QA CONSULTING

WHITE PAPER

Bringing New Medical Devices to Life: The MedTech Startup Guide to Quality Systems

It all begins with an idea.

Whether it's on the back of a napkin or a handmade prototype, it's never too early to start thinking about how to bring your idea to life safely.

As a regulated industry, medical device manufacturers must adhere to international standards and comply with regulatory controls established by the countries' governing bodies in which your product is sold and distributed.

In the United States, the Food and Drug Administration (FDA) oversees regulatory controls for medical devices. The regulatory controls and pathways to market are based on the level of risk associated with your device.

This guide is intended to help medical device startups understand the quality and regulatory environment to bring safe and effective products to market.

Start with Success: Avoid Delays and Reduce Costs

From funding and investors to supply chain and technical hurdles, medical device startups face many challenges. Quality systems, regulatory compliance, and the biological safety of their devices shouldn't be among them.

Without a quality and regulatory strategy in place, you increase the likelihood that your product will take longer than necessary to get to market, and at an increased expense.

Here are our expert tips that will help your startup bring your medical device to market most efficiently:

- **Start early.** Ideally, you should engage a quality and regulatory partner at the very beginning of your startup journey.
- **View your quality and regulatory strategy as an opportunity, not a hurdle.** Quality and regulatory requirements help you bring safer, more effective products to market - they're not just check boxes.
- **Document, document, document.** Without a documented design history file, including design verification and validation test results, you increase the likelihood that you will have to repeat expensive testing and risk regulatory delays.
- **Prepare to scale.** Implement a design transfer plan that is relevant as your company grows.
- **Keep the patient top-of-mind.** At the end of the day, you are bringing a device to market that will help improve the health and well-being of real people. You should never lose sight of how they will use and interact with your product.

7 Quality System Must-Haves

As you embark on your journey to bring your device to market, here are seven processes and procedures that will help you succeed:

1. Design Controls

The FDA stipulates that Class II and III medical devices, and a small number of low-risk Class I devices, follow the design control requirements in 21 CFR §820.30.

A simple and pragmatic design control process helps protect patients by identifying possible issues with product development. It may prevent a product redesign or a potential recall downstream.

2. Design and Development Planning

Without a design and development plan that takes into consideration the quality and regulatory requirements of the device you're bringing to market, you're sure to encounter delays and undue expenses.

A design plan that details your goals, objectives, interfaces, responsibilities, and schedules is necessary to bring your product to market most efficiently.

3. Documentation and Record Controls

In such a highly regulated industry, documentation is necessary to meet quality and regulatory requirements. Everything from your design controls to customer complaints must be documented.

Without an efficient document control system implemented effectively across your organization, a minor documentation error can lead to a delay or recall.

4. Purchasing Controls

To satisfy 21 CFR Part 820, manufacturers must document and follow procedures to ensure all products, services, and materials that are purchased adhere to a specific set of standards, including quality requirements.

Manufacturers must define, document, and maintain requirements and purchasing data. The selection of all suppliers, contractors, and consultants must meet these requirements.

5. Supplier Qualification

As a startup, you are likely outsourcing the production of your device, including the assembly and packaging.

Partnering with reliable ISO 13485 and ISO 9001 certified contract manufacturers is critical to your success. Do your due diligence to ensure the suppliers you contract with can meet or exceed your quality and regulatory objectives.

6. Risk Management

All medical devices have some level of associated risk. To mitigate possible issues, start by identifying potential hazards and prioritize the associated risks.

After you've identified potential risks, develop an ISO 14971 compliant benefit-risk profile that considers your risk tolerance.

7. Design Transfer and Process Validation

As your product moves from development into production, the output of your product must be consistent. You must prove that all processes efficiently produce results that are reliably achieved.

Validation protocols, testing requirements, and robust reporting are necessary to meet your timeline for product development.

Standard Operating Procedures (SOPs)

Standard operating procedures are the foundation of a robust quality management system if implemented effectively.

SOPs set the stage for how your startup operates and are critical to compliance with current Good Manufacturing Practices (cGMP) and the successful completion of FDA inspections and notified body audits.

An SOP should include, at minimum, the following sections: Purpose, Scope, Responsibilities, References and Procedure. A Definitions section may also be helpful if definitions are not defined elsewhere within the QMS.

- **Purpose:** This statement should directly correlate with the general statements from the relevant standard and regulation. QA Consulting recommends specifically referencing the exact section of the applicable standard(s)/regulation(s).
- **Scope:** This is typically a 1-2 sentence statement that clarifies what aspects of the company or quality system apply to the document. It is also important to clarify any exclusions within this statement as well.
- **Responsibilities:** This section summarizes the primary responsibilities identified within the procedure and who maintains that responsibility (by title and/or department), such as who conducts the activities defined within the procedure and who reviews and approves the outputs of the procedure.
- **References:** Relevant regulations, procedures, work instructions, forms, etc., referenced within the body of the procedure should be listed here.
- **Procedure:** This section details requirements for how the company will comply with the relevant standards and regulations. Requirements should make general statements about how the organization will satisfy each requirement listed within the appropriate standards/regulations relevant to the procedure at hand.

While you can purchase off-the-shelf templates, it is better to develop SOPs unique to your organization and the type of device you're selling.

Off-the-shelf SOPs are easy to obtain online for a nominal fee, but the generic nature of these templates has many drawbacks, including:

- Absence of protocols and procedures specific to your device
- Lack of understanding of the nature of startups
- Dearth of real-world implementation guidance

When it comes to SOPs, the adage 'you get what you pay for' is undoubtedly true.

Startups that invest in SOPs tailored to their unique goals and objectives upfront are far more likely to get their device to market more efficiently than those who put their blind trust in the internet.

In the long-run, you will likely save time and money with SOPs authored to meet your specific needs and training to ensure they're implemented effectively across your organization.

Timeline: 4 Steps to Bring Your Device to Market

For devices that are sold and distributed in the U.S., the FDA outlines four premarket requirements.

1. Classify your device and its associated regulatory controls

It's not as simple as just determining if your device is Class I, II, or III. You must also identify the product code that is most appropriate for your device. Once you have determined the product code, the relevant regulation listed on the FDA website for that product code will tell you the classification of your device, the submission type, and whether general controls and/or special controls apply.

The FDA walks through the process of determining the classification of your medical device in this presentation.

If you are unsure of the classification of your device, a 513(g) submission may be initiated to request more information from the FDA to assist in classifying your device. Alternatively, if you think that a new classification is relevant for your device, the De Novo process may be appropriate. Both processes are subject to a review timeline, which may further extend the time it takes to determine your device classification.

Seek the advice of a regulatory consultant who can advise if either of these options are appropriate for you.

QA Consulting recommends documenting the rationale for the classification of your device and listing the regulatory controls within a regulatory strategy. Companies often find that they may need to reference the original regulatory strategy to educate new stakeholders on a project, potential investors, and anyone who might inquire about the original approach in the future (such as auditors, regulators, etc.).

2. Identify and complete the appropriate premarket submission

Once you have identified the product code classification for your device, the regulation for the product code will indicate what type of submission, if any, is appropriate.

Visit the FDA website for more information about the required elements for various submission types:

- Premarket Notification 510(k)
- PMA Application Contents

Become familiar with the Refuse To Accept Checklist relevant for your submission. This is the tool the FDA uses upon receipt of a submission to ensure that all required elements are present before passing the submission along for formal review. This checklist can also be used as an internal guide to ensure that no details are missing prior to submission.

If you are unsure about how to satisfy required elements for your submission, a Pre-Submission Meeting may be requested. This will allow you to officially correspond with the FDA and have them review and provide feedback regarding the appropriateness of your planned approach.

We recommend partnering with a medical device consultant who has experience completing the type of FDA submission required for your device because they will have:

- Insight into the mindset of FDA reviewers
- Experience and rapport with FDA contacts to seek advice in the process of submitting your device
- Access to well-developed templates that meet the submission requirements

An experienced consultant can also serve as your Official Correspondent and take on the burden of potentially intimidating correspondence with regulators.

3. Submit documentation and interact with the FDA during the review period

Your interactions and correspondence with individuals at the FDA should be handled with the utmost professionalism as you would in any formal business setting.

Address individuals as Mr./Ms. and always include a greeting and salutation in your emails. This is not the time to be casual. Write in complete, grammatically correct sentences using a formal business tone.

You should also send written minutes recapping any verbal interactions (including phone calls, virtual meetings, in-person meetings) with the agency and ask that they reply confirming that the minutes accurately reflect the discussion.

4. Comply with the regulatory controls

To market your product, general controls for medical devices require manufacturers to operate a full Quality Management System (QMS) that complies with 21 CFR 820 Quality System Regulation.

Ideally, the SOPs that comprise your QMS were developed prior to commencing design controls for your device and prior to submission.

In the case of startups, this is often done in parallel with the design control and regulatory submission processes. In either case, the full QMS should be in place prior to submitting documentation for your 510(k) or PMA.

Continue to operate under the established QMS even as you await submission review. Any activities relevant to the manufacture of your medical device are subject to general and/or special controls throughout the product lifecycle, which includes the development process prior to FDA clearance or approval.

Don’t Overlook Microbiology and Biocompatibility Testing

Every medical device submitted to the FDA must also show biocompatibility.

The nature of the patient contact, duration of the interaction of the device with the body, and the type of materials your device is composed of determine the biological endpoints, or testing, that is required to demonstrate biocompatibility.

At a minimum, every device with patient contact, whether direct or indirect, must consider the biological endpoints of the “Big Three” tests.

Results of the “Big Three” tests required with every FDA submission are:

- Cytotoxicity
- Sensitization
- Irritation

Depending on the materials of which your device is composed and how much patient contact it has, you may require additional testing.

Appropriate types of testing are detailed in ISO 10993-1, the international standard for the biological evaluation of medical devices, with additional guidance from the FDA.

In some cases, a rationale may be accepted in place of biological endpoint testing.

Devices manufactured from materials that have been well characterized both chemically and physically and / or have a long history of safe use in marketed devices may support a rationale that the biocompatibility of a device has been established.

The medical device risk profile will also detail how much existing data may be used to support a biocompatibility rationale in lieu of biological endpoint testing.

Table A.1: Biocompatibility Evaluation Endpoints

Medical device categorization by			Biological effect												
Nature of Body Contact		Contact Duration	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity#	Degradation@
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent (> 30 d)													
Surface device	Intact skin	A	X	X	X										
		B	X	X	X										
		C	X	X	X										
	Mucosal membrane	A	X	X	X										
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O			
	Breached or compromised surface	A	X	X	X	O	O								
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O	O		
External communicating device	Blood path, indirect	A	X	X	X	X	O				X				
		B	X	X	X	X	O	O			X				
		C	X	X	O	X	O	X	X	O	X	O	O		
	Tissue+/bone/ dentin	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Circulating blood	A	X	X	X	X	O		O^		X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		
Implant device	Tissue+/bone	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Blood	A	X	X	X	X	O		O	X	X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		

X = ISO 10993-1:2009 recommended endpoints for consideration*

O = Additional FDA recommended endpoints for consideration*

Note * All X's and O's should be addressed in the biological safety evaluation, either through the use of existing data, additional endpoint-specific testing, or a rationale for why the endpoint does not require additional assessment.

Note + Tissue includes tissue fluids and subcutaneous spaces

Note ^ For all devices used in extracorporeal circuits

Note # Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, devices with relevant target populations (e.g., pregnant women), and/or devices where there is the probability for local presence of device materials in the reproductive organs.

Note @ Degradation information should be provided for any devices, device components, or materials remaining in contact with tissue that are intended to degrade.

Source: https://www.fda.gov/media/85865/download

Quality and Regulatory Advice from the Real World

From R&D to Compliance With Efficiency

Company objectives:
Eximis Surgical sought assistance in taking their startup from the early stages as an R&D company to implementing an ISO 13485 compliant QMS.

Solution:
QA Consulting, Inc. developed standard operating procedures (SOPs), wrote and executed software validation protocols, and provided flexible document control support.

Outcome:
QA Consulting provided the structure our R&D team needed to create the design history files (DHF) for our clinical product acceptable to regulatory bodies.

Why QA Consulting?
The QA Consulting team is a one-stop-shop that offered all the expertise we needed to meet our business objectives.

> *"What I appreciated is the breadth of services that QA Consulting provided, including expertise with Grand Avenue Software. They offered quick and efficient QMS SOPs, and were pleasant to work with."*
>
> **Diane Keyser**
> *Director of Quality Assurance*
> Eximis Surgical

Easy Process to Quality and Regulatory Success

Company objectives:
Stiel Tech was seeking to commercialize a wound irrigation system to treat hard-to-heal wounds.

Solution:
Using good manufacturing processes (GMP), QA Consulting, Inc. effectively guided our cleanroom set up and established a regulatory system.

Outcome:
Today, Stiehl Tech LLC is a well run FDA-compliant shop and its wound irrigation system is on the market.

Why QA Consulting? Easy process and close working relationship helped us meet our long-term business objective to commercialize a new product.

> *"The close relationship I had with the QA team made for an easy process. As our company sought to commercialize a new medical device product, their knowledge and expertise helped us get the Perilav system to market."*
>
> **James B. Stiehl, MD**
> *Founder*
> Stiehl Tech, LLC.

APPENDIX / RESOURCES:

Medical Device Quality Standards Primer

Get to know the basics of the regulatory environment for the medical device industry.

Regulations vs. Standards

Regulations are rules of law issued by a governing body or agency over which it has authority.

Standards (also known as industry or consensus standards) are voluntary and typically developed by nonprofit organizations for use by the private sector and government authorities.

Where it can get confusing is that standards are often referenced in the regulatory process.

Even though industry standards are voluntary and you're not necessarily required to follow them for FDA approval, that's not an optimal strategy. If you do not follow the consensus standards, you have to make a strong case to the FDA why you did not do so. In the immortal words of Star Trek, resistance is futile.

Therefore, understanding the basics of standards is critical to getting your medical device to market.

Standards Organizations

Get to know the organizations that develop standards for the medical device market.

ISO

The International Organization for Standardization (ISO) is a worldwide federation of national standards bodies representing 165 countries, one from each country. Based in Geneva, Switzerland, ISO is a non-governmental organization established in 1947.

ISO's mission is to promote the development of standardization and related activities in the world to facilitate the international exchange of goods and services, and to develop cooperation in the spheres of intellectual, scientific, technological, and economic activity.

ANSI

The American National Standards Institute (ANSI) is the official United States representative to ISO. As a founding member of ISO, ANSI plays an active role in its governance.

ANSI's mission is to enhance the global competitiveness of U.S. business and the U.S. quality of life by promoting and facilitating voluntary consensus standards and conformity assessment systems, and safeguarding their integrity.

AAMI

The Association for the Advancement of Medical Instrumentation® (AAMI) is a nonprofit organization founded in 1967. AAMI is the primary source of consensus standards, both national and international, for the medical device industry, as well as practical information, support, and guidance for healthcare technology and sterilization professionals.

IEC

The International Electrotechnical Commission, founded in 1906, is the world's leading organization that prepares and publishes International Standards for all electrical, electronic, and related technologies.

Do You Know Your Medical Device Standards?

The following are essential standards every medical device manufacturer should understand the basics of:

- ISO 13485 sets out the requirements for a quality management system specific to the medical device industry.
- ISO 14971 specifies the terminology, principles, and a process for risk management of medical devices.
- ISO 10993 establishes the general principles governing the biological evaluation of medical devices.
- IEC 60601 applies to the basic safety and performance of medical electrical equipment and services in the home healthcare environment.
- IEC 62304 defines the life cycle for medical device software.

ISO standards are reviewed at least every five years to determine if revisions are needed to remain current in the marketplace. Medical device manufacturers must comply with the most recent revision of the standard, and therefore must stay-up-to-date. This state of continually evolving standards is one of the primary reasons startups often select a consulting partner with specialized expertise instead of handling them independently.

If necessary, ISO Technical Committees also issue Technical Report (TR) guidance on the application of specific ISO standards. For example, ISO/TR 24971 provides guidance on the application of ISO 14971.

As it relates to federal regulations in the United States, the U.S. Food & Drug Administration (FDA) typically adopts ISO standards. Here is the complete list of the FDA's Recognized Consensus Standards. Depending on the classification of the medical device product you're attempting to bring to market, different standards may apply.