# 15 Use of Standards in Medical Device Global Regulatory Strategy

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## Introduction

At the most basic level, standards are documents providing requirements, specifications, guidelines and characteristics that can be used to ensure materials, products, processes and services consistently are fit for their purpose. The International Electrotechnical Commission (IEC) defines "standard" as a:

> "Document, established by consensus and approved by a recognized body, that provides for common and repeated use, guidelines or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context."[1]

Within the context of medical device development, using standards helps provide consistency in both how a medical device is developed and the performance and expected results for certain, typically established, medical device types. Standards' compliance may lead to faster regulatory approval and, for some countries, compliance with certain standards is required. Thus, there is a strategic advantage to understanding standards and their role in the medical device development and regulatory approval process.

Navigating standards' complexity can be confusing to both medical device development and approval process newcomers and veterans. First, there are different types of standards: process standards and product standards. The process standards provide guidance on medical device development and numerous manufacturing and assessment processes. Product standards generally provide desired results and testing and assessment means, specific to such factors as the medical device type, i.e., implantable, and the materials from which the device is made.

Second, there is no one centralized listing, database or decision tree to determine the standards to which a manufacturer needs to conform for a particular medical device's development and regulatory approval. Relevant standards can vary among regulatory authorities. Many relevant standards are written specifically for the medical device industry, while others are written generically to apply across industries, e.g., ship testing standards. Such standards are relevant to both medical device manufacturers and regulators because they provide requirements that can be used consistently to ensure the device is fit for its intended use. More frequently used standards are discussed in this chapter.

Standards are not maintained by one organization. Many organizations issue standards used in medical device development and regulatory approval. This chapter provides an overview of the largest standards development and maintenance participants. Standards change over time; some are revised, while others become obsolete and are replaced. Further, since there is no centralized body issuing standards, it can be difficult to keep up with the various revisions, especially in the middle of the product development or regulatory submission process.

Another difficulty, in most instances, is these standards organizations are separate from regulatory agencies. While regulatory agencies, such as the US Food and Drug Administration (FDA), recognize certain standards and standards' clauses, this recognition often lags behind the effective date of new revisions for certain device classes. Each regulatory agency

may recognize different standards or different standards' revisions, thus the list of standards to which a manufacturer must adhere varies among jurisdictions. If a product is intended for multiple jurisdictions, regulatory professionals should start by researching common and similar requirements simultaneously applicable to each.

To meet regulatory expectations, standards are not standalone documents, may be referenced or accepted by various regulatory authorities around the world and must be viewed in parallel with local regulations. An entity dedicated to creating standards is called a standards development organization (SDO). Standards developed by an SDO are intended to be voluntary and, as such, do not aim to replace local regulations. This is the reason certain regulatory authorities may determine standards will be mandatory in their jurisdictions; this type of determination, however, is uncommon. On certain occasions, for certain jurisdictions, even a widely used standard may not address a medical device's safety and performance concerns adequately. An example of this is FDA's *Guidance on Radio Frequency Wireless Technology in Medical Devices*.[2] This guidance states the IEC 60601-1-2 consensus standard did not address wireless technology electromagnetic compatibility (EMC) adequately at the time the final guidance was issued in August 2013. A manufacturer intending to seek market approval in multiple jurisdictions should consult international standards and local regulations in parallel.

In the US, a 'consensus standard' is one developed by an SDO using the consensus developing process, while a 'recognized consensus standard' is a standard FDA has evaluated and recognized for use and published in the *Federal Register*. The consensus developing process is described later in this chapter. If a manufacturer chooses not to comply with certain sections of a recognized consensus standard when compliance with the standard is expected (i.e., if the standard is referenced within an FDA guidance document), the regulatory submission should justify the deviation and provide the alternative used. A manufacturer must understand the risks it takes by not complying with applicable standards. If a manufacturer wishes to use a national standard of a country other than the US for US market clearance or approval, it may discuss the plans with FDA in the presubmission process. In contrast, the EU *Medical Devices Regulation* (*EU MDR*) and directives in other industrial sectors, rely on "harmonized" European Norms (EN) or standards. Those standards are prepared in response to a mandate from the European Commission (EC). They are intended to be used to demonstrate conformity to the essential requirements in one or more directives and are developed by the European standardization bodies, the European Committee for Standardization (CEN), European Committee for Electrotechnical Standardization (CENELEC) or European Telecommunications Standards Institute (ETSI). Notices on the standards are published in the EU *Official Journal*. Use of these voluntary standards confers a presumption of conformity with the directives' mandatory regulatory requirements.

In Australia and some countries in Asia and South America, the extent to which a standard is accepted or recognized may vary by local law. For example, in China, foreign manufacturers may submit a notarized quality system certificate of compliance to a standard, such as ISO 13485 *Medical Devices—Quality Management Systems—Requirements for Regulatory Purposes* or FDA's *Quality System Regulation (QSR)*, to the China's National Medical Products Administration (NMPA). It is possible the Chinese version lags behind the international version. In this case, the manufacturer has to demonstrate compliance with the Chinese standard and provide the necessary test reports. IEC 60601-1 second and third editions may serve as another example; a manufacturer would need to meet second edition test report requirements in China, while in much of the rest of the world, it would in fact meet third edition test reports. The Brazil Good Manufacturing Practice (BGMP) is similar to ISO 13485 per Brazilian Resolution RDC 185/2001; therefore, a certificate of compliance to ISO 13485 may be acceptable. It is important for regulatory professionals to consult with local regulatory agencies to understand

which international standards and editions are currently accepted and whether backward compatibility is accepted.

To summarize, the use of standards to demonstrate medical device regulation conformity differs among countries. These differences pose a challenge to the medical device regulatory professional in developing a global medical device regulatory strategy. Fortunately for the medical device industry, multiple SDOs create standards deemed to offer the presumption of conformity to specific regulatory safety and performance requirements, and these documents, as mentioned earlier, usually are the recognized standards.[3] Manufacturers may rely on documents published by the International Medical Device Regulators Forum (IMDRF), which make multiple normative references to numerous medical device standards. A later section in this chapter discusses IMDRF's work in more detail.

### *Understanding Standards Numbering*

Many regulatory professionals find standards' versioning or numbering confounding and, when dealing with standards, the numbering system indeed can be so. For example, one of the most well-known standards in the medical device industry is ISO 13485. An internet search of "ISO 13485" could yield the following results:

- ISO 13485:2016
- EN ISO 13485:2016
- CAN/CSA-ISO 13485:16
- DS EN ISO 13485:2016

Now, the question is what are the differences?

To answer this question, start with the base document: ISO 13485:2016. In general, the structure followed is:

- ISO 13485:2016
  - o the preceding letters indicate the issuing organization; in this case, the International Organization for Standardization (ISO)
  - o 13485 is the standard number
  - o 2016 is the revision year, sometimes using only the last two numbers

Then, the numbering changes as various regulatory bodies in different jurisdictions adopt the standard to meet their specific requirements. EN ISO 13485:2016 is the version of ISO 13485:2016 adopted by one of the pan-European standard bodies, CEN, CENELEC or ETSI. CEN, CENELEC and ETSI are recognized officially by the EU. Official EU recognition means these organizations may adopt European Norms (EN) that can become candidates for harmonization (recognition) in Europe under the directives. Appendices were added to indicate the aspects of the EU *Medical Devices Directive (EU MDD)* the standards satisfy. CAN/CSA-ISO 13485:16 is the ISO 13485:2016 version adopted by the Canada National Standard/Canadian Standards for use in Canada. DS/EN ISO 13485:2016 is the version adopted by Denmark's Dansk Standards Association,[4] the same version approved by the European Committee for Standardization as EN ISO 13485:2016 without any modifications.

While some regulatory jurisdictions include the year of adoption, some jurisdictions do not, such as CAN/CSA-ISO 13485:03. Reviewing the adopted version's scope is necessary to understand which standard version was adopted. For example, ISO 13485 was revised in February 2016, and various standard bodies went through their adoption process. There was a three-year transition period for ISO 13485:2016; thus, it is necessary to understand the revision to which manufacturing organizations will comply.

## Standards Developing Organization (SDOs)

As defined earlier, an SDO is an organization dedicated to developing standards. Several SDOs support the medical device industry; therefore, it is important for a regulatory professional to know who they are and understand why they exist.

An SDO provides consumers, industries and governments a platform to discuss and develop international standards. Each SDO, when appropriate, cooperates with another and its stakeholders to produce joint publications, help promote the importance of standardization

globally, coordinate any potential overlaps in work and ensure international standards are seamless and complementary with each other. Some significant SDOs are profiled in this chapter.

**International Organization for Standardization (ISO):** ISO develops and publishes international standards.[5] Created in 1947, ISO is an independent, nongovernmental organization with 164 member countries. Each member has a national committee representing ISO in its country. For example, the American National Standards Institute (ANSI) represents ISO in the US. Through ANSI, the US participates heavily in ISO technical committees (TC), such as ISO/TC 194 *Biological and Clinical Evaluation of Medical Devices.* ISO/TC 194 is responsible for publications such as ISO 10993 *Biological Evaluation of Medical Devices* and ISO 14155:2011 *Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice series*. The British Standards Institute (BSI) represents ISO in the UK. ISO representatives in specific jurisdictions can be found on the ISO members' web page.[6]

**International Electrotechnical Commission (IEC):** IEC prepares and publishes international standards for electrical, electronic and related technologies, known collectively as electrotechnology.[7] IEC members are called national committees (NCs) who represent all electrotechnical standardization concerns and conformity assessments in their countries. IEC's objective is to promote international cooperation on all questions concerning standardization in the electrical and electronic fields. IEC publishes international standards, technical specifications, technical reports, publicly available specifications (PAS) and guides, and collaborates closely with ISO. The US participates through ANSI in the medical device standards development subcommittees (SCs).

**American National Standards Institute (ANSI):** ANSI is a private, nonprofit entity coordinating and administering the US voluntary standards and conformity assessment systems. ANSI, itself, is not an SDO but accredits SDOs that adhere consistently to the ANSI Essential Requirements for openness, balance, consensus and due process, a set of procedures governing the consensus standards development process. ANSI is a founding member of ISO, and the ANSI Essential Requirements embrace ISO and IEC's globally accepted standardization principles. As the US member body of ISO, ANSI accredits US Technical Advisory Groups (TAGs). US TAGs, through ANSI, promote the use of US standards, policies and technical positions internationally and advocate the adoption of international standards as US national standards when they meet the healthcare community's needs. Because ANSI is a leader in ISO's governing body and an IEC participant, via the US National Committee, the US has immediate access to both the ISO and IEC standards development processes. As the accreditor of US voluntary consensus SDOs, ANSI ensures SDOs maintain integrity in developing American national standards.

**Clinical and Laboratory Standards Institute (CLSI):** CLSI, successor to the National Committee for Clinical Laboratory Standards, exists to develop applicable clinical and laboratory consensus standards and guidelines for clinical laboratories and promote their use globally.[8] CLSI is accredited by ANSI and actively promotes global harmonization of clinical laboratory testing standards through its participation as the Secretariat of ISO TC 212, Clinical Laboratory Testing and In Vitro Diagnostic (IVD) Test Systems. CLSI also serves as the administrator for the US TAG for ISO TC 212. The CLSI consensus process includes stakeholder experts from industry, government and healthcare professions, gathering to develop standards for improved clinical laboratory testing quality, safety and efficiency. An example of a CLSI published guideline is *Point-of-Care IVD Testing*, providing guidance to IVD device users outside a clinical laboratory setting on how to ensure results are comparable to those obtained in laboratories.

**Underwriters Laboratories (UL):** In addition to these organizations, other SDOs exist that either publish technical standards in a wide range of industries or collaborate with ISO and IEC in standards development and publications. UL develops a wide variety of standards to measure and validate performance,

environmental health and sustainability.[9] Standard UL 60601-1 Medical Electrical Equipment, Part 1: General Requirements for Safety references 36 additional UL standards that may be used in lieu of IEC 60601-1 if the differences in the two documents' particular requirements are recognized and understood for effective implementation in a global regulatory strategy. It is important to note, however, many UL standards are not recognized by regulatory authorities outside the US.

**Institute of Electrical and Electronics Engineers (IEEE):** Other professional organizations' work includes coordinating and publishing technical standards or models the medical device industry may utilize. IEEE is a professional association dedicated to advancing technological innovation. IEEE, among other services, publishes engineering technical standards and models. Medical device software engineering professionals and software medical device and mobile medical app (MMA) manufacturers continue to draw from well-established IEEE standards, such as IEEE 1012-2012 *Standard for System and Software Verification and Validation.*

**Association for the Advancement of Medical Instrumentation (AAMI):** AAMI is a nonprofit organization founded in 1967 supporting the healthcare community in developing, managing and using safe and effective medical technology. AAMI's standards program consists of more than 100 technical committees and working groups that produce standards, recommended practices and technical information reports for medical devices. Standards and recommended practices represent a national consensus and many have been approved by ANSI as American National Standards. AAMI also administers a number of international ISO and IEC technical committees as well as US TAGs.10 An example of an AAMI standard is AAMI ANSI HE75:2009(2013) *Human Factors Engineering—Design of Medical Devices*.

**National Electrical Manufacturers Association (NEMA):** NEMA represents nearly 325 electrical equipment and medical imaging manufacturers that make safe, reliable and efficient products and systems serving seven major markets. For standards for medical imaging, the **Medical Imaging and Technology Alliance (MITA)** plays key roles. MITA, a division of NEMA, is the organization for medical imaging equipment, radiopharmaceutical manufacturers, innovators and product developers. MITA is the Secretariat of **Digital Imaging and Communications in Medicine (DICOM)**. MITA technologies include computer tomography (CT) scanners, nuclear imaging, radiopharmaceuticals, magnetic resonance imaging (MRI), imaging information systems, ultrasound and medical X-ray equipment. Examples of standards include NEMA XR 26-2012 *Access Controls for Computed Tomography—Identification, Interlocks and Logs* and NEMA MS-10-2010 *Determination of Local Specific Absorption Rate (SAR) in Diagnostic Magnetic Resonance Imaging (MRI)*. Other areas NEMA covers, in addition to medical imaging, include building systems, building infrastructure, lighting systems, industrial products and systems, utility products and systems, transportation systems and manufacturers and installers of durable medical equipment.

**ASTM International:** Formally known as the American Society for Testing and Materials, ASTM International currently has more than 7,000 standards that have been adopted as the basis of national standards or referenced in regulations around the world in a wide variety of industries. These technical standards are used in product development, product testing and quality systems.[11] Examples of standards include ASTM F2516-07 *Standard Test Method for Tension Testing of Nickel-Titanium Superelastic Materials* and ASTM F1980-07(2011) *Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.*

### *Additional Related Organization*

As noted earlier, IMDRF is the successor to the Global Harmonization Task Force (GHTF). IMDRF is not an SDO but is an international group of volunteers representing medical device regulatory authorities from Europe, the US, Canada, Japan and Australia who develop medical device and IVD guidance documents. The Asian Harmonization Working Party (AHWP),[12] ISO and IEC joined IMDRF as

liaison members in 2012. AHWP represents 26 member economies.[13]

IMDRF's purpose is to continue GHTF's work, producing a series of guidance documents describing a risk-based regulatory model to ensure medical device safety, effectiveness, performance and quality. These guidance documents are intended to harmonize documentation and procedures on basic regulatory practices used to assess whether a medical device conforms to applicable regulations in each jurisdiction. These harmonized documents and procedures are aimed at reducing, if not eliminating, differences among jurisdictions, thereby decreasing the regulatory compliance costs and allowing patients earlier access to new technologies or treatments. IMDRF guidance documents reference standards,[14] such as those developed and disseminated by ISO and IEC, a regulatory professional can implement both within a global regulatory strategy and throughout the medical device's lifecycle.

Following is an example of how a global regulatory professional may benefit from understanding IMDRF's work. A manufacturer has identified Australia as a potential target market for its medical device and asked its global regulatory executive to determine market access requirements. Since Australia was a founding IMDRF member and contributed to the guidance document, many standards referenced in IMDRF documents are accepted, even if certain versions are not recognized, by Australia's Therapeutic Goods Administration[15] (TGA). By examining IMDRF documentation, a regulatory professional will be able to determine the list of applicable standards for premarket evaluation, assessment and implementation.

The same principle applies for market access in the other IMDRF founding economies of the US, Japan, Canada and AHWP. Guidance documents published by IMDRF may help a medical device global regulatory professional determine reference standards to be used as part of the conformity assessment process to meet different countries' regulatory requirements.

## Using Standards to Demonstrate Conformity With Regulatory Requirements

While differences in medical device regulations exist across jurisdictions, a regulatory professional may apply international standards to demonstrate conformity to essential regulatory elements to help get the manufacturer's technologies and treatments to patients faster. In the US, international standards often are referenced in FDA guidance documents. When developing a strategy, the regulatory professional is advised to reference and implement these standards in parallel with guidance documents to meet FDA requirements, specifications and guidelines to ensure the medical device is fit for its intended use. For example, by utilizing the internationally recognized ISO 14971 *Risk Management* standard, a manufacturer can demonstrate conformity with medical device risk management requirements. ISO 14971 is referenced in numerous FDA guidance documents, including *Guidance for Industry and Food and Drug Administration Staff: Content of Premarket Submissions for Management of Cybersecurity in Medical Devices* and *Factors to Consider When Making Benefit–Risk Determinations in Medical Device Premarket Approval and De Novo Classifications*, which addresses the intersection of the guidance with ISO 14971 in great detail.

As mentioned earlier, the IMDRF guidance documents also reference standards, such as ISO 14971. A regulatory professional developing a medical device global regulatory strategy, must apply local guidance document recommendations, reference standards and regulations to increase chances of getting medical technology to patients faster.

A standard is not a regulatory agency's recommendation or guideline presented in a guidance document. A guidance document, such as the FDA's *General Principles of Software Validation; Final Guidance for Industry and FDA Staff*, contains suggested regulatory guidelines and reflects the agency's current thinking and recommended best practices for the medical device regulatory process. Like IMDRF documents, FDA guidance documents may reference numerous process, safety and performance

standards, such as those developed and disseminated by ISO and IEC.

A standard is a not a regulation. A regulation is a national rule implementing a law, which, if violated, can result in a penalty. A national regulatory body develops a regulation. **Figure 15-1** presents a graphic representation of the hierarchical relationship between regulations, guidance documents, standards and technical reports. It is important to remember regulatory agencies issue regulations and guidance documents, while SDOs, which are nongovernmental entities, issue standards and technical reports.

**Figure 15-1. Document Hierarchy**


## Product Standards and Process Standards

Standards can be grouped into three major categories: compatibility, process and safety and performance. Universal serial bus (USB) and blue-ray disc standards are specific examples of compatibility standards. Process standards cover a medical device product's lifecycle. Process standards dictate a process or overall system's requirements but do not dictate how a medical device manufacturer should meet these requirements. Standards also can be categorized as vertical, collateral or horizontal. For medical devices, horizontal standards would be "general" standards applicable to almost all medical devices. For example, ISO 13485 *Quality Systems*, ISO 14971 *Risk Management* and ISO 15223 *Symbols for Labelling* would apply to most regulated medical devices. The collateral standards would be "group" standards applicable to certain type of products. Examples would be IEC 60601-1-2: *Electromagnetic Disturbances: Requirements and Tests* and IEC 60601-1-3 *Radiation Protection in Diagnostic X-Ray Equipment.* In contrast, vertical standards apply to specific devices or device categories, such as the IEC 60601-2 family of standards that apply to certain electromechanical medical devices.

SDOs and professional associations have developed and published numerous compatibility, process and safety and performance standards. Only standards relevant to the medical device lifecycle, from concept to market, are within this chapter's scope. While more than 1,000 standards are used in the medical device industry, a few are worth profiling in this chapter due to their broad usage and recognition.

These profiled standards, recognized and referenced by multiple regulatory authorities and generally applicable to all medium- to high-risk medical devices, include ISO 13485, ISO 14971 and IEC 62366 *Medical Devices—Application of Usability Engineering to Medical Devices*. IEC 62304 *Medical Device Software—Software Life Cycle Processes* will be profiled and, as the title indicates, is applicable to medical devices containing software, standalone software or mobile medical applications. Last but not least, ISO 14155:2011 *Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice*, also will be profiled in this chapter, since clinical investigation is a critical process by which a manufacturer collects safety and performance data to support medical device market approval.

### *ISO 13485—Medical Devices—Quality Management Systems—Requirements for Regulatory Purposes*

ISO 13485 gives available quality management system (QMS) requirements an organization can use for medical device design and development, production, installation and servicing and designing, developing and providing related services.[16]

ISO 13485 is derived from historic versions of ISO 9001 (versions prior to 2015), a standard containing QMS requirements used around the world for various manufacturing and service

industries.[17] ISO 13485 and ISO 9001 are moving farther apart: however, as ISO 9001 evolves into a true 'quality system.' In the past, most of the ISO 9001 clauses, subclauses and format were identical to those in ISO 13485, but this has changed to facilitate understanding of the differences. The latest edition of the ISO 13485 has Tables B.1 and B.2 in its Annex B to show the correspondence between ISO 13485:2016 and ISO 9001:2015.

For most jurisdictions, including the EU, Australia and Canada, the preferred method to prove conformity with regulatory requirements is certification of the manufacturer's QMS to ISO 13485. In December 2018, FDA formally announced its intention to transition away from the *Quality Systems Regulation (QSR)* per 21 CFR Part 820 and transition to ISO 13485:2016 for its audit inspections of medical device manufacturers.[18] FDA stated that "We recognize there will be a significant impact on FDA for implementation. For example: Training on ISO 13485 requirements, interpretation, best practices, etc. to CDRH staff and ORA investigators and compliance officers. Changes to the inspection model (QSIT). Revisions/updates to numerous documents. Changes to IT systems. Transition period will likely be a few years."[19]

The 2016 revision for ISO 13485 placed more emphasis on QMS across the entire supply chain and is intended to address the total product lifecycle of medical devices, among other changes to the previous edition. In March 2019, FDA discontinued accepting Declaration of Conformity to ISO 13485: 2003 for regulatory purposes and confirmed that ISO 13485:2016 should be used instead.

As described previously, process standards largely are nonprescriptive: the requirements are presented, but how to meet those requirements is not specified. The standard recognizes a wide variety of medical devices (from simple and low-risk to complex and high-risk) are developed by a multitude of organizations (from small start-ups with small staffs to large, multi-national corporations with thousands of employees); thus, processes successful for one organization will not be the same as those for another.

ISO 13485 includes general QMS requirements, management's overall QMS responsibility, resource management (both human and physical resources), product realization and measurement, analysis and improvement.

In the US, FDA stipulates a manufacturer (domestic or importer) must have a *QSR*-compliant QMS. The QMS standard, ISO 13485, was first adopted in the US as ANSI/AAMI/ISO 13485:2003. Although ISO 13485 and *QSR* elements are similar, they are not identical. A manufacturer may need to fulfill certain obligations to comply with the *QSR* that are not part of ISO 13485. One example is the *QSR* requirement to use statistical techniques not specified in ISO 13485.

At the time of writing this chapter, ISO 13485:2016 is not officially recognized by the EU Commission. Upon publication, the manufacturer must review the gap between the harmonized standard and *EU MDR* requirements to ensure compliance.

Despite these differences, using ISO 13485 still can streamline QMS establishment to meet the majority of regulatory agency requirements around the world. It is worth noting here links exist between other standards and ISO 13485. How ISO 13485 outlines the basic manufacturer QMS framework was described earlier. However, other process standards less overarching than ISO 13485 exist that help frame QMS subprocesses or subsections. Examples include ISO 14001 *Environmental Management Systems* and ISO 14971 *Risk Management.*

### *ISO 14971 Medical Devices—Application of Risk Management to Medical Devices*

ISO 14971 specifies the process to identify hazards associated with medical devices, to estimate and evaluate and control those risks and monitor the controls' effectiveness throughout the product lifecycle.[20] It is referenced in ISO 13485 and numerous other standards, as the one in which guidance related to risk management during product realization may be found.

To emphasize, this standard outlines the risk management process but does not prescribe the specific hazards and risks to be mitigated and controlled for each medical device type.

Given the wide range of medical devices, from thermometers to surgical tools, and the technologies in use, an encyclopedia of hazards and risk mitigation measures would be large, unwieldy and out-of-date as soon as it was published. The range of risks varies from device to device depending on the technology used, its intended use and its method of use. For example, dental hygienists use tools such as scalers and hand instruments to scrape bacterial deposits from teeth. Micro-ultrasonic scalers also are available for the same purpose—removing bacterial deposits—but use vibration and a pressurized stream of water. The risks of the simple hand tool scaler are much different than those of the micro-ultrasonic scaler.

As technologies evolve, new hazards will be introduced that may not be foreseen; thus, there is a need for a standardized risk identification, mitigation and control process.

The general process outlined by ISO 14971 creates a risk management plan to document how risk management activities will be performed. The next step is risk assessment to identify potential hazards and estimate the risk for each situation associated with the potential hazards. In the example of the scaler hand tool, the sharp tip presents a potential hazard.

### *IEC 62366-1 Usability in Medical Devices*

As healthcare and technology have progressed over time, more-complicated medical devices and device use by less-skilled users, including patients themselves, have followed suit.[21]

IEC 62366 was published in 2007 and amended in 2014, expanding the standard's scope to include all medical devices, nonactive implantable medical devices and active implantable medical devices. More recently, IEC 62366 was revised in 2015 to IEC 62366-1. The updated standard divides IEC 62366 into two parts: IEC 62366-1 and IEC/TR 62366-2. The first part discusses usability engineering principles and provides an overview of how usability is incorporated into medical device development. The second part is a technical report including guidance on compliance with IEC 62366-1.

This standard addresses the need for usability engineering to minimize use errors and use-associated risks. Similar to other standards discussed previously, and for similar reasons, IEC 62366 does not prescribe the specifics of a medical device user interface, but does describe the analysis, specification, design, verification, and validation usability processes related to device safety. The standard has close ties and many references to ISO 14971. If designed well, a manufacturer's risk management and usability processes will dovetail efficiently into each other. One IEC 62366 appendix includes a diagram mapping the inputs and outputs between risk management and usability processes.

### *IEC 62304 Edition 1.1 2015-06 Medical Device Software—Software Lifecycle Processes*

Software is incorporated into many medical devices. Just as it is necessary to ensure safe and effective mechanical and electromechanical devices, devices incorporating software also must be safe and effective. This standard was created in the belief that software testing alone is insufficient to ensure safe operation. Thus, IEC 62304 provides a framework for safe software design and maintenance processes throughout the product lifecycle. It assumes software activities occur within a QMS and risk management system, specifically ISO 14971. This standard includes general requirements for software development, maintenance, risk management, configuration management and problem resolution processes. Similar in nature to the standards cited above, this standard does not prescribe what software code should look like but focuses on the processes to create safe and effective software.

ISO 14971 is referenced in several of the standards mentioned above. Sometimes, an SDO publishes a Technical Report (TR) to guide a manufacturer or regulatory professional in applying a certain standard. IEC TR 80002-1—Medical Device Software—Part 1: Guidance on the Application of ISO 14971 to Medical Device Software is one example. This TR is the result of collaborative work by joint working groups IEC SC 62A *Common Aspects of Electrical Equipment Used in Medical Practice*, IEC 62 *Electrical Equipment in Medical Practice* and ISO TC 210

*Quality Management and Corresponding General Aspects for Medical Devices.* IEC TR 80002-1 is extremely helpful in understanding how to apply risk management principles in ISO 14971 to medical device software.

### *ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice*

ISO 14155 is intended to ensure Good Clinical Practice (GCP) is followed during a medical device clinical investigation to ensure subject safety.

ISO 14155 details the baseline clinical investigation requirements for market approval safely. Key stakeholders, e.g., the sponsor and principal investigators, are required to follow the standard's requirements. Recognized by FDA, ISO 14155 can be applied in parallel with FDA's GCP and guidance on an investigational device exemption (IDE); however, it should be noted, while consistent with FDA's GCP requirements, conformity with ISO 14155 alone is insufficient for US clinical investigations. Further, conformity with ISO 14155 may not be sufficient for FDA to accept data from clinical investigations conducted outside the US. A medical device global regulatory professional must understand the common principles in all these documents are pertinent when a medical device is investigational, i.e., undergoing safety and performance evaluations, under applicable laws and GCP.

Some of the additional normative standards referenced in ISO 14155 are ISO 13485, ISO 10993, ISO 15223 *Symbols to be Used With Medical Device Labels, Labeling and Information to be Supplied, Part 1—General Requirements* and EN 1041 *Information Supplied by the Manufacturer of the Medical Device.* A regulatory professional must not assume; however, that normative references in a standard are recognized automatically.

## Benefits of Using Standards

### *The Standards and Conformity Assessment Program*[22]

A key reason for complying with standards and integrating them into product development is to enable an easier approval process with regulatory bodies. Standards are voluntary but, in some jurisdictions, have a particular regulatory status and are recognized as a (the) preferred means by which the manufacturer may demonstrate conformity with the mandatory regulatory requirements. Thus, it generally is easier to conform to the standard instead of providing justification for not using it.

Standards play an important role throughout the medical device lifecycle. Various standard types exist to support all involved medical device products and processes, such as risk management and quality systems. Multiple medical device industry stakeholders are involved in developing standards and stay involved in updating them as necessary. Standards help harmonize regulatory processes to ensure medical devices' safety and performance are not compromised at any point during their lifecycle, playing an important role during medical device and diagnostic product conformity assessments.

As mentioned above, various standards exist to support medical device processes and can help manufacturers streamline their risk management processes. Standards generally are established to promote consistency and best practices leading to devices meeting current safety and effectiveness state-of-the-art expectations. Designing to a standard can mitigate potential application (use) and design risks. For example, a device's electrical power results in risks associated with shock hazards. UL 60601-1 *Medical Electrical Equipment, Part 1: General Requirements for Safety*, outlines standards for electrical safety protection methods; designing a device to comply with this standard can be documented as mitigation measures taken for shock hazard risks. This documentation also can support ISO 14971 requirements, the medical device risk management standard.

In the US, FDA's guidance, *Center for Devices and Radiological Health (CDRH) Standard Operating Procedures for Identification of Candidate Consensus Standards for Recognition,* provides an established process for standards' recognition.[23] A Standards Task Group (STG), reporting to the Standard Management Staff

(SMS), is responsible for coordinating all CDRH consensus standards' activities within its assigned technical area with relevant SDOs. The recognition process begins when an STG identifies an existing and needed standard within its technical area and prioritizes required activities per common criteria. Then, the STG coordinates an assessment of whether the standard can be used to meet a particular premarket or statutory requirement. Upon completing the assessment, it then recommends the standard be recognized, as whole or a part, through publication in the *Federal Register*. The *Federal Register* notice includes not only the newly recognized standards; it also includes modification to the previously recognized standard and identifies any previously recognized standard(s) that no longer will be recognized. Any medical device industry stakeholder may propose a standard for recognition. The process includes submitting the standard title, reference number, date and SDO. In addition, the stakeholder must list device types to which the standard would apply and a brief identification of device testing, performance and/or other characteristics a declaration of conformity to that standard would address.

In September 2018, FDA finalized the guidance, *Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices*.[24] This final guidance provides guidance to industry and FDA staff about the appropriate use of national and international voluntary consensus standards in the preparation and evaluation of premarket submissions for medical devices.

In accordance with amendments made to Section 514 of the *Federal Food, Drug and Cosmetic Act* by the FDA Reauthorization Act of 2017, and as part of the enactment of the *Medical Device User Fee Amendments* of 2017, FDA intends to implement a pilot conformity assessment initiative, entitled the Accreditation Scheme for Conformity Assessment (ASCA). This voluntary, pilot program is designed to increase consistency and predictability in FDA's approach to assessing conformance with ASCA-eligible standards in medical device premarket reviews.

The ASCA pilot is intended to reduce regulatory burden by enhancing product reviewers' confidence in medical device testing, which should decrease the need for internal FDA consultations, complete test report reviews and additional information requests for standards that are part of the pilot program. Ultimately, the ASCA pilot is intended to help FDA ensure safe, effective and high-quality medical devices are available to patients without avoidable delay.[25] The ASCA guidance document is expected to be finalized in late 2020 or early 2021.

Outside the US, several regulatory authorities have processes in place to recognize standards within their jurisdictions. Globally, SDOs have established standards development processes, described in the following section.

## Standards Development Process

A 'consensus standard' is designated as such because it takes all stakeholders' interests into consideration and defines what they have agreed.

Consensus is considered a general agreement, characterized by the absence of sustained opposition to substantial issues by any important stakeholders, through a process that takes all concerned parties interests into account and reconciles conflicting arguments. However, it is important to remember consensus need not imply unanimity but rather agreement to most of the proposed requirements or guidelines by the majority of the stakeholders. Care also is taken to ensure a standard does not confer a competitive advantage on individual operators.

The standardization process encompasses standards' development, promulgation, implementation and compliance. While some governmental bodies develop standards, most are written by nongovernmental entities, several of which were profiled earlier in this chapter. Those organizations follow a transparent process open to public scrutiny, where participation is balanced and an appeals process is included. Behind each medical device standard is a comprehensive process including extensive data gathering, analysis and discussion from all stakeholders' perspectives and agreement on critical factors. Stakeholders, such as regulatory agencies and IMDRF, support standards' use by referencing them in guidance documents and publications. National regulatory authority

experts in some countries participate in standards development.

Finally, medical device SDOs rely on standards' sales to support their programs' and services' continuous improvement. By charging for standards, an SDO also can ensure it is not influenced unduly by a single party's interests.

## How to Choose Medical Device Standards

A regulatory professional needs to consider standards from design and development through the medical device's lifecycle. This is an integral part of global regulatory and clinical strategy, since standards help demonstrate a device's safety, performance and efficacy to meet regulatory requirements.

### *Case Study: Standards' Use in Developing a Hypothetical Artificial Pancreas Device System (APDS)*

This case study assumes the manufacturer is responsible for developing an APDS and its clinical investigation approval in the US and EU. An APDS is a complex, connected IVD device system comprising several components, and is an excellent example of the use of vertical and horizontal standards. An APDS device includes a glucose meter, an insulin pump, an insulin reservoir, a sensor, a display for acquired glucose values and a transmitter. The device also contains some complex software. This device is an improvement on the traditional continuous glucose monitoring system design because the sensor monitors cell glucose values continuously and transmits these values to the insulin pump. The device's software allows it to be programmed to carry out one of three specific tasks:

1. deliver insulin automatically should glucose level fall below a predefined threshold
2. control insulin delivery based on predefined low and high thresholds
3. control insulin delivery to a predefined glucose target level.

The meter component is designed to measure and display glucose values continuously, so basal insulin may be calculated and delivered. A reporting feature reports glucose trending information in real time. The device can be programmed to stop or suspend insulin delivery automatically for two hours when the sensor detects the glucose level has fallen below a preset value. The glucose sensor is inserted through the patient's abdomen and senses or measures glucose values. These values are transmitted to the insulin pump and displayed for the patient to see. The insulin is delivered by the pump through the infusion set.

Since an APDS is a complex system, the device's failure can cause death or serious injury; therefore, it falls under the highest risk classification, Class III, in both the US the EU.

How are standards chosen for this device? Fortunately, for this case study, several guidance documents exist, including *Final Guidance for Industry and the Food and Drug Administration Staff: The Content of Investigational Device Exemption (IDE)* and *Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems*. Horizontal and vertical standards comprise the body of knowledge to help a regulatory professional choose the correct standards. In addition, FDA has compiled a guidance entitled, *Frequently Asked Questions on Recognition of Consensus Standards*, as a primary guide to understanding the agency's current thinking on how to identify standards applicable to a certain medical device and why to apply standards to US and EU submissions.[26] The device development team can reference this guidance to demonstrate the device is safe and works as intended, as can the regulatory and clinical teams, to ensure the device is investigated to conform to local regulations and international standards.

A regulatory professional should start by identifying US Code of Federal Regulations notice(s) on Essential Requirements for medical device safety and efficacy or performance based on functionality and mode of action, intended use, site of action and mode of operation. A search for a relevant FDA guidance document would be conducted. Standards referenced in the relevant guidance document then can be selected. Using standards will help the manufacturer identify the device's preclinical and clinical testing and critical postmarket requirements.

Fortunately, there is an FDA APDS guidance document. The guidance references several horizontal and vertical standards. In addition, a summary of safety and effectiveness data (SSED) for a similar device or precedent, if one exists, may be examined. From these documents and the referenced standards, a fairly comprehensive list of standards can be obtained that might cover the majority of, if not all, preclinical testing requirements and bench performance objective performance criteria, EMC, biocompatibility, sterility assurance, packaging, shelf life, shipping, software and human factors.

The various research and development, engineering, quality and clinical cross-functional groups within the organization will need to ensure all regulatory requirements are met. In addition, a discussion about standards should occur since standards play a significant role in helping establish and communicate baseline expectations at each APDS product lifecycle stage. A few examples of the applicable numerous horizontal and vertical standards for disparate APDS components are discussed below.

Since the APDS insulin set component is inserted under the patient's skin, regulators would be interested in the set materials' biocompatibility. Certain parts of the ISO 10993 series may be examined to understand and meet APDS biocompatibility requirements within a risk management process. An FDA blue book memo, entitled *Use of International Standard ISO 10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing*, can be consulted in parallel.[27] A manufacturer will need to provide biocompatibility testing result summaries, since the standard, itself, does not include pass/fail criteria. ISO 11137 *Sterilization of Health Care Products—Radiation* helps in understanding sterility testing and validation requirements. The device system's sensor component, which is a single-use disposable device, is intended to be inserted under the patient's skin and remain there for up to six days. In addition to the sensor, the pump, transmitter, reservoir, and infusion set also are sterile components. ISO 11137 provides baseline requirements for the electron beam sterilization process and validation used to sterilize all components provided as sterile, regardless of whether they are for single or multiple use. ISO 11607 *Packaging for Terminally Sterilized Devices*, ASTM D4169 *Standard Practice for Performance Testing of Shipping Containers and Systems* and ASTM D642-00 *Standard Test Method for Determining Compressive Resultant of Shipping Containers, Components and Unit Loads* were applied to sensor packaging. For the manufacturer to ensure baseline packaging and shipping requirements are met for this sterile, single-use device, these three standards were applied to validate the sensor is packaged for device sterilization and protection adequately. Packaging standards for device components provided sterile, as opposed to those provided non-sterile differ. IEC 62366-1:2015, discussed previously, helps analyze, specify, design, verify and validate the device's usability for safety. Finally, ISO 14155:2011 is applied in global APDS clinical investigation. ISO 13485 for quality systems and ISO 14971 for risk management also would apply.

Standards cited in the discussion above are not intended to be comprehensive. This case study is intended to demonstrate the breadth of standards applicable to a typical, complex, highest-risk IVD device system. Identifying, understanding and applying relevant standards may help the manufacturer's cross-functional team develop a device that eventually will meet regulatory requirements in the US and other countries.

### *Case Study: Use of Standards in Developing a Hypothetical Replacement Heart Valve*

The replacement heart valve provides another case study of the application of both vertical and horizontal standards in developing a medical device. Heart valves are high-risk devices, Class III in the US28 and under the *EU MDD.*29 Heart valves are in constant contact with the patient's blood and can cause death or serious injury if they fail. The widely publicized failures of the Shiley Heart Valve in the 1980s led to heightened awareness of valves by all stakeholders, including doctors and patients, regulators and manufacturers. Concerns about the Shiley Heart Valve and other devices were factors in enacting the *Safe Medical Devices Amendment* of 1990.[30]

Replacement heart valves can be made of various materials. Mechanical heart valves usually consist of one or two tilting discs or "leaflets" operating inside a ring or housing. The discs often are made of ceramic, such as pyrolytic carbon; the housings also can be made of ceramic or a metal, such as titanium. Tissue heart valves use animal-derived tissue, such as bovine pericardium or an intact porcine valve. The tissue is treated during the manufacturing process, often with glutaraldahyde or a similar fixative. Most surgically-implanted valves also have a "sewing ring," often of polyester, to enable the surgeon to suture the prosthetic valve into the patient's native tissue annulus.

However, for this case study, assume the device manufacturer wants to incorporate the latest technological innovations. To treat patients at a high risk of complications in traditional open-heart surgery, the valve will be delivered via a catheter. The catheter will be introduced into the patient's groin, will pass through the femoral artery and up through the aorta. The valve then will be released from the catheter and fixed in place of the patient's native aortic valve. The valve itself will need to be flexible and compressible to be loaded onto a catheter. To avoid potential risks associated with tissues of animal origin, the manufacturer has decided to manufacture the valve housing and leaflets from a polymer material.

The manufacturer intends to offer this valve to patients worldwide and has developed a regulatory strategy to begin clinical studies in the US and then use those data to submit marketing applications in other regulated countries.[31]

The manufacturer will adhere to a rigid design control process that will include adequate periods of time to define user needs and develop design input leading to design output. Further, the manufacturer will schedule a series of design reviews to act as gating mechanisms throughout the development process. As certain milestones are reached during design and testing, these reviews will either confirm the design is meeting expectations and move activities into the next phase, or direct the design and development team to return to the previous phase for retesting or design revision. The development team will be expected to establish an overall protocol for verifying and validating the design, relying on state-of-the-art thinking about valves and the most appropriate available standards and guidance.

Because the manufacturer intends to study and market the valve first in the US, the development team should be knowledgeable about FDA expectations. FDA first published *Draft Guidance for Industry and FDA Staff, Heart Valves—Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications* in 1994.[32] The guidance was revised and reissued in 2010. ISO first published ISO 5840 Cardiovascular implants—Cardiac valve prostheses in 1996.[33] The standard was revised in 2005 and reaffirmed in 2010. This standard has since been revised by ISO 5830-2:2015 *Cardiovascular Implants—Cardiac Valve Prostheses—Part 2: Surgically Implanted Heart Valve Substitutes.*[34]

The manufacturer, then, would use guidance documents and standards in parallel in the development process. ISO 5840 provides an excellent outline of general requirements, even specifying design input, output and transfer, and risk management.[35] The standard goes on to identify further general requirements, such as material property assessment, hydrodynamic performance assessment, structural performance assessment, etc., with some specific requirements defined in the annexes.

The FDA guidance provides more detail in some areas and is intended to be complimentary to ISO 5840. Specific requirements are identified for *in vitro* testing, including durability, fatigue, dynamic failure mode and cavitation. Similar levels of detail are provided for preclinical animal testing, along with specific recommendations on how to submit the data in IDE and PMA applications. As expected, the guidance provides a great deal of information about clinical testing, including objective performance criteria. Finally, there is a section on labeling. The appendices also provide a wealth of detail regarding shelf life, cavitation, verification of Bernoulli's principle and a protocol for echocardiographic assessment.

The sponsor would develop an overall testing protocol for the valve carefully, following the ISO standard and paying particular attention to the FDA guidance. Sponsors may elect to develop the protocols themselves or contract with third-party experts to develop the protocols or conduct testing. The manufacturer probably would want to consult with FDA prior to commencing lengthy and expensive testing to ensure the agency's expectations would be met.

**Note:** FDA guidance even calls out the presubmission process to make sponsors aware of these options.[36]

The manufacturer would use not only the international standard and FDA's heart valve guidance but also look to a number of applicable horizontal standards. Because the heart valve is implantable and, further, because the manufacturer has elected to use a polymer, a material with limited usage in this application, the materials' biocompatibility will be of particular interest to the manufacturer and regulators. ISO 10993 provides biocompatibility testing requirements. The manufacturer also should consult FDA's final guidance on the use of ISO 10993.[37]

Other horizontal standards would be necessary in the development process to help define requirements common to all implantable medical devices, e.g., symbols and labeling, packaging, and sterilization. Other broad horizontal standards critical to any development process include ISO 14971 for risk management and the ISO 13485 or QSR for QMS.

Finally, because this hypothetical heart valve will be delivered by catheter, a specific part of the vertical standard, ISO 5840-3:2013 *Cardiovascular Implants—Cardiac Valve Prostheses—Part 3: Heart Valve Substitutes Implanted by Transcatheter Techniques*, defining operational conditions and performance requirements for the catheter delivery system must be applied.[38]

This case study illustrates, even though the device design output is innovative and incorporates features uncommon or even unavailable in some markets, the manufacturer and the development team have an available body of knowledge based on years of experience with replacement heart valves. Through the available horizontal standards, and especially the vertical standards and guidance, the manufacturer is able to identify FDA and other regulators' expectations. The manufacturer can develop an overall test protocol and even vet that protocol with FDA through the presubmission process. The sponsor can test the device and challenge the results through the manufacturer's own design assurance process. Through the appropriate and rigorous application of international standards and regulatory guidance, the manufacturer can establish the device's safety and effectiveness and provide valid scientific evidence to support PMA approval in the US and marketing approval in other countries.

## How to Find Standards for a Medical Device

Several SDOs provide search engines to locate standards. Most standards must be purchased in electronic or paper form from the SDO's website. Many standards developers collaborate with re-sellers authorized to market the documents on their behalf.

In addition to visiting SDO websites, regulatory professionals may utilize one of many standards search engines. These search engines interface with specialized databases that aggregate all major developers' standards. One such search engines is the ANSI-based NSSN http://www.nssn.org/. When the key search term 'medical device' is entered, a list of device-relevant standard documents with associated titles and SDOs' names appears. Other search terms to be considered include the device's primary function and application, i.e., drug delivery, therapy, ablation.

Some regulatory authorities like FDA and bodies like the EC medical devices unit also have databases a manufacturer can search for recognized consensus standards applicable to the device being developed. For FDA, one helpful method is determining potential predicate(s) for the device under development and the corresponding FDA product code classification (e.g., DTC is the Pacemaker Generator Function Analyzer product code). FDA's database for recognized consensus standards can be searched to locate those associated with the same DTC

product code. In this example, two recognized consensus standards appear: ISO 27185:2012 *Cardiac Rhythm Management Devices—Symbols to be Used With Cardiac Rhythm Management Device Labels and Information to be Supplied—General Requirements* and ISO 27185 First Edition 2012-02-15 *Cardiac Rhythm Management Devices—Symbols to be Used With Cardiac Rhythm Management Device Labels, and Information to be Supplied—General Requirements.*

**Note:** This example also illustrates the importance of regulatory strategy. For many new technologies and potential medical devices, no clear predicate is on the market, but options exist for combining and choosing predicates. Because the associated consensus standards vary with each predicate, this search can determine the necessary effort to bring the product to market under various regulatory strategies.

Since clear product or process standards for a particular medical device may not exist, a regulatory professional may be unable to find specific relevant standards for a device. Typically, this situation would occur if the device utilizes a particularly novel technology and/or claims an especially innovative intended use. In such a case, standards may not be able to cover all aspects of the device under development. The earliest endovascular grafts utilized standards for surgically implanted grafts, intravascular catheters[39] and vascular stents.[40] Applicable sections of each of the separate standards were incorporated into design input for the new endovascular grafts.[41] Similarly, some of the early catheter-delivered heart valves drew from standards established for surgically implanted valves and catheter delivery systems. Design teams need to be current on standards for all of their devices' design characteristics and draw broadly from standards that may even target a different device type.

For the EU (IMDRF for Australia, Japan, Singapore and Canada), the device's claimed intended use, purpose and primary intended mode of action must be identified first. *MDD* Essential Requirements (IMDRF Essential Principles) of safety and performance must be reviewed to identify those relevant to the particular device, the technologies it embodies and the processes by which it is to be manufactured.

A list of key words then can be generated to serve as key search terms for relevant standards using an SDO or service's (e.g., TechStreet or IHS Engineering Workbench) standards search engine. The resulting standards' lists then can be examined for specific applicability and narrowed further per search terms.

A similar approach could be followed for the US, although FDA does not use the Essential Requirements model. For the US, the regulatory professional would begin by reviewing the US CFR to identify relevant regulations for the device. This review can be conducted using the database at http://www.ecfr.gov. FDA also encourages manufacturers to discuss plans to use standards or any specific issues relating to use of standards during a presubmission meeting.

### *Case Study: A Hypothetical Magnetic Needle and Suturing Thread Device*

In this case, a regulatory professional is unable to locate relevant standards for a medical device easily. The manufacturer is developing a novel magnetic needle and suturing thread with a magnetic tip.[42] The search terms based on the claimed intended use, device's purpose, primary mode of action, Essential Requirements, technology and manufacturing processes could yield the following list:

- suture
- suturing
- surgical needle
- magnet
- magnetized instruments
- suture thread

Using these search terms, a list of standards is created:

- GME B 040 0367 Magnet Powder Paste
- BS 7507 Malleable Wires for Use as Sutures and Other Surgical Applications
- A-A-51410 Suture, Nonabsorbable, Surgical, Polypropylene, Monofilament, Single Armed

A review of these abstracts may eliminate certain nonapplicable standards. In this example, the Magnet Powder Paste standard would be eliminated because the magnet will not be in powder paste form. The remaining standards would be reviewed next. Reviewing the standards' texts is recommended to determine whether all or only certain clauses would apply to device development, evaluation and manufacturing, all critical global regulatory strategy elements.

It is important to remember a standard search is an iterative process dependent on the device development stage. A device in the conceptual or early development phase may change as new features, technologies, intended uses and/or purpose evolve. These changes, in turn, would affect the key search term list and resulting list of potential, applicable standards.

### *Case Study: A Hypothetical APDS With a Design Change*

In this case, the manufacturer is developing a new and improved infusion pump for the hypothetical APDS device presented earlier in the chapter. The improvement is the introduction of a Bluetooth wireless communication device utilizing artificial intelligence in an MMA, allowing caretakers and healthcare providers to monitor basal insulin dosage delivery remotely. Key search terms now could include Bluetooth, wireless communication, software medical device, and mobile medical device. Once a list of standards is generated, the manufacturer would examine the standards for relevance and select those matching its search criteria.

In this example, if the manufacturer intends to distribute the device in the US, FDA's presubmission process may be utilized to discuss a standard selection plan, any specific issues regarding the standards used relating to the specific design change, etc.

### *Finding Standards*

This section examines a few additional scenarios where a regulatory professional may not find medical device standards easily. Examples include: a keyword search yielding an unreasonably long list of relevant standards; an existing standard no longer reflecting a particular medical device's state of the art; a standard currently being used changing in the middle of medical device development or regulatory review; subsequent revisions to existing standards used in the original device design process being incorporated retroactively in devices already in commercial distribution; and the standard used previously being revised and resulting in a device design change.

It is possible, even after examining the list of standards for specific applicability and narrowing it further, numerous standards appear relevant. One approach is to determine whether any of these standards overlap in any way or each addresses a set of unique topics. If one addresses performance requirements and another test methodologies, both would apply. If one addresses a set of topics (EN ISO 13485:2016) and another an adoption of the same topics for a different jurisdiction (CAN/CSA-ISO 13485:16), the one most-aligned with the target jurisdiction should be selected. Any standard on the list that is a recognized standard in any target jurisdiction should be identified. It is important the regulatory professional look for common and similar requirements applicable in various target jurisdictions. A gap analysis is recommended. The extent of commonality or differences would impact the overall regulatory strategy greatly. If compliance with a standard's differences in any target jurisdiction leads to significant design and development changes and, therefore, increased time-to-market, the regulatory professional may recommend dropping the target jurisdiction.

A regulatory professional may find an existing standard no longer reflects a particular technology's state of the art. Typically, there is a lag between a new technology's introduction and its general acceptance as state of the art. It takes the user community and stakeholders several years to gain comprehensive knowledge of the technology, assess it and accept it until it can be formalized in a standard. If technology utilized in a device surpasses the standard, the manufacturer should assess the risk of incorporating it in a device under development. Factors to consider in this assessment include whether the perceived state of the art truly can become

the new state of the art and benefits and downsides of using the state of the art compared to the existing standard's recommendations. If the existing standard also is a recognized standard in a certain jurisdiction, the manufacturer should be ready to explain why the device does not comply with that standard. Presumably, the justification explains how the new technology meets or exceeds the standard's intent.

A regulatory professional also may find a standard has changed while a device is under development or regulatory review. Before considering approaches, the regulatory professional should review the standards development process. SDOs release drafts for a comment period, address those comments and release the final version. Upcoming revisions to widely used standards generally are publicized by the SDO and industry through publications to make stakeholders aware of proposed upcoming changes. Since standards are subject to periodic review and revision, it is possible for a standard to evolve into a newer version in the middle of medical device development or regulatory review. If this occurs, the manufacturer should gather as much information as available on pending changes and determine whether there is a transition period for adopting the new revision and whether this is a recognized standard. This information can be used to determine the impact on the manufacturer's device development timeline and process. The manufacturer may choose from a few options:

1. Design to both the current standard and what the manufacturer understands will be the new revision, assuming provisional changes do not conflict and add significant, additional development time.
2. Design to the current standard if the manufacturer believes by doing so it can achieve quicker market access with the current device. The manufacturer then will modify its next-generation device to meet the new revision's changes. This option is recommended in instances when:
    - there is uncertainty about the revision's release date
    - there is doubt the revision will become a recognized standard
    - the adoption transition period is known and the adoption deadline falls after the next generation device's planned launch
3. Design to the revised standard if the revision has been released already, the adoption transition period is known and occurs prior to the manufacturer's planned market approval and launch target dates.

It is important to note the adoption transition period for revised standards can vary from jurisdiction to jurisdiction, however, generally it is published by the SDO. One example is the known and expected transition period of 0 days between ISO 14971 and EN ISO 14971 in 2012. One caveat to revisions in the US is the revised version no longer may be recognized by a regulatory authority even if the previous version was an FDA-recognized standard.

A regulatory professional may learn a newer version of a previously utilized standard has been released after devices already are in production or commercial use. Whether subsequent revisions to existing standards used in the original device design process must be incorporated retroactively largely depends on the jurisdiction where the device currently is commercialized. In the US, FDA's Frequently Asked Questions on Recognition of Consensus Standards state changes in a recognized standard do not affect a product's clearance or approval status retroactively, so a revision is not required.

Finally, a manufacturer that declared conformance to a previous standard may need to modify a device. For this scenario, the regulatory professional may assume the current revision is recognized by FDA. In determining whether to comply with all parts of the revised standard, the regulatory professional should consider the effect that the modification has on the device's safety and effectiveness. "For some types of changes to a device, the Agency believes that submission of a new 510(k) is not required and that reliance on existing Quality System (QS) requirements (21 CFR 820) is the least

burdensome approach to reasonably assure the safety and effectiveness of the changed device."[43] If the modifications significantly affect safety and effectiveness, then a new premarket submission is generally required, as well as a new declaration of conformity, if the manufacturer choose to use one, and the new declaration of conformity would be for the revised standard(s) recognized by FDA. It may not be necessary for the manufacturer to comply with all portions of the revised standard(s), but the declaration of conformity should describe the portion(s) of the revised standard(s) the device does not meet and the rationale for them.

This section addressed approaches to handling a few atypical situations where the regulatory professional cannot locate a set of relevant standards easily. In many situations, the regulatory professional may want to follow or become involved directly in the standards review or development process. In addition to being able to tackle atypical situations, there are several benefits to getting involved, which are discussed in the next section.

## How to Get Involved

A medical device regulatory professional can become involved in the standards development or revision process by joining the working group in which he or she is most interested. The professional may start by exploring an SDO's website to understand various subcommittees', technical committees' or working groups' objectives and contacting the appropriate group. Generally, the group secretariat (lead) and local jurisdictional member organizations or members are posted on the SDO's website, for example:

1. Enter "Medical Device" and other relevant terms in the search box online, e.g., http://www.iso.org/iso/home.htm.
2. Numerous standards supporting medical device products and processes will appear as search results. Select ISO 10993-1:2018 Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing Within a Risk Management Process.
3. The next step is to select the link to TC/SC: ISO/TC 194.
4. Finally, select 'Contact details' to locate information for the TC/SC Secretariat and 'Participating Countries' for local country contacts.

Even without being a member of a national standard committee or SDO technical committee, interested regulatory professionals may monitor developments and submit comments on draft standards, either directly or through industry associations. It is possible to join SDO email list services at no charge. As an example, steps for joining the ISO newsletter are:

1. Access http://www.iso.org/iso/home.html
2. Scroll down to "Keep up to date with ISO."
3. Select the subscribe button to enter contact information.

There are business advantages for manufacturers that invest resources in standards' development work. Having early access to information that could shape the market in the future and impact device development programs provides awareness of standards' development trends. Manufacturers can become involved by sharing experiences and expertise, and their interests potentially can be addressed by a standard under development or revision. Participation in voluntary working groups provides not only a way to add technical contributions to standards' development but also learn other contributors' concerns and discuss approaches to addressing those concerns.

Finally, if a US manufacturer believes it may benefit from submitting a standard for FDA recognition, it may review *Federal Register* Notice 63 FR 9531 of 25 February 1998 for specifications. A medical device manufacturer interested in proposing a standard for recognition would follow an established process, including submitting: the standard title, reference number, date, and SDO; list of device types to which the standard would apply; and brief identification of the devices' testing, performance and/or any other characteristics that would be addressed by a declaration of conformity to that standard.

## Conclusion

Standards, by definition, are documents established by consensus and approved by a recognized body. Medical device standards provide for common and repeated use, guidelines or characteristics for activities or their results, aimed at achieving the optimal degree of order. In the medical device global regulatory strategy context, standards are considered "norms" in some countries that must be followed during the conformity assessment process to meet regulatory Essential Requirements. Using standards confers a presumption of conformity with mandatory regulatory requirements of these countries. In other countries, standards, in the context of meeting regulatory requirements, are not standalone documents and must be applied in parallel with local regulations. Generally, standards developed by SDOs are voluntary and should be utilized in consultation with local laws and IMDRF guidelines.

**Guidances, Resources and Standards**


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# 16 Global Medical Device Marketing Strategy

Updated by Charles Tam, MBA

## Introduction

It is critical for a company selling medical devices to have an executive business strategy updated on an annual basis. From the onset of all projects, it is essential to ensure close integration between the marketing and regulatory strategies. Failure to understand the impact of regulatory requirements supporting the executive strategy places the entire plan at risk and can result in unnecessary expense, costly delays or failure to obtain approval.

## Global Executive Strategy Development for Medical Device Companies

A medical device company's executive team selects its global strategy based on the company's target disease state and medical condition, focus and technological competency. For example, cardiovascular (CV) disease is a very broad disease state, and CV medtech companies may specialize in one or more selected areas of CV treatment or therapy segments. For example, interventional cardiology is focused on the treatment of coronary vascular obstructions (stents, balloons). Electrophysiology devices are used to treat another CV disease state, conductive aberrations in the heart (ablations, pacemakers, etc.) or body; these devices may be diagnostic or interventional. Structural heart disease includes congenital cardiac defects or those caused by abnormalities of the valves and vessels (aortic valve implants, patent foramen ovale (PFO) closure devices). Each of these medical conditions, among many others within CV, is strategically different and requires a different medical device strategic planning process. This results from the difference in call points, technologies, treatments, reimbursement funding discussions (public payor health systems), service expectations from physicians and hospitals and even the general personality of the medical specialty's physicians. As a broad generalization, physician specialties tend to have consistent levels of risk tolerance. Anecdotally, some specialists are perceived to be risk takers who are faster and more willing to adopt new technologies in treating disease than other medical specialty peers. The medical device company's executive team should assess and adapt to these differences.

A large medical device company could have a broad CV product portfolio of offerings to address multiple disease states, while smaller CV companies may specialize in only a few or even just one. Once the disease state and corresponding technologies are selected, the executive team defines a market strategy further based on company shareholder and expected stakeholder returns. There are four basic categories of products from which to select—existing product portfolio, new products, products or services for adjacent markets or whitespace research (advanced technologies in early development stages, i.e., first-in-human clinical investigational testing)—each requiring a different strategy. In some cases, the executive team will select a mix of product types to support the company's growth and profitability goals (**Table 16-1**). This chapter examines regulatory and business strategies for the two most common categories: the existing product portfolio and new products.