Medical Devices

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Introduction

Today's global medical devices industry faces many challenges. From providing basic treatments, through to utilizing sophisticated new technologies, companies are operating in a highly regulated and increasingly competitive environment. The long-term goal is to seek or secure harmonization across the regulations. Some of this is being driven by the International Medical Device Regulators Forum (IMDRF). This group has a number of differing regulatory projects under development, some of which have already been released – such as the Medical Device Single Audit Program (MDSAP).

In this regulated market, published standards also have a significant role to play. Although many of these standards may have originated at a local or national level, the efforts of organizations such as ISO and IEC, ensure that there is an increasing international consensus. This allows for manufacturers to design and produce a smaller number of variants to access different markets, thus helping them to be more effective and efficient in managing their cash, raw materials and finished goods stock.

Both ISO and IEC have committees managing a wide range of standards for use in the design, development and manufacture of medical devices. ISO committees also cover what might be described as the horizontal standards. These are applicable across all medical devices and cover topics such as quality management systems, risk management, symbols and labeling, sterilization, bio-compatability and toxicology.

All standards exist in a constant cycle of update and review. Committees of experts ensure every standard reflects the latest thinking by following due process as specified by the individual standards organizations. Many of these experts come from companies or organizations working directly in the relevant fields. Getting involved in these committees gives businesses the opportunity to influence the content and direction of the final published standard, putting them at the forefront of the latest developments.

For companies that are not able to participate, it is nonetheless important that they ensure their use and application of all relevant standards is current and up to date. Furthermore when a later revision of the standard is published, they will need to have processes and systems in place to assimilate these changes to maintain continuing regulatory compliance.

This report will look at some of the most recent changes in regulatory requirements for the manufacturers of medical devices. It also looks at how integrating standards into every stage of a product's development cycle is essential to its eventual success in international markets ●

Paul Sim, Regulatory Affairs Manager, BSI

"BSI is dedicated to promoting excellence throughout the medical devices sector. Working with organizations of all sizes in 182 countries worldwide, we improve performance, reduce risk and increase resilience right the way through the supply chain."

Howard Kerr, Chief Executive, BSI

Contents

4 Quality management: Key considerations for medical device manufacturers

A look at the recent revisions to ISO 9001 and ISO 13485 and the implications for companies and organizations working in the medical device supply chain.

6 Visibility for the road ahead:

Why it is essential for innovators and entrepreneurs to integrate standards from the very start of product development.

8 Key standards and regulations for the development of medical devices

10 Understanding changes in EU medical devices regulations

Outlining some of the main considerations for medical device manufacturers and exporters, in light of recent changes to EU regulations.

12 Why choose BSOL?

A faster, easier way to work with standards.

14 BSI training and certification

BSI provides the widest range of standards-related training available.

Quality management:

Key considerations for medical device manufacturers

Quality management standards are essential for everybody involved in the medical device supply chain. They have a direct and significant impact on all aspects of a product's lifecycle, from the first initial stages of design and production, right through to the effect it has on the quality of life of the end user. But perhaps most importantly, they are a vital component in meeting regulatory requirements when bringing a product to market.

The two main quality management standards for manufacturers of medical devices, ISO 9001 and ISO 13485, have both seen recent revisions and a resulting divergence in some of their content. The most obvious difference between the two standards is in their focus and scope. ISO 9001:2015 is concentrated on providing a quality product and is a general and generic standard for all quality management systems. ISO 13485:2016, however, is specific to the medical device sector and driven by the need for regulators to ensure that equipment produced is both safe and effective.

This regulatory emphasis manifests itself most fully in the required processes. ISO 13485:2016 maintains the necessity to record key processes and related documentation in a quality manual, whereas ISO 9001 gives more flexibility, allowing an organization to determine which documentation is maintained to ensure consistent results.

ISO 13485 has been revised to help manufacturers comply with global medical device regulations, building on the knowledge from all previous versions. It also includes expertise from quality system experts around the world, bringing increased requirements throughout the document, which covers all aspects of the device lifecycle. ISO 9001 allows much greater flexibility, with top management being able to assign responsibilities and authorities. It also has a much stronger emphasis on operational processes and how these enable an organization and its products to meet customer demands.

Key standards

ISO 9001: Quality management systems	With more than a million organizations certified to ISO 9001, it's the most widely recognized standard in the world. It sets out requirements for quality management systems and is suitable for all types of organizations
ISO 13485: Medical Devices Quality management systems	ISO 13485 specifies the requirements for a quality management system for organizations involved in one or more stages of the life cycle of a medical device. It provides the basis for ensuring consistent design, development, production, installation and delivery of products that are safe for their intended purpose.

Another significant difference between the two standards is how they facilitate continual improvement. ISO 9001 continues its focus on customer satisfaction, meanwhile ISO 13485 requires organizations to concentrate on the continuing suitability, adequacy and effectiveness of the quality management system, and the safety and performance of the medical device. Yet it is the similarities between the two standards that remain far more prevalent, and when working together, they provide a comprehensive quality management system for organizations operating within the sector's supply chain.

Both standards underline that the adoption of a quality management system is a strategic decision, which must be integrated into planning to ensure it aligns with commercial imperatives. Both standards require organizations to be clear in their role and purpose in the supply chain, and both start the product realization process by determining customer needs to drive product specifications.

In addition, both revised standards have maintained the use of the process approach, with the Plan-Do-Check-Act (PDCA) cycle as their core methodology. They also both advocate the use of risk assessments as the basis of decision-making, as well as the application of risk management to the quality management system processes.

Both standards have also been updated to reflect a shift from the identification of training needs, to the competency of employees. Both have a renewed emphasis on the determination of the necessary buildings, equipment and other resources, such as information technology, that are essential to processes and for ensuring product conformity. And both emphasize the use of statistical data analysis to guide actions and decisions.

But perhaps most importantly, when businesses are engaged in the implementation of a quality management system, they need to understand how the similarities and differences between ISO 9001 and ISO 13485 could influence the direction of future development. Is the priority to meet the demands of the regulator, the customer, or both? It is essential that an organization's senior management should seek to recognize how each of these two revised standards can work separately or together to achieve their goals and objectives ●

Visibility for the road ahead:

Why it is essential to integrate standards from the very start of product development

New ideas are not exclusive to big companies and organizations. Innovation comes from everywhere and many of today's medical device entrepreneurs are likely to have very little previous exposure to the requirements of a heavily regulated sector. In the early stages of development resources can be limited, so it is crucial that products are brought quickly and efficiently to market. This pressure to drive forward can result in an apparent conflict between the rapid deployment of a new concept, and the need to consider and meet a number of regulatory requirements.

However, there is no inherent reason for innovation to be chaotic, and there are many benefits to embracing the standards and structures that will be required to meet regulatory requirements right from the start. By applying the processes embodied by regulations, it is possible to proceed confidently towards final regulatory approval by the most efficient and effective path.

Formulated and continually reviewed by committees of international experts, standards are the physical embodiment of decades of industry experience. Utilizing them from the design stage provides the assurance that as each new phase of development is embarked upon, the design team hasn't overlooked something that could jeopardize success.

The reality is that a lack of structure can lead to entrepreneurs moving forward on the basis of bad assumptions, resulting in wasted time and, ultimately, a lack of the detailed documentation necessary to demonstrate compliance. One of the most common causes for the failure of start-ups is in reaching a relatively mature design stage only to discover that much of the early work will not meet final regulatory requirements.

At some point in the development of most new products, it is highly likely that funding will need to be secured. Whether approaching venture capitalists, investment bankers or government grant applications, anyone putting their resources behind a project will want to be reassured of the highest possible chance of success. Generating the appropriate amount of documentation will be of significant value when writing a grant application or business justification for independent financiers.

Many types of documentation will be needed to finally deliver a product to market. Quality plans, project schedules, risk management files, regulatory strategies, verification and validation matrices, as well as packaging, sterilization and usability requirements, will all have a significant role to play. For the major markets of the world, directives include Directive 90/385/EEC regarding active implantable medical devices, Directive 93/42/EEC regarding medical devices and Directive 98/79/EC regarding in-vitro diagnostic medical devices. Related regulations include FDA 21CFR part 820 (USA), Regulation (EU) 2017/745} and 2017/746, CMDR (Canada), PMD Act (Japan)

Entrepreneurs and innovators will rarely have the in-house systems and resources to negotiate the regulatory landscape and it is important that they partner with regulatory and compliance consultants to help them understand some of the less visible pitfalls on the road ahead. There are many considerations, for example, that need to be taken into account when upscaling for production, such as whether the device needs to be sold sterile? If so, which unique environmental controls will be needed?

The ultimate end game of all regulation is to achieve full risk management. The final device must be as safe as possible within the context of its clinical function and anyone with a product to sell must be able to demonstrate that all potential sources of harm have been identified, understood and prevented. In today's integrated world, regulatory requirements are fundamentally similar. By embracing internationally recognized standards from the earliest stages of conception and design, new medical devices will have the best chance of success in the global market ●

Key standards and regulations for the development of medical devices

1: CONCEPT

2: PLANNING

ISO 13485	Medical devices. Quality management systems. Requirements for regulatory purposes.
BS EN 60601-1	Medical electrical equipment. General requirements for basic safety and essential performance.
ISO 14971	Medical devices. Application of risk management to medical devices.
ISO 14155	Clinical investigation of medical devices for human subjects. Good clinical practice.
ISO 10993	Biological evaluation of medical devices. Tests for irritation and skin sensitization.
BS EN 62366-1	Medical devices: Application of usability engineering to medical devices.
ISO 15223-1	Medical devices. Symbols to be used with medical device labels, labeling and information to be supplied. General requirements.

Note: The above publications are generally referred to as 'horizontal standards', applicable to all types of medical devices. More detailed, product-specific requirements can be found in what are known as 'vertical standards', for example ISO 80601-2-13 Medical Electrical Equipment Particular Requirements for basic safety and essential performance of an anesthetic workstation.

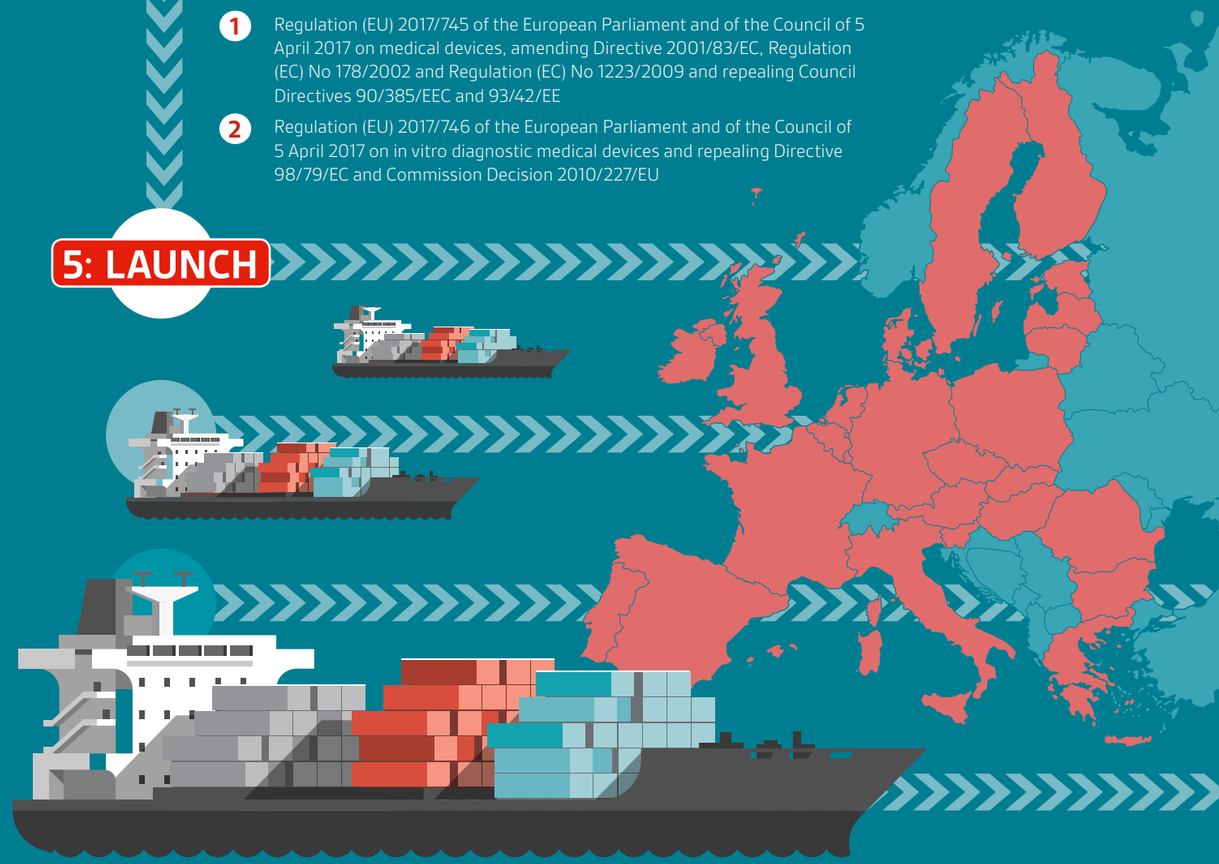
3: DESIGN

4: VALIDATION

Regulations

1. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EE
2. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

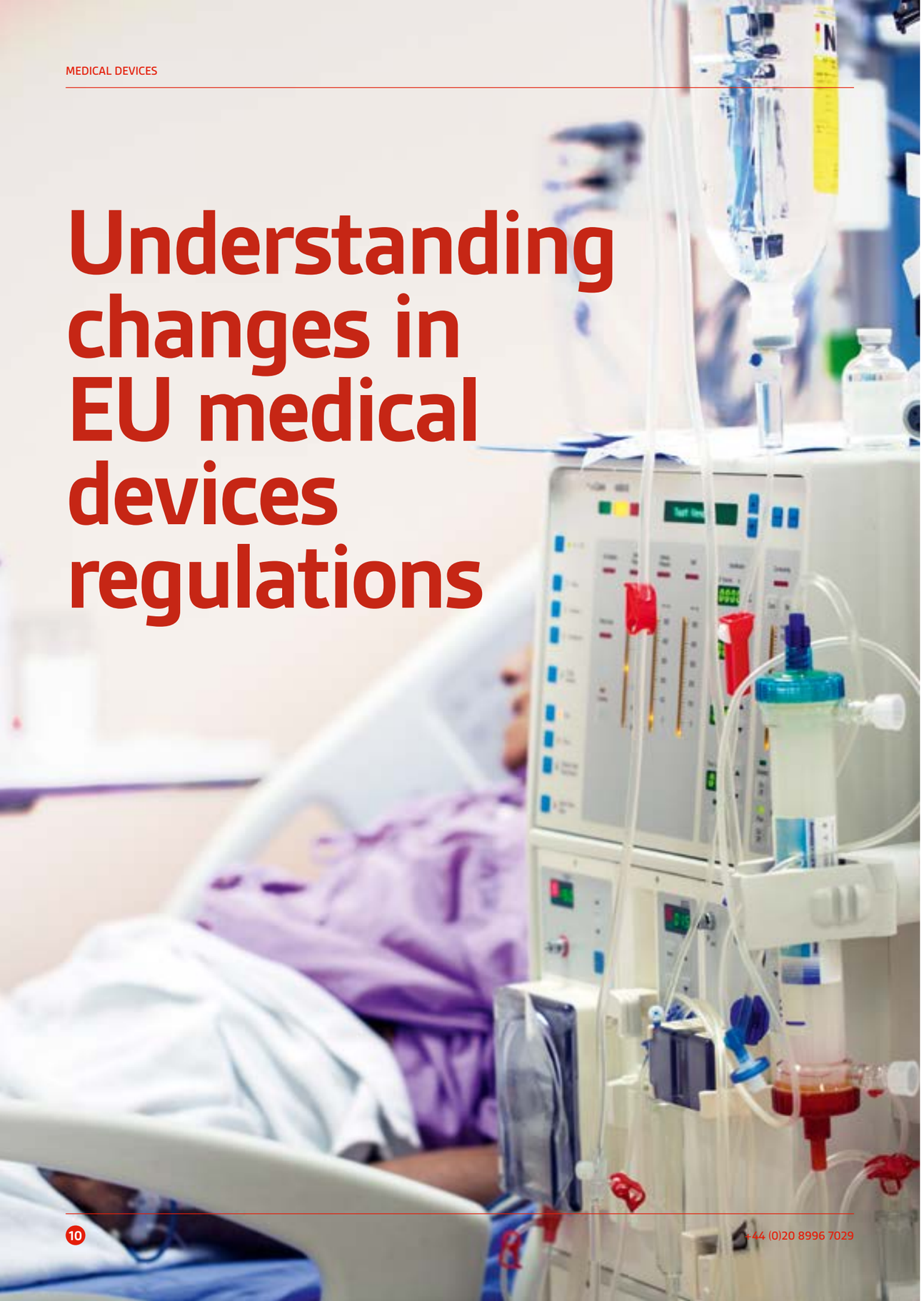
5: LAUNCH



Medical devices imported by the EU in 2015

- **Medical instruments** — US $39.7 billion
- **Orthopedic appliances** — US $25.3 billion
- **Medical x-ray apparatus** — US $2.02 billion
- **Medical, surgical or laboratory sterilizers** — US $245 million
- **Medical apparatus using alpha, beta or gamma radiation** — US $112 million

Understanding changes in EU medical devices regulations



The publication of the staple text of the European Union (EU) Medical Devices Regulation, and the In Vitro Diagnostic Medical Devices Regulation, in May 2017, documents the political agreement between the three EU institutions – the Commission, the Parliament and the Council – on the contents of the revision of the EU legislation for medical devices.

The revision extends the scope of the legislation beyond the manufacturer to cover the responsibilities of operators throughout the supply chain and will have a significant impact on anyone providing medical devices to countries in the EU. The availability of the text means manufacturers, authorized representatives, importers and distributors will be able to access how they will be affected by the changes and plan the necessary steps they need to take to meet any new regulatory requirements.

There will be no automatic acceptance (i.e. grandfathering) of existing CE-markings. Changes to the definition of what constitutes a 'medical device' means that all products will need to be reviewed against the revised requirements. It is essential for businesses and organizations to fully understand how these changes in definition will affect their current product portfolios. For example, 'medical devices' now include some products that were previously defined as 'accessories', such as those intended for cleaning, disinfecting or sterilizing.

Consequently, sterilization indicators that were previously outside the EU Medical Devices Directive are now defined as accessories to the sterilizing equipment and are, thus, covered by the regulation. There is also clarification that software intended to be used for medical purposes, is an 'active medical device', whereas software for general purposes (even when used in a healthcare setting or for lifestyle and wellbeing applications) is not. Also, included for the first time are requirements for products without an intended medical purpose, for example contact lenses with no correction for vision.

Clinical evidence will need to be reviewed, especially where it relies on demonstration of equivalence with a comparator. There must be no significant difference in the performance and safety of a device and the comparator and it will be necessary to justify that the device is equivalent, based on its technical, biological and clinical characteristics. This needs careful review as the regulations require a formal contract to be in place between the device manufacturer and the manufacturer of the 'predicate' device to which equivalence is being claimed. Many internal procedures will need to be adapted to the requirements of the Regulation. Design and development plans will need to be adjusted to address the increased requirements for clinical evidence, as well as considering many other factors, such as the use of hazardous substances and post-market clinical follow-up (PMCF).

Updating the quality management systems (QMS) will be a critical step in being able to CE-mark a device under the Regulation. It requires the QMS to be the place where the regulatory requirements come together to be implemented systematically throughout the life cycle of the device. It is the QMS that will need to drive the changes in the organization's processes and it is the QMS that will define and document the roles and responsibilities necessary. Ultimately, manufacturers must have a person responsible for regulatory compliance available within their organization, unless they are recognized as a micro or small enterprise, in which case it is permissible to utilize consulting support, provided the manufacturer has unimpeded access.

The Regulation defines additional detail for the content of the technical documentation and requires that the information be presented in a clear, organized, readily searchable and unequivocal way. It also requires manufacturers to have sufficient financial coverage for potential liabilities in the event of claims for compensation for damage caused by their devices.

There are many implications for the information that manufacturers are required to provide on labels and in instructions. Whether on the device, the packaging, a website or in the instructions for use, everything is likely to need to be changed to comply with the requirements. The Regulation also contains significant changes in manufacturers' approach to the post-market area, including post-market surveillance (PMS) planning and implementation, vigilance reporting and handling field safety corrective actions.

Further changes are likely and there are more than 40 identified areas where additional detail will be produced by the European Commission in the form of delegated and implementing acts that are yet to be published. In addition, it is likely that a substantial body of guidance will be needed to ensure that the implementation is uniform.

The Medical Device and In Vitro Diagnostic Medical Device Regulations are the result of the planned revision of the EU Medical Devices Directives and represent the most significant change to the European legislation for medical devices for nearly 20 years. Understanding the requirements is key to developing an implementation plan in order to ensure continuing regulatory compliance and the ability to provide the EU market with safe medical devices that perform as intended ●

Disclaimer

While this paper is focused on the Medical Devices Regulation, in many aspects the requirements of the In Vitro Diagnostics Medical Devices Regulation parallel the Medical Devices Regulation. The material presented here is intended to be as generic as possible and applies in large part to both regulations.

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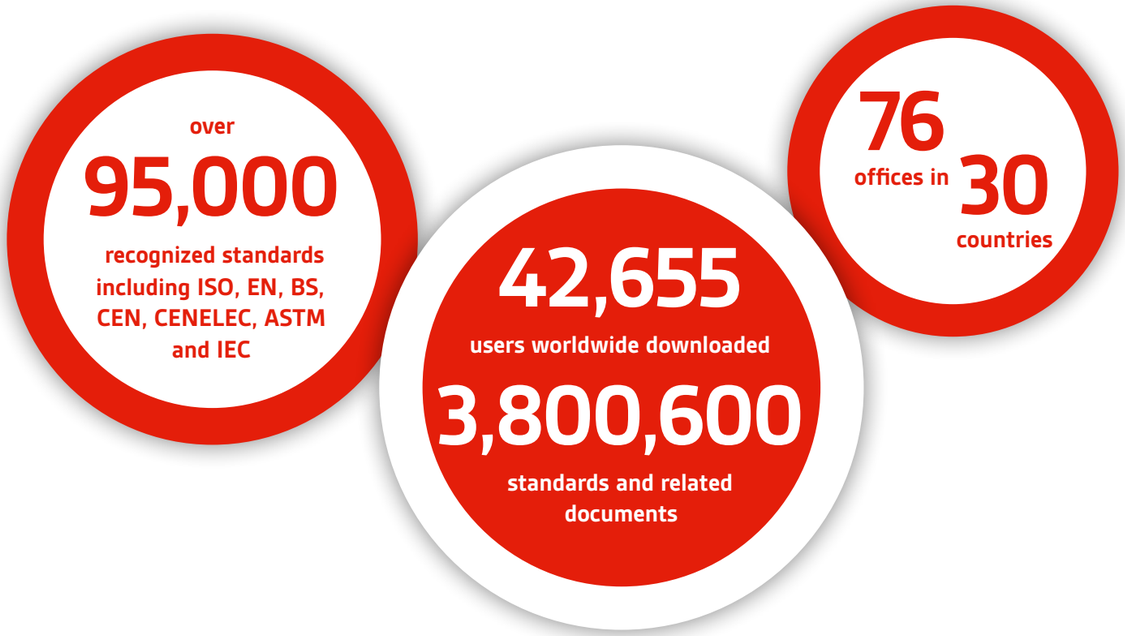
Martin Lockton, Regulatory Affairs Manager, Specsavers



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References

Pg 4 & 5: Quality management: Key considerations for medical device manufacturers

This article is based on the original BSI white paper:
The differences and similarities between ISO 9001:2015 and ISO 13485:2016. Can we integrate these quality management standards?
By Mark Swanson, President and Lead Consultant, H&M Consulting Group.
More detail on these topics and more can be found across a range of healthcare and medical device white papers, see here:
https://www.bsigroup.com/en-GB/medical-devices/resources/whitepapers/

Pg 6 & 7: Visibility for the road ahead

This article is based on the original BSI white paper:
Negotiating the innovation and regulatory conundrum.
by Mike Schmidt, Principal Consultant and owner of Strategic Device Compliance Services Jon Sherman, Director, Sustaining Engineering, Atricure inc.
More detail on these topics and more can be found across a range of healthcare and medical device white papers, see here:
https://www.bsigroup.com/en-GB/medical-devices/resources/whitepapers/

Pg 10 & 11: Understanding changes in EU medical devices regulations

This article is based on the original BSI white paper:
Planning for implementation of the European Union Medical Devices. Regulations – Are you prepared?
By Eamonn Hoxey, Vice President, Quality & Compliance, Johnson & Johnson Medical Ltd.
More detail on these topics and more can be found across a range of healthcare and medical device white papers, see here:
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