 2020

⁵²Freckmann G, Nichols JH, Hinzmann R, Klonoff DC, Ju Y, Diem P, et al. Standardization process of continuous glucose monitoring: Traceability and performance. *Clinica chimica acta; international journal of clinical chemistry*. 2021;515:5-12. Epub 2020/12/29. doi: 10.1016/j.cca.2020.12.025

Furthermore, POCT05 does not address the impact of study procedures on performance metrics like MARD.^{53,54,55} The guidance does not provide the detailed requirements for study procedures, and minimum performance criteria are missing as well. Therefore, the level of standardisation among CGMs that can be achieved by following POCT05 is limited.

The FDA special controls for CGMs define specific minimum performance criteria, based also on point and trend accuracy. Most of the topics covered by POCT05 are included in these special controls as well. However, these special controls only apply to products that meet the definition of the FDA assigned term “iCGMs⁵⁶” (note, the FDA definition of iCGM is not restricted to CGMs that are intermittently viewed, see reference below). According to FDA, “iCGMs are designed to reliably and securely transmit glucose measurement data to digitally connected devices, including automated insulin dosing systems, and are intended to be used alone or in conjunction with these digitally connected medical devices for the purpose of managing a disease or condition related to glycaemic control”.³⁵ Thus, CGMs that are intended to supplement, but not replace, conventional SMBGs do not fall under the CGM designation, and neither do systems that do not transfer data to connected devices.

As is the case for POCT05, the FDA CGM special controls do not address standardisation of study procedures, so that the reliability of performance metrics cannot be assured.

⁵³Kirchsteiger H, Heinemann L, Freckmann G, Ludwig V, Schmelzeisen-Redeker G, Schoemaker M, et al. Performance Comparison of CGM Systems: MARD Values Are Not Always a Reliable Indicator of CGM System Accuracy. *J Diabetes Sci Technol.* 2015;9(5):1030-40

⁵⁴Reiterer F, Polterauer P, Schoemaker M, Schmelzeisen-Redecker G, Freckmann G, Heinemann L, et al. Significance and Reliability of MARD for the Accuracy of CGM Systems. *J Diabetes Sci Technol.* 2017;11(1):59-67. doi: 10.1177/1932296816662047

⁵⁵Heinemann L, Schoemaker M, Schmelzeisen-Redecker G, Hinzmann R, Kassab A, Freckmann G, et al. Benefits and Limitations of MARD as a Performance Parameter for Continuous Glucose Monitoring in the Interstitial Space. *J Diabetes Sci Technol.* 2020;14(1):135-50. doi: 10.1177/1932296819855670

⁵⁶ FDA definition of iCGM for product code QBJ “An integrated continuous glucose monitoring system (iCGM) is intended to automatically measure glucose in bodily fluids continuously or frequently for a specified period of time. iCGM systems are designed to reliably and securely transmit glucose measurement data to digitally connected devices, including automated insulin dosing systems, and are intended to be used alone or in conjunction with these digitally connected medical devices for the purpose of managing a disease or condition related to glycemic control.” <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpd/classification.cfm?id=682> Accessed 05/05/2021

7. DISCUSSION

This section will take the analysis of current practices and make recommendations that may assist manufacturers and assessment bodies in ensuring that the SMBGs and CGMs available for use in LMICs and in other settings are fit for purpose. Recommendations will be made for aspects to be considered in the development of any new guidance for these devices. The evolving regulatory landscape, not only in LMICs, but also in Europe, provides an opportunity to highlight the issues impacting on performance and also to provide solutions for their mitigation.

7.1. Tools for Improvement: General

ISO 15197 and FDA guidance for over-the-counter SMBGs are intended to be applied when SMBGs are introduced to the market and, as outlined above, both define numerous requirements regarding quality of SMBGs. In the last years, however, several independent post-marketing evaluations of system accuracy showed that a number of the SMBGs available on the European and US markets do not fulfil the respective requirements.^{57,58,59}

As outlined earlier in this report, efforts have been made towards standardising performance assessments of CGMs. However, the current status of standardisation can be improved, for example by addressing unresolved issues. In 2019, a working group on CGM was created by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)^{60,61}. The working group remains active with the work of standardization of CGM performance continuing.

The following recommendations could help to improve the quality of SMBGs and CGMs on the market.

7.1.1. Verification of performance by the regulatory authority

7.1.1.1. Pre-approval independent verification of performance claims

Although performance must be established by all SMBGs brought to the market, a manufacturer-independent evaluation of the claimed performance of SMBG or CGMs is not mandatory. Thus, the manufacturer remains the sole generator of performance data. Manufacturer-independent evaluations before market introduction can help to ensure the quality of available SMBGs and CGMs. A Scandinavian institution supported by the government, the Scandinavian Evaluation of Laboratory Equipment for Point of Care Testing (SKUP), performs structured SMBG evaluations. In Norway, for example, an SMBG needs a positive evaluation outcome following testing by SKUP in order for the product to be reimbursed by health insurance. Similarly, in the EU, all high-risk blood screening tests are required to have independent verification of results by an EU reference laboratory before market approval, under the forthcoming IVDR.

⁵⁷Pleus S, Baumstark A, Jendrike N, Mende J, Link M, Zschornack E, et al. System accuracy evaluation of 18 CE-marked current-generation blood glucose monitoring systems based on EN ISO 15197:2015. *BMJ open diabetes research & care*. 2020;8(1). Epub 2020/01/21. doi: 10.1136/bmjdr-2019-001067

⁵⁸Klonoff DC, Parkes JL, Kovatchev BP, Kerr D, Bevier WC, Brazg RL, et al. Investigation of the Accuracy of 18 Marketed Blood Glucose Monitors. *Diabetes Care*. 2018;41(8):1681-8. Epub 2018/06/15. doi: 10.2337/dc17-1960

⁵⁹Yu-Fei W, Wei-Ping J, Ming-Hsun W, Miao OC, Ming-Chang H, Chi-Pin W, et al. Accuracy Evaluation of 19 Blood Glucose Monitoring Systems Manufactured in the Asia-Pacific Region: A Multicenter Study. *J Diabetes Sci Technol*. 2017;11(5):953-65. doi: 10.1177/1932296817705143

⁶⁰International Federation of Clinical Chemistry and Laboratory Medicine. Working Group on Continuous Glucose Monitoring (WG-CGM) 2019 [accessed 27 Mar 2020]. Available from: <https://www.ifcc.org/ifcc-scientific-division/sd-working-groups/wg-cgm/>

⁶¹Freckmann G, Nichols JH, Hinzmann R, Klonoff DC, Ju Y, Diem P, et al. Standardization process of continuous glucose monitoring: Traceability and performance. *Clinica chimica acta; international journal of clinical chemistry*. 2021;515:5-12. Epub 2020/12/29. doi: 10.1016/j.cca.2020.12.025

Inclusion of independent evaluations may be beneficial, not only because of the inherent conflict of interest of testing by the manufacturer influencing claims, but also to detect problems in the manufacturing process. For example, errors in the calibration of an SMBG or CGM may not be detected if the manufacturer uses the same study procedures for calibration and for pre-market performance assessment. As part of best practice, results of this independent testing should be published.

7.1.1.2. Lot release testing

The performance of an SMBG or CGM relies on evidence generated by the manufacturer before market introduction. Regular evaluations such as independently organized testing of each new lot of test strip could, therefore, help to ensure continued quality throughout the whole life cycle of an SMBG. This testing would require use of an accepted reference method (that is, a state-of-the-art laboratory-based assay), and the manufacturer would be required to send samples of strips or sensors from each lot/batch to a reference laboratory before release of that lot to the market. Such a requirement exists as part of regulatory authorization in the EU and the USA for the high-risk devices used for screening of the blood supply.

Although pre-market confirmation of performance as a condition of regulatory approval are mechanisms usually applied only to the highest risk IVDs, there is a strong argument for their application for SMBGs and CGMs. Three strong reasons support this approach:

- According to WHO,⁶² diabetes is one of the top 10 causes of death globally. Self-monitoring is a critical tool in the response to this disease, and has the potential, when devices are accurate and information from the device is acted on appropriately, to significantly reduce mortality and morbidity. As such, the incidence of this disease should be taken into account in the regulatory risk classification.
- These devices are used by lay users, whose trust in the results cannot afford to be negatively impacted due to poorly performing devices. The lay user has far fewer resources at their disposal to verify performance than a professional using a glucose measuring device in a laboratory. From a regulatory perspective, this represents a high risk.
- These medical devices do not come with controls or international standards to confirm the performance.

As such, the proposals for the additional regulatory interventions listed above is based on a risk-based approach for the identification of appropriate controls.

7.1.2. Standardised reference method

Mass spectrometry-based methods are recognized as reference methods for glucose concentrations in whole blood and blood plasma. They do not (yet) cover interstitial fluid, which limits traceability of CGMs (see below). Despite recent development towards easy-to-use analysers with rapid measuring times, these methods are comparatively expensive and they lack throughput, so that SMBG and factory-calibrated CGMs are usually calibrated using a laboratory method. The most common laboratory methods for glucose concentration measurements are based on enzymatic reactions, implementing glucose oxidase or hexokinase, followed by electrochemical or photometric principle of detection. These laboratory methods, however, are reported to differ by up to 8%.⁶³ Even with the same model of laboratory analyser, differences of up to several percent have been reported.⁶⁴ This systematic difference is, for example, compounded by the tolerance limit of up to ± 15 mg/dl (0.83 mmol/l) / 15% difference allowed by ISO 15197 / FDA OTC guidance.

⁶²<https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death#:~:text=Leading%20causes%20of%20death%20globally&text=The%20world's%20biggest%20killer%20is,8.9%20million%20deaths%20in%202019> (Accessed 29 March 2021)

⁶³Twomey PJ. Plasma glucose measurement with the Yellow Springs Glucose 2300 STAT and the Olympus AU640. *Journal of clinical pathology*. 2004;57(7):752-4. doi: 10.1136/jcp.2003.013417

⁶⁴Bailey TS, Klaff LJ, Wallace JF, Greene C, Pardo S, Harrison B, et al. Fundamental Importance of Reference Glucose Analyzer Accuracy for Evaluating the Performance of Blood Glucose Monitoring Systems (BGMSS). *J Diabetes Sci Technol*. 2016;10(4):872-5. doi: 10.1177/1932296816634356

ISO 15197 and the FDA OTC guidance have similarly vague requirements for reference measurement procedures (comparison methods). The reference method has to be traceable and it has to have proven trueness and precision. These requirements, as well as requirements for CGMs, should be complemented by more specific criteria for allowed bias to reference methods / reference materials of higher order (e.g., mass spectrometry methods or materials whose glucose concentration has been assigned by mass spectrometry methods) and precision, in order to standardise reference methods used for calibration and performance analyses of SMBGs and CGMs.⁶⁵

Requirements in quality assurance of IVDs used for healthcare in laboratories do not necessarily ensure adequate performance of reference methods. In Germany, for example, the external quality assurance allows deviations of up to $\pm 15\%$ from a target value determined with an isotope dilution gas chromatography–mass spectrometry method.⁶⁶ Although tighter criteria (± 6 mg/dl (0.33 mmol/l) or $\pm 10\%$) are applied in the US, consensus values can be used as target values, and thus, metrological traceability is not adequately considered.⁶⁷

In order to establish valid glucose concentrations for the comparison samples, the number of replicate measurements should be informed by the analyser's imprecision. However, at least duplicate measurements should be performed with the comparison method so that erroneous measurements can be more easily identified. In addition, taking two comparison samples as required by ISO 15197, one before and one after measurements with the SMBG, enables the detection of sample stability as well as potential issues with the comparison method.

7.1.3. Clinical impact assessment

This section will look at clinical impact from three perspectives; the first related to the tools at hand to estimate clinical impact, the second reports on studies of test inaccuracy and the third looks at potential impacts on self-monitoring devices based on changing clinical guidelines.

7.1.3.1. Revised assessment tools needed

As noted earlier, an error grid is a statistical tool to assess the clinical (as opposed to analytical) accuracy of a blood glucose value. It describes the potential clinical outcome associated with basing a treatment decision on a glucose result.

The application of a revised error grid (e.g., surveillance error grid) instead of the outdated consensus error grid would provide a more precise indication of the clinical impact of measurements errors. According to Klonoff et al,⁶⁸ "Currently used error grids for assessing clinical accuracy of blood glucose monitors are based on out-of-date medical practices. Error grids have not been widely embraced by regulatory agencies for clearance of monitors, but this type of tool could be useful for surveillance of the performance of cleared products. The Diabetes Technology Society, together with representatives from the FDA, the American Diabetes Association, the Endocrine Society, and the Association for the Advancement of Medical Instrumentation, and representatives of academia, industry, and government, have developed a new error grid, called the surveillance error grid as a tool to assess the degree of clinical risk from inaccurate blood glucose monitors". Compared to traditional error grids, surveillance error grids are continuous, that is, each point of the grid has its own risk value.

⁶⁵Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem*. 2011;57(6):e1-e47

⁶⁶Bundesärztekammer. Neufassung der Richtlinie der Bundesärztekammer zur Qualitätssicherung laboratoriumsmedizinischer Untersuchungen – Rili-BÄK. *Dtsch Arztebl International*. 2019;116(51-52):2422. doi: 10.3238/arztebl.2019.rili_baek_QS_Labor20192312

⁶⁷<https://www.law.cornell.edu/cfr/text/42/part-493> (Accessed 27 March 2021)

⁶⁸Klonoff DC, Lias C, Vigersky R, Clarke W, Parkes JL, Sacks DB, Kirkman MS, Kovatchev B; ErrorGrid Panel. The surveillance error grid. *J Diabetes Sci Technol*. 2014 Jul;8(4):658-72.

7.1.3.2. Clinical impact on the individual and the healthcare system

Although individual measurement errors may have a relevant clinical impact on a specific therapeutic decision, this might not represent the overall impact of the SMBG's level of accuracy (or inaccuracy) on long-term therapy management.

Simulation studies have been performed in the past to assess the long-term impact of SMBG accuracy.^{69,70} As expected, the level of accuracy impacted clinical outcomes. In case of negative bias (systematic measurement difference), glycated haemoglobin (HbA1c) readings tended to increase, whereas positive bias was associated with lower HbA1c readings and increased risk for severe hypoglycaemia. Higher levels of imprecision also tended to increase risk for severe hypoglycaemia. This decrease in quality of glucose control was associated with higher healthcare costs.

For CGMs, the same relationship can be expected, although it has not been studied in such detail. For example, considerable systematic differences were found between systems in the low glucose concentration range,⁷¹ and therapeutic parameters derived from CGMs were found to differ in head-to-head settings.^{72,73}

Although SMBGs sold in Europe or the US should provide sufficiently accurate results, this is not always the case.^{74,75} Therefore, the lack of analytical accuracy likely still has a relevant impact on healthcare costs. Whether the additional financial burden will outweigh any potential price difference between insufficiently and sufficiently accurate SMBGs would have to be assessed separately for different countries. According to anecdotal reports, newer-generation SMBGs are sold in LMICs only after considerable delay, and third-party strips with questionable accuracy might be more prevalent there. If these reports were confirmed to be true on a relevant scale, additional efforts would likely have to be made to ensure access to an adequate level of diabetes therapy.

7.1.3.3. Impact of changing clinical guidelines

A current concern of experts has the potential to ultimately impact management of diabetes in LMICs. HbA1c is seen as the gold standard with regards to monitoring the treatment regimen of people with diabetes. Limitations of this measure are that it provides an average of blood glucose levels over a period of a few months with the argument being that an individual with periods of high and low blood glucose levels may have an average that is similar to someone who has a more constant level. In the last three to four years, with new CGMs coming to market, the concept of “time in range” has gained traction. This concept looks at the time the individual spends below or above a given range of blood glucose levels. These have been defined as 70–180 mg/dL (3.9–10.0 mmol/L) for individuals with type 1 diabetes and 63–140 mg/dL (3.5– 7.8 mmol/L) for people with type 2 diabetes.

⁶⁹Campos-Nanez E, Fortwaengler K, Breton MD. Clinical Impact of Blood Glucose Monitoring Accuracy: An In-Silico Study. *J Diabetes Sci Technol*. 2017;11(6):1187-95. Epub 2017/06/02. doi: 10.1177/1932296817710474

⁷⁰Fortwaengler K, Campos-Nanez E, Parkin CG, Breton MD. The Financial Impact of Inaccurate Blood Glucose Monitoring Systems. *J Diabetes Sci Technol*. 2018;12(2):318-24. doi: 10.1177/1932296817731423

⁷¹Fokkert MJ, van Dijk PR, Edens MA, Abbes S, de Jong D, Slingerland RJ, et al. Performance of the FreeStyle Libre Flash glucose monitoring system in patients with type 1 and 2 diabetes mellitus. *BMJ open diabetes research & care*. 2017;5(1):e000320. Epub 2017/03/01. doi: 10.1136/bmjdr-2016-000320

⁷²Michalak A, Pagacz K, Mlynarski W, Szadkowska A, Fendler W. Discrepancies between methods of continuous glucose monitoring in key metrics of glucose control in children with type 1 diabetes. *Pediatr Diabetes*. 2019;20(5):604-12. doi: 10.1111/peidi.12854

⁷³Freckmann G, Pleus S, Schauer S, Link M, Jendrike N, Waldenmaier D, et al. Choice of Continuous Glucose Monitoring Systems May Affect Metrics: Clinically Relevant Differences in Times in Ranges. *Exp Clin Endocrinol Diabetes*. 2021. Epub 2021/01/30. doi: 10.1055/a-1347-2550

⁷⁴Pleus S, Baumstark A, Jendrike N, Mende J, Link M, Zschornack E, et al. System accuracy evaluation of 18 CE-marked current-generation blood glucose monitoring systems based on EN ISO 15197:2015. *BMJ open diabetes research & care*. 2020;8(1). doi: 10.1136/bmjdr-2019-001067

⁷⁵Klonoff DC, Parkes JL, Kovatchev BP, Kerr D, Bevier WC, Brazg RL, et al. Investigation of the Accuracy of 18 Marketed Blood Glucose Monitors. *Diabetes Care*. 2018;41(8):1681-8. Epub 2018/06/15. doi: 10.2337/dc17-1960

With the use of this metric gaining prominence in the scientific literature, the concern is that only continuous monitoring tools can measure time in range and that this will have an impact on the use of blood glucose meters which only provide a snapshot of blood glucose levels. This is of importance in clinical practice, especially in countries where the price of CGMs is prohibitive. With EU regulation requiring evidence of state of the art in medicine for CE marking, SMBGs may potentially no longer qualify as a state-of-the-art method for self-monitoring. For the many countries that accept CE marking as the main regulatory reliance mechanism, this could potentially result in a lack of supply. Beyond this potential impact on the market, some would argue more is needed with regards to the impact both on the individual and the provider side of having 24 hours/day 365 days/year of information to manage, analyse and act upon. The psychological impact of this burden needs to be considered in the manufacturer's risk benefit analysis. This complex situation provides a ripe environment for innovation and invention. As with many non-communicable diseases, the tsunami is silently arriving and gathering force, and time is of the essence to provide alternative, affordable and quality solutions.

7.1.4. Adverse event reporting

People with diabetes using self-monitoring devices should be encouraged to report problems not only to their source of strips or sensors (e.g., product distributors), but also to the regulatory authorities. There is a lack of knowledge of both the availability and the utility of this feedback mechanism. Device labelling should always make the user aware of their right to report. In addition, databases held by regulators should be easy to access and should provide useful information relating to performance problems. The FDA's MAUDE database and TPLC searches are considered good examples.

In addition, requirements within regulation, as are being introduced in the EU Regulations, should enhance legal responsibilities of importers, suppliers and distributors to report problems back to the manufacturer and to cooperate with enquiries relating to product safety and performance to the regulatory authorities.

7.1.5. Substandard and falsified devices

Under-reporting of adverse events is always a challenge to understanding the real safety profile of a medical device. This is a problem in high-income countries, but very little is known of the quality of self-monitoring devices in LMICs. Many LMICs do not have strong regulation of devices and little capacity to act in the post-marketing setting, even if they are using reliance mechanisms for pre-market. As such, they are highly vulnerable to receiving substandard products. Furthermore, there are a number of technical specificities associated with reporting adverse events in LMICs that make under-reporting an even greater issue. These include how and to whom to report, and using what means, e.g., mobile phone or app, to a general physician or to a hospital or to the regulator. Language also becomes a problem with reporting, with most manufacturer lead-reporting mechanisms only being suitable for English.

As noted earlier, counterfeit and substandard devices are a grave concern in all jurisdictions. Regardless of the stringency of regulatory oversight, criminal activity will endure. Anecdotally, lot/batch dumping by manufacturers of strips that do not meet the performance standards expected for sale in well-regulated settings has been reported. It is hoped that the prevalence is significantly curbed with current regulatory measures to ensure greater traceability and transparency such as the introduction of the UDI. In the meantime, a study is urgently warranted to understand in some manner the extent of substandard and falsified product in the market in LMICs.

7.1.6. Specific requirements in LMICs

Self-monitoring of blood glucose in LMICs may be associated with additional requirements for validation of SMBG or CGMs. Many SMBG and CGMs are geared towards use in the market for which they were developed, e.g., Europe or the US, with distinct purchasing power, and specificities in climate, nutrition, co-morbidities and level of user education, etc.

Test strip shelf-life, as well as measurement performance, are typically affected by both high and low temperatures as well as relative humidity. Storage of reagents (e.g., test strips) at room temperature is easier in temperate climates or if air conditioning is available, whereas dry storage might be a challenge in the tropics. Performing control solution tests may indicate whether the specific test strip lot is still viable. However, at least in the US and EU, control solution tests are rarely performed.⁷⁶

Manufacturers of SMBGs and CGMs must undertake interference testing according to both ISO 15197 and FDA's OTC guidance using a risk-based approach. This testing investigates whether the accuracy of the test is influenced by interfering factors, that is, chemicals or proteins that may impact test performance. The base list of substances in these guidances does not cover a number of important potential factors to be considered when the product is used outside of a high-income setting. For instance, the potential interfering impact of antiretroviral or antimalarial medication should be tested where the strips are intended for Africa. The decision is left to manufacturers to test for relevant additional medication.

A potential issue in LMICs can be literacy. If measurements are intended to be performed by individuals with diabetes themselves, the complexity of instructions for use should be geared specifically to the intended users. Specific or extensive training and education in the use of SMBG and CGMs might be a helpful approach, as well as redesign of instructions for use, or the creation of job aids, all undertaken under the control of the manufacturer.

Another approach to monitor and assure quality is through the organisation of a centralised lot release scheme at the medical goods storehouse. In situations where the level of infrastructure available at the specific testing site might prohibit the use of a large laboratory analyser, smaller bench-top analysers or even high-quality hand-held over the counter or point-of-care blood glucose meters might provide sufficiently reliable results, or samples might be processed on-site but then shipped for centralised measurement.⁷⁷

It seems pragmatic to use a risk-based approach for individual countries or regions to identify shortcomings of current standards that are relevant for the specific country or region. Such efforts could be made internationally since some overlap can be expected.

7.2. SMBGs

7.2.1. Adjusted protocols

As described above, the comprehensive pre-marketing evaluations as described by ISO 15197 or the FDA guidance should be complemented by regular post-marketing evaluations to ensure continued quality of SMBGs. Furthermore, reporting of all measured values, as intended by FDA guidance, could be beneficial for making an informed decision during approval of SMBGs. There is value if the performance is verified by an independent laboratory using protocols established by subject matter experts. The need for this is highlighted by the practice of some manufacturers to compare capillary SMBG results with those from venous comparison samples. This practice can lead to deviations independent from the quality of the assessed SMBG.^{78,79} Accuracy studies should focus on like-with-like comparisons. If the system is intended to be used with capillary samples, the comparison samples should also be capillary blood.

⁷⁶Heinemann L. Control Solutions for Blood Glucose Meters: A Neglected Opportunity for Reliable Measurements? *J Diabetes Sci Technol.* 2015;9(4):723-4. doi: 10.1177/1932296815587602

⁷⁷Pleus S, Freckmann G, Baumstark A, Haug C. Stability of Glucose Concentrations in Frozen Plasma. *J Diabetes Sci Technol.* 2020;1932296820963657. doi: 10.1177/1932296820963657

⁷⁸Choukem SP, Sih C, Nebongo D, Tientcheu P, Kengne AP. Accuracy and precision of four main glucometers used in a Sub-Saharan African Country: a cross-sectional study. *The Pan African medical journal.* 2019;32:118. doi: 10.11604/pamj.2019.32.118.15553

⁷⁹Freckmann G, Pleus S, Baumstark A. Comment on "accuracy and precision of four main glucometers used in a sub-Saharan African country: a cross-sectional study" by Choukem et al. *The Pan African medical journal.* 2019;33:271. doi: 10.11604/pamj.2019.33.271.19704

Independent performance evaluations do not necessarily have to implement the complete ISO 15197 or FDA OTC protocols, but could instead use reduced-scale protocols focusing on the most relevant performance metrics. For example, a system accuracy evaluation in which at least duplicate measurements are performed from subject samples would simultaneously allow for estimation of precision based on variability within the replicates across subjects. With higher numbers of replicates, this estimate could be improved. Two or more independent lots of devices should be used in such a study.

Hematocrit influence could be estimated as well, at least for the range spanned by the subject samples. This estimate could be based on a regression line, or hematocrit values could be categorised, and average values could be calculated for each category. If the numbers of samples in specific glucose concentration categories were pre-defined at least for the majority of samples, this could help make performance assessments easier to compare, especially if SMBGs exhibit concentration-dependent performance.

Reduced-scale protocols certainly do not allow drawing conclusions with the same level of statistical confidence as the full-scale protocols,⁸⁰ because the number of independent samples is reduced. Nevertheless, such evaluations could allow conclusions to be drawn regarding changes in accuracy from one evaluation to the next, so that the effort associated with performing full-scale protocols would not be required for release of every reagent lot.

A reduced-scale standardised protocol could also help countries in performance evaluation of tender bidders, when making large-scale tender purchase decision.

7.3. CGMs

7.3.1. Metrological traceability

Neither POCT05 nor the FDA CGM special controls adequately address metrological traceability. Establishing metrological traceability for CGMs, at least in the conventional sense as per ISO 17511, is currently impossible, because interstitial fluid, where CGMs measure glucose concentrations, cannot be obtained in sufficiently large volumes over a sufficiently short time. Furthermore, no reference methods, i.e., methods of highest metrological order, are currently available for interstitial fluid.⁸¹

Most CGMs are intended to supplement or replace conventional SMBG in home use by people with diabetes. Comparing CGM measurement results with SMBG measurement results might be an adequate way forward until other methods become available. Due to physiologic differences in interstitial and capillary blood glucose concentrations, many CGMs use algorithms to model, and correct for, these differences so that capillary glucose concentrations are approximated. This results in such CGMs displaying glucose values that are neither directly comparable to interstitial nor capillary glucose concentrations.

As long as manufacturers clearly indicate how measurement signals are converted to CGM values, a basic level of traceability could be established, even if this resulted in comparably high levels of uncertainty.⁸²

⁸⁰Klonoff DC, Lias C, Beck S, Parkes JL, Kovatchev B, Vigersky RA, et al. Development of the Diabetes Technology Society Blood Glucose Monitor System Surveillance Protocol. *J Diabetes Sci Technol*. 2016;10(3):697-707. doi: 10.1177/1932296815614587

⁸¹Joint Committee for Traceability in Laboratory Medicine. Database of higher-order reference materials, measurement methods/procedures and services 2015 [accessed 11-Mar-2021]. Available from: http://www.bipm.org/jctlm/viewResults.do?type=isRMP&searchString=Glucose&searchStringIUPAC=&searchStringMined=&analyteCategory=&matrixCategory=&uniqueNominationNumber=&sortBy=Analyte_Name&status=P&id=C3RMMPI9*1*10&id=NRMeth+4*2*10&x=22&y=9

⁸²Freckmann G, Nichols JH, Hinzmann R, Klonoff DC, Ju Y, Diem P, et al. Standardization process of continuous glucose monitoring: Traceability and performance. *Clinica chimica acta; international journal of clinical chemistry*. 2021;515:5-12. doi: 10.1016/j.cca.2020.12.025

7.3.2. Study procedures

As described earlier, study procedures can impact performance metrics like MARD.^{83,84,85} By stipulating detailed requirements for study procedures, this effect could be mitigated to some degree. For example, the time delay between changes in interstitial and capillary glucose concentrations is more pronounced when glucose concentrations are rapidly changing. Insulin-treated people with diabetes tend to exhibit larger glucose variability than people with diabetes who are not on insulin therapy. Participants in clinical studies should include the intended use population, and if substantial differences in the performance are expected, subgroups should be sufficiently large to be analysed separately.

7.3.3. Other requirements

Quality assurance in general might be a bigger issue with CGMs than with SMBGs. Whereas SMBGs are IVDs, measuring samples outside of the body, CGMs measure glucose concentrations in vivo. Traditional quality assurance schemes by users are therefore not applicable; sensors of CGMs cannot be removed from the body for control measurements and then reinserted. Still, quality assurance by the user would be beneficial since it would reflect performance under actual use conditions.

⁸³Kirchsteiger et al. Performance Comparison of CGM Systems: MARD Values Are Not Always a Reliable Indicator of CGM System Accuracy. *J Diabetes Sci Technol*. 2015 Sep 1;9(5):1030-40.

⁸⁴Reiterer et al Significance and Reliability of MARD for the Accuracy of CGM Systems *J of Diabetes Sci Technol*. 2017, Vol. 11(1) 59-67

⁸⁵Heinemann *et al*. Benefits and Limitations of MARD as a Performance Parameter for Continuous Glucose Monitoring in the Interstitial Space. *J Diabetes Sci Technol*. 2020 Jan;14(1):135-150

8. RECOMMENDATIONS

This section will take the analysis of current practices and make recommendations that may assist manufacturers and assessment bodies in ensuring that the SMBGs and CGMs are fit for purpose. It is hoped that these findings will assist regulators and others involved in the evaluation of these devices. The evolving regulatory landscape, not only in LMICs but also in Europe, provides an opportunity to highlight the issues impacting on performance and provides solutions for their mitigation.

Recommendations:

8.1. Effective implementation of regulations

The majority of regulatory agencies globally use reliance mechanisms based on CE marking and/or FDA approval to allow market access of SMBGs and CMGs. Thus, it is critical that the assessment that results in a CE mark or a 510 (k) approval is based on application of appropriate standards by manufacturers and pre-market assessment by those with an in-depth understanding of the science behind the devices. The standards that are recognised for the purposes of demonstrating conformity to the performance requirements of the regulation must have international consensus as being the most appropriate for these devices. The manufacturer must comprehensively demonstrate conformity to these standards, and the CAB must ensure that those assessing the technical and clinical evidence are competent for this task. (Refer to IMDRF “Competence and Training Requirements for Regulatory Authority Assessors of Conformity Assessment Bodies Conducting Medical Device Regulatory Reviews” IMDRF/GRRP WG/N63FINAL:2020). The requirements for competence of notified body assessors should, according to the new regulations in the EU, mitigate problems identified under the Directives that resulted in CE certificates issued without sufficient evidence that the device would perform as intended.

Achieving consistency with the validation of these important devices requires agreement regarding the pre-analytical, analytical, clinical and user assessments that should be undertaken by the manufacturer. Greater harmonisation of guidance (for instance with the requirements of ISO and FDA guidance) can achieve this. Further consistency could be achieved if an international standard is created for CGMs that is then recognised by all jurisdictions. In addition, requirements for reporting of verification and validation studies could be harmonised internationally to enable ready comparison of data from different sources.

In the absence of any mandatory inspection activities carried out for an FDA issued 510 (k) notification, further post-marketing reporting mechanisms, such as those required for the IVDR and MDR in the EU, may strengthen confidence in devices where market access relies on US FDA authorisation.

8.2. Enhanced post-market activities by manufacturers

Manufacturers of SMBGs should enrol their device in appropriate External Quality Assessment Schemes, even if these schemes are provided for laboratory-based devices. The results should form part of their post-market performance surveillance and of any updates to the clinical performance report.

8.3. Understanding the critical impact of temperature and humidity on performance of SMBG strips

The critical negative influence of factors including humidity and temperature means that, for SMBG strips, manufacturers selling in countries with extremes of these environmental factors should ensure that the strips have been designed to be robust in extreme conditions. Warnings relating to storage conditions should be apparent.

The CAB assessing stability must understand the importance of appropriately designed stability studies, including transport stability. WHO guidance, EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION *Technical Guidance Series for WHO prequalification of in vitro diagnostic medical devices Establishing stability of in vitro diagnostic medical devices–TGS-2 and Annex to TGS 2 Establishing component stability for in vitro diagnostic medical devices* can be considered best practice for this purpose.

8.4. LMICs activities in the absence of strong in-country regulation

For many LMICs, a lack of a strong regulatory agency poses a high level of risk of substandard devices being made available. However, there are a number of ways that LMICs can ameliorate that risk.

8.4.1. Survey of quality of self-management devices on the LMIC market

Although it is assumed that the lack of strong regulation in many LMICs will mean that a proportion of devices for self-management of diabetes currently on these markets may be substandard, it is important that empirical evidence of this is sought. The size and nature of the problem needs to be understood before effective countermeasures can be put in place.

8.4.2. Recognition and Reliance

Where there is a legal framework, LMICs should ensure that there is the possibility to recognise and leverage the efforts of mature regulatory agencies. It is highly recommended that devices for self-management of diabetes be either CE marked or have FDA authorisation. Consideration can be given to decisions of other regulatory agencies; however, a comprehensive understanding of the decision-making process by the agency should be made beforehand to understand the extent, if any, of pre-market assessment and requirements for these devices. Once WHO Prequalification of SMBGs commences, recognition of the assessments carried out by this body should also be added as an alternative requirement.

8.4.3. Pre-distribution QC activities

In LMICs, the majority of medical products for use via the public sector come into the country and are placed in a central medical store (CMS) before further distribution. At this point, lot verification activities should be encouraged for SMBG strips. The CMS would require a point of care instrument capable of measuring glucose with a high level of accuracy. Such instruments can be identified through results in External Quality Assessment Schemes and through the peer-reviewed scientific literature. This would be deployed to prepare and quantitate glucose in fresh blood samples for testing new batches of SMBG strips. Development of a standardised lot verification protocol that can be implemented easily at the country level would be beneficial.

8.4.4. Assuring temperature-controlled supply of SMBG strips

Taking into account the labile nature of SMBG strips, all efforts should be made to ensure that the strips are stored properly, according to the conditions noted on the labels. This requirement will not be unique to SMBG components, as many rapid tests supplied to LMICs have similar issues, relying on maintenance of cold room storage to ensure adequate performance. All stakeholders in the supply chain, and the end user, need to be aware of the importance of this.

8.5. UDI and Increased stakeholder awareness

Implementation of the UDI by regulatory authorities will result in significant benefits for all stakeholders as it becomes a requirement in an increasing number of jurisdictions. For people living with diabetes, they will be able to access more information regarding their device. UDI assists in understanding the provenance of a device, providing a strong mechanism to ensure a device is from the manufacturer on the label. For distributors, the ability to electronically scan labels and devices provides a powerful tool to efficiently manage inventory, reduce manual errors and improve better delivery. For the manufacturer, benefits include better traceability and efficiency in recalls and improved quality of information through the use of a standardised data model across the industry. For the regulator, the benefits are similar to that for industry.

8.6. Enhancing awareness of regulatory support in people living with diabetes

The importance of reporting problems in device performance to the regulator is often underestimated or even not known by end users. It is important that people living with diabetes are aware that they can report any concerns regarding the safety or performance of their self-monitoring device to both the manufacturer and the regulator. Regulatory bodies rely on passive reporting of problems in the market. For these agencies, it is important that problems are reported as these are used by the regulator to identify issues which might not have been previously known about. The regulator then reviews the issue and, if necessary, can take action to minimise risk and maximise benefit to patients. Even lack of clarity of the instructions for use is an issue that requires reporting. This can be a significant issue in countries where translations of original instructions are required.

8.7. Reference Institutions

The establishment of national or supranational reference institutions with competence to assess devices for self-monitoring would be helpful to ensure sustained quality of SMBGs or CGMs^{86,87}. It is likely that certain laboratories will be chosen to support WHO Prequalification, via a comprehensive assessment of the laboratory's ability to undertake specific reference activities in this area. The establishment of WHO collaboration centres for devices used with diabetes may be one avenue that would attract the necessary support to sustain such centres of excellence. Regulatory authorities can also create formal ties with such institutions.

⁸⁶Heinemann L, Freckmann G, Koschinsky T. Considerations for an Institution for Evaluation of Diabetes Technology Devices to Improve Their Quality in the European Union. *J Diabetes Sci Technol*. 2013;7(2):542-7

⁸⁷Freckmann G, Pleus S, Heinemann L, Koschinsky T. Regulatorische Defizite bei Medizinprodukten. *Der Diabetologe*. 2016;12(8):558-65. Epub 2016/11/28. doi: 10.1007/s11428-016-0158-6

9. APPENDIX 1. REGULATION OF DEVICES BY THE UNITED STATES OF AMERICA FOOD AND DRUG ADMINISTRATION

9.1. Overview of regulation of devices within FDA

Within the FDA, medical devices are regulated under the same regulatory schemes as IVDs. There are two centres for evaluation of medical devices: the Centre for Biological Evaluation and Research (CBER); and the Center for Devices and Radiological Health (CDRH). CBER is the centre within FDA that regulates biological products for human use and devices used for blood screening and associated activities are assessed in this branch. The majority of devices fall under the auspices of CDRH, responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the US.

Medical devices in the US are classified into Class I, II, and III. Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type. Most Class I devices are exempt from Pre-market Notification 510(k); most Class II devices require Pre-market Notification 510(k); and most Class III devices require Pre-market Approval.

The basic regulatory requirements that manufacturers of medical devices distributed in the U.S. must comply with are:

- Establishment registration
- Medical Device Listing
- Pre-market Notification 510(k), unless exempt, or Pre-market Approval (PMA)
- Investigational Device Exemption (IDE) for clinical studies
- Quality System (QS) regulation
- Labeling requirements
- Medical Device Reporting (MDR)

9.1.1. Pre-market notification 510(k)

Most devices that are regulated in the USA are subject to a 510(k) pre-market submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, by proving to be substantially equivalent to a legally marketed device. Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalence claims. The legally marketed device(s) to which equivalence is drawn is commonly known as the "predicate." Although devices recently cleared under 510(k) are often selected as the predicate to which equivalence is claimed, any legally marketed device may be used as a predicate.

A device is substantially equivalent if, in comparison to a predicate it:

- has the same intended use as the predicate; and
- has the same technological characteristics as the predicate; or has the same intended use as the predicate; and
- has different technological characteristics and does not raise different questions of safety and effectiveness; and
- the information submitted to FDA demonstrates that the device is as safe and effective as the legally marketed device.⁸⁸

If novel features of the device determine that substantial equivalence cannot be demonstrated, then the device will require a different pre-market pathway such as the *de novo* pathway.

9.1.1.1. Requirements for 510 (k)

Compliance with 21 CFR 820 is required for Class II devices in the US. However, the FDA does not usually undertake an on-sight audit to confirm compliance at time of application. Instead, the

⁸⁸ <https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k> (Sourced 06 Jan 2021)

manufacturer submits evidence of a compliant quality system. This may include an ISO 13485:2016 certificate or a Medical Device Single Audit Program (MDSAP)⁸⁹ certificate as evidence of compliance. This certificate must be submitted with a 510(k) application.

There are currently several pathways available for devices that require a 510(k) clearance, including a traditional 510(k) pathway or an abbreviated pathway. The Abbreviated 510(k) Program uses guidance documents, special controls, and/or voluntary consensus standards to facilitate FDA’s pre-market review of 510(k) submissions. FDA believes that its review of abbreviated 510(k)s may be more efficient than that of traditional 510(k) submissions. This pathway provides an option of facilitated review of 510(k)s through a reliance on “summary reports” that briefly describe and summarise the testing performed to support the submission as recommended in relevant guidance document(s).⁹⁰

Devices that have 510(k) clearance are, in general, obliged to have applied the unique device identifier (UDI) labelling to the product.

9.2. FDA regulation overview of SMBGs

From a search of relevant data bases, the following FDA details will apply to self-testing blood glucose monitoring systems and their components:

| | |
|--------------------------------|---|
| Regulation Number | CFR 862.1345 Glucose test system “Identification. A glucose test system is a device intended to measure glucose quantitatively in blood and other body fluids. Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia, and idiopathic hypoglycemia, and of pancreatic islet cell carcinoma.” |
| Device | Blood Glucose |
| Regulation Description | Clinical Chemistry |
| Product Codes | NBW: System, Test, Blood Glucose, Over The Counter LFR: Glucose Dehydrogenase, Glucose CFR: Hexokinase, Glucose CGA: Glucose Oxidase, Glucose |
| CPT Code (For CLIA Waiver) | 82962 “Blood glucose by glucose monitoring devices cleared by the FDA for home use.” |
| Pre-market Review | Office of In Vitro Diagnostics and Radiological Health |
| Submission Type | 510(k) |
| Classification | Class II |
| GMP Exempt? | No |
| Recognised Consensus Standards | 7-284 CLSI EP37 1st Edition “Supplemental Tables for Interference Testing in Clinical Chemistry” 7-301 CLSI GP42 7th Edition “Collection of Capillary Blood Specimens” 13-88 IEEE ISO 11073-10417 Third edition 2017-04 “Health informatics - Personal health device communication - Part 10417: Device specialization - Glucose meter” |

⁸⁹ <https://www.fda.gov/medical-devices/cdrh-international-programs/medical-device-single-audit-program-mdsap> (Sourced 22 Feb 2021)

⁹⁰ *The Abbreviated 510(k) Program Guidance for Industry and Food and Drug Administration Staff* Issued 13/09/2019.

13-90 IEEE Std_11073-10417-2015
"Health Informatics - Personal Health Device Communication, Part
10417: Device Specialization - Glucose Meter"
7-284 CLSI EP37 1st Edition
"Supplemental Tables for Interference Testing in Clinical Chemistry"
7-301 CLSI GP42 7th Edition
"Collection of Capillary Blood Specimens"
13-88 IEEE ISO 11073-10417 Third edition 2017-04
"Health informatics - Personal health device communication - Part
10417: Device specialization - Glucose meter"
13-90 IEEE Std_11073-10417-2015
"Health Informatics - Personal Health Device Communication, Part
10417: Device Specialization - Glucose Meter"

9.2.1. Regulatory requirements – general controls for Class II devices

Class II devices are subject to the following regulatory requirements known as "General Controls", including but not limited to those governing:

- Adulteration/Misbranding
- Electronic Establishment Registration
- Electronic Device Listing
- Pre-market Notification [510(k)]
- Quality Systems, including design control
- Labeling, and
- Medical Device Reporting (MDR).

Although not included as a consensus standard, the FDA guidance *Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use Sept 2020* provides a detailed description of FDA's expectations for a manufacturer's design verification procedures and the validation of performance by the intended users.

9.3. FDA regulation of Continuous Glucose Monitoring Systems (CGMs)

CGMs usually consist of a glucose sensor, a transmitter, and a primary receiver. The device contains software to calculate glucose values. Until 2018, CGMs were classified at the highest risk class, Class III. Class III devices require the highest level of pre-market oversight by the FDA: a Pre-market Approval (PMA). The first FDA approved its first CGM—the Minimed Continuous Glucose Monitoring System—in 2000. In the intervening years, not only was more experience gained with these devices, but the devices themselves evolved to a point where the mix of both known risk profile and better design resulted in the down-classification of the devices to a Class II in 2018 with a fifth-generation CGM. These fifth-generation systems are factory calibrated and no longer require user calibrations, whereby self-monitoring of blood glucose fingerstick values via a home blood glucose meter is required to correlate the sensor signal with a patient's blood glucose value. **Note: some CGMs may, due to specific attributes, fall into the higher risk class, Class III.**

Unlike SMBGs that can be sold in the US over the counter, these products are only available by prescription.

9.3.1. FDA Regulation Overview of CGMs

The following applies to CGM systems for the US FDA:

| | |
|----------------------|--|
| Regulation Number | 862.1355 |
| Device | Integrated Continuous Glucose Monitoring System, Factory Calibrated |
| Definition | An integrated continuous glucose monitoring system (iCGM) is intended to automatically measure glucose in bodily fluids continuously or frequently for a specified period. iCGM systems are designed to reliably and securely transmit glucose measurement data to digitally connected devices, including automated insulin dosing systems, and are intended to be used alone or in conjunction with these digitally connected medical devices for the purpose of managing a disease or condition related to glycemic control. |
| Physical State | Glucose sensor, a transmitter, and a primary receiver. The device contains software to calculate glucose values. |
| Technical Method | A transcutaneous glucose sensor that is factory calibrated. The sensor is inserted at home by the end user and is used in conjunction with the associated transmitter and receiver to monitor glucose levels for the management of diabetes. |
| Product Code | QBJ QLG |
| Pre-market Review | Office of In Vitro Diagnostics and Radiological Health (OIR) |
| Submission Type | 510(k) |
| Device Class | II with Special controls |
| GMP Exempt? | No |
| Recognised standards | <p>7-209 CLSI POCT05-A* (Replaces POCT05-P) Performance Metrics for Continuous Interstitial Glucose Monitoring; Approved Guideline.</p> <p>13-72 IEEE Std 11073-10425-2014 Health informatics - Personal health device communication, Part 10425: Device Specialization - Continuous Glucose Monitor (CGM)</p> <p>13-88 IEEE ISO 11073-10417 Third edition 2017-04 Health informatics - Personal health device communication - Part 10417: Device specialization - Glucose meter</p> <p>13-90 IEEE Std 11073-10417-2015 Health Informatics - Personal Health Device Communication, Part 10417: Device Specialization - Glucose Meter</p> |
| consensus | |

*** NOTE: The latest version of this CLSI standard was published in November 2020. It is not yet recognised as a consensus standard.**

Of interest, even though the sensor would be considered by GHTF/IMDRF definitions as a medical device, for the FDA this type of device is only considered an implantable device if it rests in the body for 30 days or more. If not considered implantable, it is assessed by the Office of In Vitro Diagnostics and Radiological Health (OIR) and reviewed by the clinical chemistry section of this office. Despite this, the assessment applied recognises the essential principles that are applied to implantable devices.

9.3.2. Regulatory Requirements

The general regulatory requirements for Class II devices noted above for SMBGs apply equally to CGMs. However, CGM systems bring new risks that require evidence of mitigation.

A letter from the FDA to an applicant making the first application to the agency of a fifth-generation CGM system, lists the controls to be applied to successfully be approved by the FDA⁹¹.

⁹¹ https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170088.pdf Sourced 10 February 2021

10. APPENDIX 2. REGULATION OF DEVICES IN THE EU

10.1. The regulatory framework in the EU

In comparison with the FDA, where the efforts of the regulatory approval system are placed on efficacy of a device compared to a predicate, the EU regulatory framework for all medical devices (including IVDs) places an emphasis on whether a device can safely perform its intended function and whether it is considered state-of-the-art. Also, the regulatory framework is applied in other ways.

The EU regulatory frameworks for medical devices and IVDs aim to provide a more agile mechanism for pre-market approval, by use of designated certification bodies that are responsible for pre-market assessment. These bodies are referred to as “notified bodies”. They are private entities, but designation as such occurs under the control of the European Commission. A manufacturer directly engages the notified body of choice. As these bodies are for-profit, fee for service is paid.

Following approval by a notified body, the manufacturer may apply the CE mark to their product. The efforts of the competent authority (government regulatory agency in each Member State) are in the designation of the notified bodies and for market vigilance. Each competent authority can also issue derogations from aspects of the regulations in the case of a public health emergency, as has happened with the COVID-19 pandemic.

Although this system of notified bodies has provided manufacturers with faster approval times, the lack of uniform assessment by the multiple notified bodies has resulted in a major shakeup to the regulation of devices in the EU. As such, at time of publication, the EU is currently transitioning from the IVD Directive 98/79/EEC (IVDD) to the IVD Regulation EC 2017/746 and the Medical Device Directive 93/42/EEC and the AIMD Directive 90/385/EEC to the single regulation for medical devices, EC 2017/745 (the MDR). In the period leading up to 26 May 2025, some devices can be legally on the market with a CE mark obtained under a directive or under a regulation. A major difference between directives and regulations in the EU is that directives were transposed into the law of each Member State. Transposition allows for interpretation on the intent of the directive. As such, some aspects of the EU Directives for devices were implemented in significantly different means by each Member State. The regulations in contrast, must be incorporated into Member State law in their entirety. This will enable greater consistency in implementation.

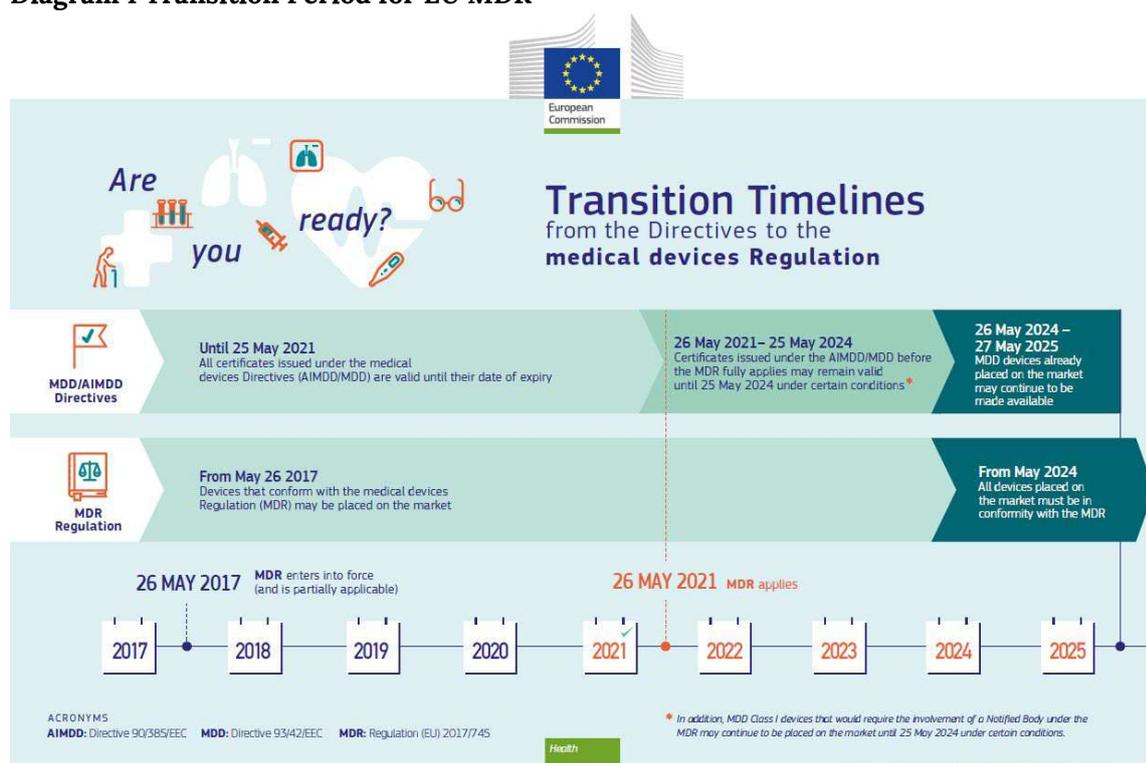
Another driver for changes to EU law was the variable quality of assessment from the notified bodies, the conformity assessment bodies for CE marking. To be designated as a notified body for the new regulations, there is much greater scrutiny by the designation authorities, including the European Commission, of the expertise and practices of these bodies. The goal is to ensure greater quality and consistency of the pre-market assessment by notified bodies.

Both the new regulations, the IVDR and the MDR, have been implemented to ensure a stronger emphasis on a life-cycle approach to safety, backed up by clinical data. Although the previous directives, the MDD and the AIMD, are not significantly different compared to the new regulation—the MDR brings more stringent requirements for the designation of Notified Bodies, with increased control and monitoring by the NRAs and the European Commission. As requirements under the regulations regarding the qualification of Notified Body assessment staff is greatly strengthened, there is the possibility that products assessed positively under the directives will not be considered “good enough” with a more informed and critical opinion of subject matter expert assessor. This enhanced oversight applies equally to the new IVDR.

Although the change from directives to regulations is an incremental change for medical devices, it is relatively an enormous change for IVDs. Approximately 85% of IVDs are self-declared by their manufacturer as meeting the requirements for CE marking under the IVDD. This figure will be the reverse under the IVDR, with most IVDs requiring a notified body pre-market assessment for CE marking.

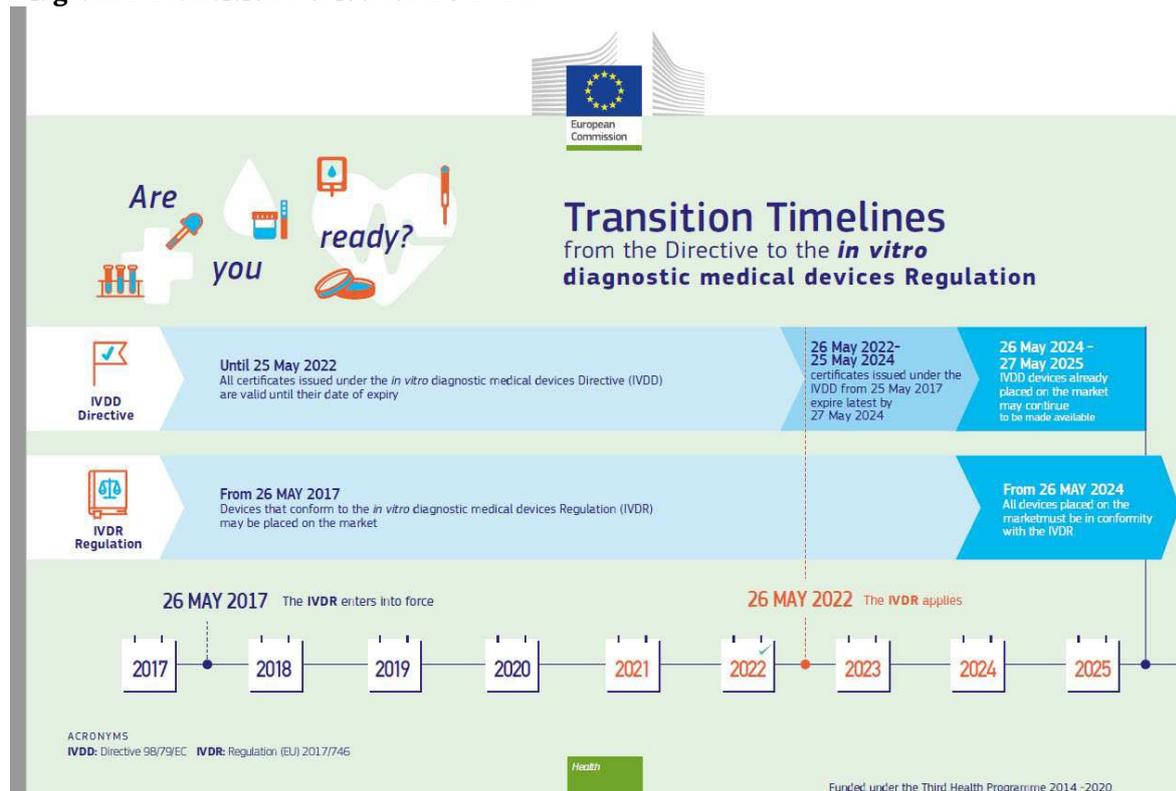
The diagrams below indicate the timelines for transitioning to the new regulations. The diagrams indicate that if a device has a certificate issued by a notified body under a relevant directive, the product may benefit from an extended transition period, provided the certificate has not expired. Regardless of the date of expiration, no product can be made available to the market after 26 May 2024, and, from 27 May 2025, all goods that are distributed to end users must comply with the new regulations. However, from 26 May 2022, all devices must meet the new, enhanced, post-market requirements of the regulations, even if they are CE marked according to the Directives. Of interest, although many IVDs do not have certificates issued by notified bodies according to the IVDD, those for self-tests do.

Diagram 1 Transition Period for EU MDR⁹²



⁹² https://ec.europa.eu/health/sites/health/files/md_newregulations/docs/timeline_mdr_en.pdf accessed 19 Jan 2021

Diagram 2 Transition Period for EU IVDR⁹³



As per the WHO regulatory framework, the GHTF guidance, and as per the FDA and the EU regulation of medical devices, albeit under the directives or the regulation, follows the basic principles of adapting pre- and post-market controls according to the risks that the devices poses. The MDD, AIMD and MDR recognise four risk classes of medical devices, from the lowest risk, Class I, with classes IIa, IIb and finally to the highest risk group, Class III. Under the directives, an analysis of products on the market by the European Network for Health Technology Assessment (EUnetHTA)⁹⁴ indicate that CGMs are often regulated under the MDD and not as active implantable medical devices under the AIMD, although it can be argued that sensors meet the definition of active implantable devices. From 26 May 2021, they will fall under the MDR. Use of international standards is endorsed in the regulations as effective mechanisms for demonstrating conformity.

The IVDR, in contrast, represents a major shift in identifying the risk class of IVDs. Under the IVDD, the risk class was pre-assigned, with two lists: a high-risk list known as List A of Annex II of the IVDD, of products used in screening of the blood supply, and a lower risk group, known as List B of Annex II of the IVDD, which includes SMBGs. All other IVDs, which according to recent analyses, accounts for approximately 90% of IVDs, only require self-declaration for CE marking. No notified body assessment pre-market is required to assign the CE mark. This has, as seen in the COVID-19 pandemic, been abused by often well-meaning manufacturers who have CE marked products that do not meet the requirements.

Regardless of the need (or not) for pre-market independent assessment, all IVDs under the IVDD must meet the basic Essential Principles of safety and performance described in Annex I of the IVDD, and any other EPs as described in this Annex. A quality system aligned with ISO 13485 will

⁹³ https://ec.europa.eu/health/sites/health/files/md_newregulations/docs/timeline_ivdr_en.pdf Accessed 19 January 2021

⁹⁴ Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ), Main Association of Austrian Social Security Institutions (HVB), The Norwegian Institute of Public Health (NIPHNO). *Continuous glucose monitoring (CGM real-time) and flash glucose monitoring (FGM) as personal, standalone systems in patients with diabetes mellitus treated with insulin*. Joint Assessment. Zagreb: EUnetHTA; 2018. Report No.: OTJA08.

meet the QMS requirements of the Directive. Certain technical documentation supporting the analytical performance of the device, and for SMBGs, its use in the hands of self-testers, must be kept on file and reviewed by the notified body. A notified body, when accepting an application for an SMBG will examine the design of the device and assess the design-related requirements of the directive. They will ensure that testing has been undertaken in the hands of lay users and is suitable and works for this testing group. They will also ensure that the information provided with the device on its label and its instructions for use. Under the IVDD, the notified body will also assess the impact of changes to the device on its conformity to the regulation. The CE mark is dependent on a positive assessment of conformity of the device and its manufacturing. Manufacturers often utilise relevant international standards to demonstrate conformity for the IVDD.

The IVDR and MDR thus represent a giant leap in regulatory requirements for many devices, including for those that have already undergone notified body scrutiny (i.e. those that are Class IIa, IIb or Class III medical devices, or are List A or B under Annex II of the Directive). Although there are many new requirements, few existing requirements have been removed.

The new regulations bring more stringent requirements for the designation of Notified Bodies, with increased control and monitoring by the national competent authorities and the European Commission. This means that the quality of pre-market assessment is expected to be much more thorough and accountable.

For many stakeholders, a significant achievement that the regulations bring is the enhanced traceability and effectiveness of post-market safety-related activities. This is aided by the requirements for a unique device identifier (UDI), that will track the manufacturer, the product and its manufacturing information, such as lot number. The information stored on this unique bar code is readable with scanners that most distributors of the product will hold, as well as the manufacturer and the regulatory agency. Of importance for devices for diabetes, this should act as a deterrent to counterfeiting. Transparency will also be increased because of the enhancements to the functions of the European Database for Medical Devices (Eudamed). More information on the market authorisation of devices as well as clinical studies will be made public. Manufacturers are responsible for entering the necessary data on Eudamed, which includes the UDI database, and for keeping it up to date. The notified body will check the veracity of the information provided.

Under the Regulations, every manufacturer must have a role within the business known as “the person responsible for regulatory compliance, or PRRC” (Article 15 IVDR, MDR). An abbreviated list of the duties of the PRRC includes:

- Check conformity of devices with QMS procedures before they are released
- Make sure all Technical Documentation and Declarations of Conformity are up to date
- Ensure all post-market surveillance and reporting obligations are met

As with the current Directives, manufacturers outside the EU/EEA shall have a contract with an authorised representative inside the EU. This role takes on legal liability for the product.

Manufacturers of some implantable devices will have to provide an implant card for the patient. The aim of introducing an IC has been to achieve three main objectives:

1. Enable the patient to identify the implanted devices and to get access to other information related to the implanted device (e.g., via Eudamed, and other websites).
2. Enable patients to identify themselves as persons requiring special care in relevant situations (e.g., security checks).
3. Enabling emergency clinical staff or first responders to be informed about special care/needs for relevant patients in case of emergency situations.

It is not clear at this point if this implant cards will be a requirement for CGMs.

The new regulations reinforce the requirements for clinical evaluation (Article 61 of the MDR) or, in the case of IVDR, performance evaluation (Article 56 of the IVDR). The notified body oversight of these requirements will be stringent and therefore this represents some of the biggest changes compared to the previous regimes. The shift in the MDR is that most implantable devices will now need to undergo clinical investigations. Frequently, the use of published experience gained with other equivalence devices, similar to the use of a predicate device in the US, was the major source of clinical evidence. This may no longer be sufficient.

For IVDs, under the IVDD it was important to demonstrate analytical performance, and for self-tests, testing in the hands of lay users. Under the IVDR, these requirements expand significantly. There must also be evidence of scientific validity, the GHTF termed adopted to indicate clinical association of the marker and the disease, i.e., glucose and diabetes. There must also be clinical evidence. Though this can be drawn from the literature, there is still the need to demonstrate performance in the hands of self-testers.

In the EU, certain international and other consensus standards are officially recognised as representing best practice and/or state of the art, and go through an official assessment process of harmonisation, whereby the content therein is mapped to the EU regulatory requirements. These standards become what is known as EN standards. For the various Directives, lists of harmonised standards are provided on the EC website^{95,96,97}. EN ISO 13485, for QMS and EN ISO 14179 for Risk Management of devices, are common horizontal standards applying to both medical device and IVD Directives. A well-known vertical standard for IVDs is EN ISO 15197:2015 *In vitro diagnostic test systems - Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus*. Most manufacturers with IVDD compliant, CE marked SMBGs will have utilised this standard to demonstrate performance in the hands of self-testers for their devices.

At the point of publication of this report, no standards have been recognised as harmonised for the MDR or the IVDR. Manufacturers must assess whether, in light of the other sources, such as the new FDA guidance on SMBGs, if EN ISO 15197 still represents state-of-the-art for their devices. Any solution to demonstrate conformity must be justified.

A significant part of the whole of lifecycle approach of the new regulations is the increase in requirements for manufacturers to ensure ongoing conformity in the post-market environment. Post-market surveillance mechanisms must include proactive measures. With IVDs that are self-tests, this is not simple. A manufacturer can include in their arrangements with distributors to receive regular updates on complaints or other feedback given to the final vendor by the purchasing diabetic. They can also ensure patients are encouraged to give feedback in any instructions provided with the strips. In contrast, the latest FDA guidance on SMBG's includes requirements for test strip lot release criteria and sampling plans for testing to be included in a 510(k) application. Regardless, despite the enhanced requirements in the EU, implementation of pro-active measures for self-tests will prove difficult. The regulations also require increased vigilance by regulators, enhanced follow-up by notified bodies to ensure post-market commitments are being implemented by the manufacturer, and greater communication between the regulators of the Member States.

Performance requirements are laid out in the Essential Requirements of the Directives and the General Safety and Performance Requirements of the Regulations. These requirements are always identified in Annex I of the laws, indicating their importance to the law. Both the directives and regulations describe the types of studies expected to be undertaken to demonstrate performance, but the new regulation takes the evaluation of the studies one step further. A manufacturer must demonstrate how the validated performance meets the clinical needs. To do this, study design

⁹⁵ https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/implantable-medical-devices_en Accessed 19 January 2021

⁹⁶ https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/iv-diagnostic-medical-devices_en Accessed 19 January 2021

⁹⁷ https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/medical-devices_en Accessed 19 January 2021

must include an assessment of how any acceptance criteria will lead to a clinically relevant result. The manufacturer must also justify why the results of the studies scientifically demonstrate that the intended clinical benefit or benefits and safety will be achieved, according to state-of-the-art in medicine. As such, greater justification for a test's performance is required. The enhanced post-market surveillance requirements are in place to ensure that the performance remains constant and is state of the art. Products without such evidence will lose their CE mark when re-assessed during ongoing surveillance audits by the notified bodies. These audits, scheduled annually, include at least one announced audit.

10.2. Regulation of Self-Monitoring Blood Glucose Test Systems (SMBGs) in the EU

The table below compares regulation of SMBGs under the IVDD and IVDR. For the EU regulations, the individual components of a system are considered separately. However, the performance evaluation made by the manufacturer, which is reviewed during notified body assessment of the strips, will include information on the performance of the glucose meter.

EU Product Regulation Overview_SMBGs

| Self-Monitoring Blood Glucose systems: Glucose Strip | IVDD | IVDR |
|--|--|---|
| Classification | Annex II List B | Class C (Annex VIII 2.3 Rule 3k98) |
| Conformity assessment with a notified body? | Yes | Yes |
| Conformity assessment route | Annex IV (full quality assurance) OR Annex V (EC type-examination) WITH: Annex VI (EC verification) OR Annex VII (production quality assurance). | Annex IX Conformity assessment based on QMS and assessment of technical documentation, OR Annex X Conformity assessment based on type Examination WITH Annex XI Conformity assessment based on production quality assurance |
| Notified body auditing of manufacturer's quality management system | Risk based approach over 5 year certification cycle. No mandatory requirements. | Annual review over the 5 year certification cycle including one unannounced on-site audit. |
| Post market requirements | Reactive post market surveillance | Reactive and pro-active post market surveillance, Submission of a yearly Post market surveillance update report to the notified body. |

The assessment of a SMBG by a notified body under the IVDD includes an assessment of the design, manufacture and performances of the system. This will include aspects affecting its suitability for non-professional users. As the UK was until 1 January 2021 an EU Member State, the MHRA published relevant guidance for the assessment of self-tests by a notified body⁹⁹. This clarified requirements to ensure that test reports provide sufficient data to support all performance claims. The guidance also highlighted the necessity to ensure that sample type noted in the labelling had been validated, as had acceptable usage ranges for environmental factors such as temperature and humidity; that the product was robust with respect to mechanical resistance; that the product had been subjected and proved safe with respect to aspects such as electrical and mechanical hazards; and that any associated software had been appropriately validated. The guidance also proposed that lay user studies would be performed for all self-test devices unless similarity to previous devices renders this unnecessary. If not included, the notified body should

⁹⁸ Devices are Class C if they are intended (k) for management of patients suffering from a life-threatening disease or condition.

⁹⁹Competent Authority (UK) Medicines and Healthcare products Regulatory Agency July 2012 "Guidance for notified bodies on the regulation of IVDs for self-testing" <https://www.fdanews.com/ext/resources/files/archives/0/07/07-16-12-IVD.pdf> Sourced 31 January 2021

critically assess the documented rationale for this decision. The guidance also stressed the importance of how and what information was included in the instructions for use. Although this guidance was created to support the assessment of all self-testing devices, it drew heavily on the requirements as described in the harmonised version of ISO 15197 *In vitro diagnostic test systems - Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus*. Thus, ISO standard 15197 forms a cornerstone of state of the art for compliance with EU requirements for SMBGs.

Under the IVDR, an application for a self-test must not be bundled with other IVDs, as is possible for Class C and B IVDs that are not for self-testing. A subject matter expert will assess the clinical and analytical performance of the system, another will assess the technology. Finally, a clinical opinion will be provided. Manufacturers of Class C IVDs must annually update the performance evaluation report that they have initially submitted to their notified body. The update must reflect the findings of the performance and safety of the device post-market, using both reactive and proactive surveillance methods. In addition, on an annual basis, the manufacturer must prepare a periodic safety update report, again, reflecting the findings of the post market surveillance relevant to the device. Thus, along with the potential for an unannounced audit, there will be a need for a manufacturer to be seriously monitoring the ongoing compliance of their SMBG.

10.3. Regulation of Continuous Glucose Monitoring Systems (CGMs) in the EU

Under the MDD, most sensors were classified as Class IIb. Under the new MDR, the following aspects may apply to CGMs. Classification rules for the MDR take into account a number of factors, including duration. If a sensor is in place for between 60 minutes and 30 days, the duration is considered short-term, any longer and it is considered long-term. Sensors that are placed subcutaneously are considered surgically invasive (MDR Annex VIII Rule 2.2). They are also considered active devices intended for diagnosis and monitoring (MDR Annex VIII Rule 2.4). Depending on their features, CGMs may fall into several classes, ranging from Class IIa to Class III, if they are associated with the delivery of insulin. Clinical trials are expected to be performed for Class III medical devices and for implantable devices in the EU. The risk class in the EU under the MDR does not impact on the depth of assessment of a medical device by a notified body. For low-risk medical devices, a manufacturer is able to apply for technical documentation assessment of a group of related devices. The lower the risk class, the bigger the grouping is possible. The notified body chooses one product on a representative basis to undertake an initial in-depth technical and clinical assessment, and the other technical files are then relegated for assessment during the certification five-year cycle. The requirements for both active and reactive post-market monitoring that apply to SMBGs also apply to CGMs. No specific harmonised EN standards are available in support of performance of CGMs, however, an ISO series ISO/IEEE 11073 provides guidance for interoperability and related aspects for communication functionality of CGM devices.