Sparta Systems

How Evolving Regulatory Pressure Will Impact Emerging Life Science Companies

Whitepaper

Executive Summary

Historically, regulators and manufacturers were most concerned with ensuring a manufacturer's quality processes and systems complied with the specifics of a regulation—in essence checking the compliance box. But today, the U.S. Food and Drug Administration (FDA) and other regulators want a manufacturer to prove not only its compliance, but also its commitment to instilling quality into every aspect of its operations—from design and manufacturing all the way through to patient outcomes.

The life sciences industry is undergoing a fundamental shift, with a growing focus on quality as regulators, payers, clinicians and patients demand exacting safety standards, access to affordable drugs and devices and improved outcomes. The FDA and other regulators have enacted new guidelines and regulations to drive manufacturers to establish systems and processes that proactively identify and prevent issues.

Fundamental to this shift is a manufacturer's ability to provide regulators and executives with greater visibility into its operations and quality processes. Many of the new regulations and guidelines require that manufacturers make substantial changes to their quality systems, data management and submission processes—including:

- **Digital/Electronic Submissions:** Manufacturers must transition from paper to electronic regulatory submissions.
- **Quality Data:** Manufacturers must provide more in-depth data and documentation, including evidence of quality system effectiveness.
- **Supplier Collaboration:** In many cases, these changes apply not only to the manufacturer, but also to its suppliers, as they too will have to provide greater visibility into their quality operations.

Most enterprise life sciences companies have been building out their quality systems for years, therefore they will likely be able to adapt to these regulatory trends without major updates. On the other hand, these changes will have a disproportionate impact on mid-sized and emerging life sciences companies as they have typically done the minimum with regards to updating their systems, and have been able to "fly under the radar" for the most part when it comes to regulatory scrutiny.

In this paper, we examine:

- Why the life sciences industry must emphasize quality over mere compliance.
- Current and emerging guidelines and regulations aimed at improving medical device and pharmaceutical product quality.
- The challenges posed to mid-sized and emerging life sciences manufacturers.
- Why companies should act quickly to align to these upcoming guidelines and regulations.

The Drive for Quality

As in the past, regulators still demand that life sciences manufacturers comply with their various regulations in order to sell products in their respective markets. The difference today is that manufacturers must bear the added burden of proving to regulators that they are leveraging quality to improve manufacturing processes—reducing cycle times, shortages and recalls—the results of which improve patient safety and outcomes.

Quality Issues: Medical Device

The impetus for this change has been building for many years. On the medical device side, the FDA issued its 2011 report: Understanding Barriers to Medical Device Quality, which found[1] :

- Failures in product design and manufacturing process control caused more than half of all product recalls.

- Serious adverse event reports related to medical device use have outpaced industry growth by 8% per annum since 2001.
- Quality risk is not evenly distributed across the industry. This reflects the heterogeneity and complexity of the devices, manufacturers, and use environments. Cardiovascular, in vitro diagnostic (IVD), and general hospital/surgical devices account for nearly 60% of adverse events reports. Only 20 of the 1,189 active product codes account for 65% of all serious adverse events reports between 2005 and 2009.

"We have heard that too much of a focus on compliance with FDA regulations, rather than on device quality, drives some companies to focus on making FDA inspectors happy and checking the quality system regulation requirements boxes rather than focusing on innovating around device quality. The Agency realizes that in the past, the focus of the relationship between FDA and industry may have been on managing compliance rather than on a shared goal for continuously improving quality."

- Jeff Shuren, M.D., Director of the FDA's Center for Devices and Radiological Health (CDRH)*

* Matlis, Daniel, R., FDA Shares the Secret to Stopping Inspections, MedTech Intelligence, January 23, 2017

Quality Issues: Pharma

With regard to pharmaceuticals, the FDA data has uncovered the following problems in pharmaceutical manufacturing and its regulation[2]:

- Product recall and defect reporting data demonstrate unacceptably high occurrences of problems attributed to inherent defects in product and process design; these data further indicate failures in the implementation of manufacturing process scale-up as well as routine production.
- There have been alarming shortages of critical drugs over the past few years. Many of these shortages were caused by the use of outdated equipment, reliance on aging facilities operating at maximum production capacity, and lack of effective quality management systems.
- Current regulatory review and inspection practices tend to treat all products equally, in some cases without considering specific risks to the consumer or individual product failure modes. A disproportionate amount of regulatory attention is devoted to low-risk products and issues, diverting resources needed for the assessment of high-risk products.
- FDA has only limited information about the current state of pharmaceutical quality. FDA has no formal means for quality surveillance, except through inspections, and lacks resources to comprehensively review annual reports and other data (e.g., recalls and Field Alert Reports), which may provide significant amounts of pharmaceutical quality information. Furthermore, inspection findings have not been a reliable predictor of the state of quality.
- Inspection is not well-connected to knowledge gained from product review. Inspections often cannot cover all products and processes, so they rely on a limited subset of representative products and processes, often without reference to the specifics in the approved application. Likewise, product review is often conducted based on pre-marketing data from exhibit or clinical batches; there may be a significant disconnect between these data and the conditions under which the material is manufactured during commercial production.

Pressures on Regulators to Change

Uncovering problems in life sciences product quality is a "Pandora's Box" for the FDA and other regulators. They recognize that they must enhance their oversight, but do not have the bandwidth to do so within their current models. They are facing increased pressure from end users and patients at a time when they are struggling to keep up with the demands of a life sciences industry that is changing and growing at an unprecedented rate.

Consider the following:

- There has been significant growth in drug products applications.
- The global pharmaceutical development and manufacturing environment has become increasingly complex.

"The (pharma) industry is saddled with a set of products whose process design has been geared for speed to market, not for quality in mass production; there are few incentives to reformulate and retest products that were proven effective decades ago. Very few pharmaceutical manufacturers have found ways to make low-cost updates to existing processes and face expensive change controls or regulatory filings, which means that known quality issues or underperforming processes can linger for years. Additionally, there is a persistent sentiment that 'if we dig too deeply into quality issues, we may learn something we're better off not knowing. Indeed, the risk and costs of these counter-incentives slow the progress that pharmaco executives want.'"

- McKinsey & Company, Flawless: From Measuring Failure to Building Quality Robustness in Pharma, February 2015

- There has been an upsurge in drug shortages, recalls, and other quality issues.
- Medical technologies are becoming increasingly complex and varied with the introduction of new medical software, artificial intelligence, and combination products.[3]
- Inspections are increasingly global, although highly consistent. International inspections are up more than 200%, although 80% of inspection issues are in one of a few code sections.[4]
- Multiple agencies are increasing staff in India and China[5].

New and Emerging Regulations

Pressures to improve quality within the life sciences industry have prompted a number of new guidelines and regulations, most of which require manufacturers to shift from paper to digital/electronic submissions; become more data-driven in their operations and documentation; and collaborate more closely with suppliers to ensure quality throughout the product lifecycle.

"CDRH envisions a future state where the medical device ecosystem is inherently focused on device features and manufacturing practices that have the greatest impact on product quality and patient safety."

- Center for Devices and Radiological Health (CDRH) 2016-2017 Strategic Priorities

The FDA's Case for Quality Initiative[6]

In conjunction with its 2011 report: Understanding Barriers to Medical Device Quality (cited above), the FDA launched the Case for Quality, a program that "helps the FDA and manufacturers understand and sustain the link between a quality improvement approach and the benefits such approach provides."

The program is designed to help the FDA identify device manufacturers that consistently produce high-quality devices. That way, the agency can focus more of its efforts on helping manufacturers with quality issues raise their level of quality. This program also helps the FDA "identify and promote practices that support consistent quality manufacturing, and align its regulatory, enforcement, and compliance approaches with those practices."

The Case for Quality consists of three core components:

- **Focus on Quality:** The FDA treats compliance attainment as the baseline and looks for the inclusion of critical-to-quality practices that result in higher quality outcomes. The FDA has been working with stakeholders* to promote manufacturers' implementation of critical-to-quality practices during device design and production. These practices range from design improvements to meet customer needs to controlling production errors and increasing speed of detection for quality issues.

- **Enhanced Data Transparency:** The FDA proposes to leverage the broad array of quality related data it receives, including information from recall and adverse event reports and inspection results, through multiple strategies that support device quality. For example, to enhance independent analyses by stakeholders, the agency is publishing this data so that it can be automatically accessed and searched by external analytical tools.
- **Stakeholder Engagement:** The FDA works with the Medical Device Innovation Consortium (MDIC) and other stakeholders on Case for Quality to approach medical device compliance and quality more collaboratively, and to launch initiatives that vary from the agency's traditional oversight models.

*Stakeholders are defined by the FDA as "industry, health care providers, patients, payers, and investors."

On October 18, 2017, the FDA is holding a public workshop to announce a proposed framework and preliminary outline for a voluntary pilot program that "recognizes an independent assessment of manufacturing and product quality.[7]" The FDA, in collaboration with MDIC, developed the framework based on the Capability Maturity Model Integration (CMMI) model, which is a process level improvement, training and appraisal program that has been leveraged successfully by other industries.

According to the FDA's announcement of the workshop in the Federal Register, the CMMI Institute "certifies and coordinates third party appraisers evaluating voluntary industry participants and any data necessary to demonstrate product performance. The appraiser would evaluate the firm's quality system maturity and manufacturing processes, and identify any gaps or where a participating firm is performing above a compliance baseline."[8]

The agency notes that "the CMMI maturity appraisal process is not intended to serve as an FDA inspection nor is it intended to be a new regulatory requirement." Rather, it is "intended to be a driver of continuous process and product improvement and business value to voluntary participants in the pilot program."

The FDA's Quality Metrics Program*

In January 2015, the FDA established the Office of Pharmaceutical Quality (OPQ) within its Center for Drug Evaluation and Research (CDER), which encourages pharmaceutical firms to embrace continuous improvement and foster a culture of quality by collecting and reporting manufacturing quality data.

Six months later, in July 2015, the FDA issued its Request for Quality Metrics draft guidance. The guidance described how CDER intends "to collect data and quality metrics to help ensure that policies and practices continue to support continuous improvement and innovation in the pharmaceutical manufacturing industry."

Under the OPQ, the FDA plans to leverage its authority to collect product and site-specific quality metric records in place of or in advance of an inspection, and for companies with plenty of quality metrics data that could mean reduced on-site inspections. The focus of the initiative is to promote proactive quality management behavior to deliver better quality and safer products versus adopting a reactive inclination by just monitoring with post market surveillance.[9]

In November 2016, the FDA issued revised draft guidance[10] , where it announced that it was initiating a voluntary reporting phase of the program. Beginning in early 2018, the agency anticipates accepting voluntary submission of data from owners and operators of certain human drugs establishments, especially manufacturers of covered drug products and active pharmaceutical ingredients (API) used in covered drug products.[11]

With regards to the quality metrics themselves, the FDA requests the following primary metrics:

- Lot Acceptance Rate (LAR) as an indicator of manufacturing process performance. LAR = the number of accepted lots in a timeframe divided by the number of lots started by the same covered establishment in the current reporting timeframe.
- Product Quality Complaint Rate (PQCR) as an indicator of patient or customer feedback. PQCR = the number of product quality complaints received for the product divided by the total number of dosage units distributed in the current reporting timeframe.
- Invalidated Out-of-Specification (OOS) Rate (IOOSR) as an indicator of the operation of a laboratory. IOOSR = the number of OOS test results for lot release27 and long-term stability testing invalidated by the covered establishment due to an aberration of the measurement process divided by the total number of lot release and long-term stability OOS test results in the current reporting timeframe

> *"The (FDA's Quality Metrics) program is voluntary in 2018, but most manufacturers should still assess their quality systems, update the metrics and prepare metrics data for submission. As a keystone initiative, quality teams can use this program to revitalize their processes and systems."*
>
> **- Aravindhan (Arvi) Ramakrishnan, Manager within KPMG's Life Sciences Advisory Practice***
>
> *5 Important Takeaways From The FDA's Revised Quality Metrics Guidance, Pharmaceutical Online, February 23, 2017

The FDA intends to launch an electronic portal in January 2018, through which manufacturers can submit voluntary data. Once the voluntary phase is completed, the FDA will perform a data analysis and then publish initial findings and the quality metric reporters list on its website. From there the agency intends to develop a mandatory quality metrics reporting program.

* For additional details on the program, please read our white paper entitled, Guide to FDA's Quality Metrics Initiative.

The FDA's Electronic Medical Device Reporting (eMDR)*

The FDA's eMDR final rule requires device manufacturers and importers to submit MDRs to the FDA in an electronic format that the FDA can process, review, and archive. As of August 13, 2015, manufacturers and importers were required to submit all MDR reports electronically.

The eMDR process requires submitting organizations to create an XML file and then transmit it electronically via electronic data interchange (EDI) to the FDA's Electronic Submissions Gateway (ESG). EDI transfer ensures security and data integrity by assuring that data transmission is securely encrypted and verified. This process is controlled with Digital Certificates that are used to authenticate both the sender and receiver to one another to ensure files are delivered securely. Once the FDA has received the eMDR information, three separate acknowledgments are sent back to the reporting organization, confirming that the data has been received by the FDA, CDRH, and the adverse event database (MAUDE).

Like all regulations, the FDA's eMDR final rule continues to change and evolve. In the first half of 2017, the FDA made a variety of enhancements to the eMDR system stressing that "AS2 submitters should begin planning updates to comply with these eMDR changes as soon as possible."[12] On the next page is a table of these changes.

2017 eMDR System Enhancements[13]

Summary	Comments	Schedule
Mandatory B5 and H1	Manufacturer initial reports must include a value for B5 and H1. Reports that contain only whitespace for B5 will be rejected. Reports that do not indicate Death, Serious Injury, or Malfunction in H1 will be rejected.	Production deployment on February 2, 2017
D4 UDI guidance update	Submitters were previously instructed to enter the full human-readable UDI in the D4 UDI field. This guidance has been updated to request that manufacturers include only the DI portion of the UDI in this field. User Facility reporters that are not aware of the suspect medical device's DI should continue to enter the full human-readable UDI printed on the device.	Effective immediately
3500A version 9/30/2018 updates	The eMDR system will be updated to include fields from the newest version of the 3500A form. The major addition is section A5 (Ethnicity/Race). This field is not mandatory for eMDR submissions, but FDA is requesting that AS2 submitters add this field to their systems by July 1, 2018. Details will be included in a future version of the eMDR implementation package, which will be available prior to this change.	Live in test eMDR on June 12, 2017. Live in production eMDR and eSubmitter on June 29, 2017
HL7 ICSR R2 XML format update	The eMDR system will be updated to accept HL7 ICSR R2 format XML. Although the R2 schema allows for multiple devices and multiple patients in a single report, eMDR will continue to accept only one device and one patient per report. AS2 submitters will be able to indicate whether their XML is in R1 or R2 format using a new schema element (submissions without this element will continue to be processed as R1). After a one year grace period, eMDR will cease to accept R1 format submissions on July 1, 2018. Details will be included in a future version of the eMDR implementation package, which will be available prior to this change.	Live in test eMDR on June 12, 2017. Live in production eMDR and eSubmitter on June 29, 2017
Combination product fields added	The new eMDR ICSR R2 XML will include elements from sections C and G of the 3500A that contain drug information. This will allow submitters to include information regarding to up to 20 drugs within a device-led combination product adverse event report in eMDR. AS2 submitters using ICSR R1 format will not be able to provide drug information. Details will be included in a future version of the eMDR implementation package, which will be available prior to this change.	Live in test eMDR on June 12, 2017. Live in production eMDR and eSubmitter on June 29, 2017
FDA Device Problem Codes update	The list of FDA Device Problem Codes used in F10 and H6 will be updated to harmonize with Annex A of the IMDRF Adverse Event Reporting terminologies. IMDRF codes will not yet be accepted by eMDR, but the new DPC hierarchy posted on FDA.gov will include a one-to-one mapping of IMDRF codes to FDA codes. FDA codes that are being retired during this update will continue to be accepted by eMDR until December 31, 2017. A separate announcement will be made when the new code hierarchy is published on FDA.gov.	Live in production eMDR and eSubmitter on July 7, 2017
Environment and Submission Type elements added to Ack3	A new element indicating the submission environment (production or test) will be added to both the HTML and XML Ack3. This element will allow submitters to detect when they have accidentally submitted to the wrong environment. Also, a new element indicating the CDRH submission type (3500A for eMDR) will be added to both versions of Ack3. AS2 submitters are advised to parse the Ack3 XML file using the XPath of each element, as the XPath of the previous Ack3 elements has not changed. This update was originally scheduled for production deployment on June 1, 2017, but was delayed due to industry feedback.	Live in test eMDR on April 7, 2017. Live in production eMDR on October 1, 2017

* For additional details on the program, please read our white paper entitled, Electronic Reporting: What you need to know to Comply with eMDR.

The FDA's Unique Device Identification (UDI) Rule*

A prime example of the shift to improved device quality and safety, the FDA's UDI rule requires manufacturers of most Class I, II and III medical devices to assign unique identifiers to their products and apply the UDIs to all levels of packaging down to the lowest unit

of use in both human and machine readable formats. Manufacturers are also required to submit data on their products to the FDA's Global UDI Database (GUDID), which is accessible to the public, most notably healthcare providers. The FDA published the final rule on September 24, 2013, and since that time compliance dates have been rolling out on a risk-based schedule (see compliance dates table below).

Compliance Dates Established by FDA in Conjunction with UDI Final Rule[14]

Compliance Date	Requirement
1 year after publication of the final rule (September 24, 2014)	The labels and packages of class III medical devices and devices licensed under the Public Health Service Act (PHS Act) must bear a UDI. § 801.20. Dates on the labels of these devices must be formatted as required by § 801.18. Data for these devices must be submitted to the GUDID database. § 830.300. A 1-year extension of this compliance date may be requested under § 801.55; such a request must be submitted no later than June 23, 2014. Class III stand-alone software must provide its UDI as required by § 801.50(b)
2 years after publication of the final rule (September 24, 2015)	The labels and packages of implantable, life-supporting, and life-sustaining devices must bear a UDI. § 801.20. Dates on the labels of these devices must be formatted as required by § 801.18. A device that is a life-supporting or life-sustaining device that is required to be labeled with a UDI must a bear UDI as a permanent marking on the device itself if the device is intended to be used more than once and intended to be reprocessed before each use. § 801.45. Stand-alone software that is a life-supporting or life-sustaining device must provide its UDI as required by § 801.50(b). Data for implantable, life-supporting, and life-sustaining devices that are required to be labeled with a UDI must be submitted to the GUDID database. § 830.300.
3 years after publication of the final rule (September 24, 2016)	Class III devices required to be labeled with a UDI must bear a UDI as a permanent marking on the device itself if the device is a device intended to be used more than once and intended to be reprocessed before each use. § 801.45. The labels and packages of class II medical devices must bear a UDI. § 801.20. Dates on the labels of these devices must be formatted as required by § 801.18. Class II stand-alone software must provide its UDI as required by § 801.50(b). Data for class II devices that are required to be labeled with a UDI must be submitted to the GUDID database. § 830.300.
5 years after publication of the final rule (September 24, 2018)	A class II device that is required to be labeled with a UDI must bear a UDI as a permanent marking on the device itself if the device is a device intended to be used more than once and intended to be reprocessed before each use. § 801.45. The labels and packages of class I medical devices and devices that have not been classified into class I, class II, or class III must bear a UDI. § 801.20. Dates on the labels of all devices, including devices that have been excepted from UDI labeling requirements, must be formatted as required by § 801.18. Data for class I devices and devices that have not been classified into class I, class II, or class III that are required to be labeled with a UDI must be submitted to the GUDID database. § 830.300. Class I stand-alone software must provide its UDI as required by § 801.50(b).
7 years after publication of the final rule (September 24, 2020)	Class I devices, and devices that have not been classified into class I, class II, or class III that are required to be labeled with a UDI, must a bear UDI as a permanent marking on the device itself if the device is a device intended to be used more than once and intended to be reprocessed before each use. § 801.45.

Unique device identification impacts all aspects of quality management and manufacturers must make many significant changes to data, processes, and systems for compliance. Effective master data management is a critical component of compliance with the UDI rule, as manufacturers are required to acquire product attributes from various internal and external sources, aggregate this data into a single repository, configure it according to FDA requirements, submit it to the FDA's GUDID and ensure the product data within the GUDID is kept timely and up-to-date in accordance with FDA guidelines (e.g. data is resubmitted based on product changes, new products are added, etc.).

* For additional details on the UDI rule, please read our eBook entitled, Five Steps to UDICompliance Through EQMS.

The Drug Supply Chain Security Act (DSCSA)

The life sciences supply chain is constantly growing, both in scope and complexity, as manufacturers engage with suppliers and other collaborators across the globe, and extend their reach into new markets. Maintaining quality throughout the product lifecycle has become extremely challenging for manufacturers who operate in this environment of diverse players that cross geographical, cultural, and regulatory boundaries.

> *"Today's life sciences company has an increasingly fluid and innovative product portfolio and operates in a growing number of developed and developing markets. As a result the supply chain is increasing in complexity at the same time as scrutiny from national and international regulators is intensifying. The compliance capabilities of the industry are being tested by the need to interpret and comply with existing and emerging legislation and implement any necessary changes to the supply chain in response to these regulations in a coordinated, cost-effective and timely manner. Getting it right can be a source of competitive advantage."*
> **- Unravelling complexity: The challenge of compliance in the life sciences supply chain, Deloitte Centre for Health Solutions, April 2017**

In recognition of the patient safety risks that come from counterfeit, stolen, contaminated, or otherwise harmful pharmaceuticals in the pharmaceutical supply chain, Congress enacted Title II of the Drug Quality and Security Act (DQSA), in November 27, 2013. The Act outlines steps to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the U.S. The system is intended to protect U.S. consumers by improving the detection and removal of potentially dangerous drugs from the supply chain.

On June 30, 2017, FDA issued a draft guidance for industry entitled, Product Identifier Requirements Under the Drug Supply Chain Security Act – Compliance Policy, which updated the latest round of serialization requirements. The FDA encourages manufacturers and repackagers to serialize packages using a product identifier, serial number, lot number and expiration date by November 27, 2017, and will begin enforcing the regulation on November 27, 2018[15].

Additional Pharmaceutical Serialization Guidelines and Regulations

In addition to the FDA, a number of other regulators across the globe have implemented, or are in the process of implementing, pharmaceutical serialization regulations. It is estimated that by the year 2020, track and trace regulations will cover more than 80 percent of the global drug supply[16]. These regulations include:

- **Australia:** Therapeutic Goods Administration regulation requiring barcoding and enhanced labeling for all medicines for the Australian market.
- **Brazil:** National Agency of Sanitary Surveillance (ANVISA) RDC 54 pharmaceutical serialization and tracing regulation.
- **China:** State Food and Drug Administration (SFDA) national track-and-trace strategy.
- **Egyptian:** Drug Authority proposed serialization and track and trace reporting regulation.

- **European Commission (EC):** Falsified Medicines Directive (FMD).
- **India:** Directorate General of Foreign Trade (DGFT) track and trace system.
- **Russian:** FGIS MDLP federal repository and tracking system.
- **Saudi Arabia:** Ministry of Health bar code regulation and pending serialization requirements.
- **Taiwan:** Food and Drug Administration (TFDA) proposed regulation for pharmaceutical barcoding and serialization.

Medical Device Single Audit Program (MDSAP)[17] *

In the spirit of accelerating international medical device regulatory harmonization and convergence, the International Medical Device Regulators Forum (IMDRF) established a Medical Device Single Audit Program (MDSAP), which is a standard set of requirements for auditing medical device manufacturers' quality management systems that satisfies the requirements of multiple regulatory jurisdictions.

An audit of a medical device manufacturer conducted by an MDSAP recognized auditing organization (AO) fulfills the requirements of the following regulatory bodies:

- The U.S. Food and Drug Administration (FDA)
- Therapeutic Goods Administration of Australia
- Brazil's Agência Nacional de Vigilância Sanitária
- Health Canada
- Japan's Ministry of Health, Labour and Welfare, and the Japanese Pharmaceuticals and Medical Devices Agency

While MDSAP has the potential to save medical device manufacturers time, labor and money, these audits are rigorous in nature, covering quality management system requirements found in ISO 13485:2003, the Brazilian Good Manufacturing Practices, the FDA's Quality System Regulation (21 CFR Part 820), and additional requirements of all regulatory agencies taking part in the program, including registration, licensing and adverse event reporting. The MDSAP program demonstrates how regulatory bodies are continually reinterpreting Code of Federal Regulations Title 21 (21 CFR) with today's tools and processes.

From January 2014 through December 2016, the participating regulatory bodies conducted a MDSAP pilot program, and published a report on its findings on June 29, 2017. In the report the MDSAP Regulatory Authority Council (the international MDSAP governing body) determined that the MDSAP Pilot had "satisfactorily demonstrated the viability of the Medical Device Single Audit Program."

While the MDSAP pilot was voluntary to medical device manufacturers, the FDA stopped accepting ISO 13485:2003 Voluntary Audit Report Submissions as of March 31, 2016, to assist transitioning manufacturers over to MDSAP. Furthermore, as of January 1, 2019, Health Canada will accept only MDSAP certificates. These actions provide evidence that all participating regulatory agencies could require MDSAP audits in the future. In the six months following the pilot conclusion, the number of participating manufacturing sites in the MDSAP program doubled.

Commenting on the Health Canada move, the MDSAP pilot report authors state: "In order to assure a smooth transition from CMDCAS to MDSAP, manufacturers are encouraged to transition sooner than later. Early participation will help mitigate potential burdens on auditing organization capacities as the end of the transition period approaches."

* For additional details on MDSAP, please read our white paper entitled, How to Prepare for the Medical Device Single Audit Program

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Updates to ISO 13485:2016

The International Organization for Standardization's (ISO) ISO 13485, Medical devices – Quality management systems – Requirements for regulatory purposes, is an internationally agreed standard that describes the requirements for a quality management system specific to the medical device industry. It specifies requirements for a quality management system where an organization needs to demonstrate its ability to provide medical devices and related services that consistently meet customer and applicable regulatory requirements

ISO reviews all of its standards every five years to determine if revisions are required. In 2016, the organization issued ISO 13485:2016, which it "designed to respond to latest quality management system practices, including changes in technology and regulatory requirements and expectations." This latest version of the standard places "greater emphasis on risk management and risk-based decision making, as well as changes related to the increased regulatory requirements for organizations in the supply chain."

Challenges to Life Sciences Manufacturers

Today, most mid-sized and emerging life sciences manufacturers are managing their quality operations manually in spreadsheets, or in disjointed systems where they are unable to electronically share information. This infrastructure may have been adequate in the past, but as regulations and guidelines become broader, more electronic and increasingly data driven, manufacturers must adapt with them.

- **Inability to access data:** While most of the regulations and guidances aimed at improving the quality of life sciences products require a shift from paper to electronic documentation and reporting, many midmarket companies are still highly manual in their quality operations. It is not uncommon for manufacturers in this category to track quality data manually in spreadsheets. The process of accessing, aggregating, and formatting quality data in order to meet regulatory requirements is time, labor and cost intensive. In an increasingly electronic world where regulators and others are demanding the quick turnaround of accurate data, most of these manufacturers will fall short.
- **Lack of visibility:** Mergers and acquisitions (M&A) within the life sciences industry have resulted in midmarket manufacturers that have acquired quality systems from a variety of legacy companies. As a result, quality operations are managed in silos and various parties to the process may not have visibility to each other's processes and information. Furthermore, they have no enterprise-wide view. If a manufacturer does not have visibility into its own quality operations, how can it become more transparent in its quality to the FDA and other regulators?
- **Greater responsibility and risk:** The FDA and other regulators are taking a more risk-based approach to industry oversight, providing manufacturers the opportunity to prove they are quality driven, therefore at less risk for errors and subsequent product failures. There is a clear transfer of obligation from regulators to the industry occurring. In essence, regulatory bodies are telling manufacturers to update their systems, take the reigns and become more proactive when it comes to quality. A manufacturer that is unable to demonstrate to a regulator that it is achieving quality goals/objectives throughout its operations may find itself a prime target for on-site inspections.
- **Risks to supplier/partner relationships:** Even if a midmarket manufacturer is not required to comply with a specific regulation due to size, markets served or other factors, the larger companies to which it supplies products are most likely subject to the increased regulatory scrutiny. More and more, larger manufacturers are changing service agreements to require their suppliers to provide quality metrics, including proof that quality measures have been followed and tracked accordingly.

How to Shift From a Culture of Compliance to a Culture of Quality: 6 Success Factors for Effective Quality Management

The global life sciences industry is rapidly focusing beyond a culture of compliance to a culture of quality—and there is no turning back. Even if a manufacturer is not currently subject to one of the current regulations presented in this paper, they will be soon either directly or indirectly through one of their business partners. Like every aspect of life sciences quality operations—preventative action is far less risky, complex and costly than corrective action. Here are the six quality management success factors that are necessary to meet the evolving regulatory landscape.

1. **A single electronic source of truth:** A quality management system must serve as the single source of truth for a manufacturer's enterprise-wide quality operations. It must have the ability to track and store quality data related to the entire product lifecycle from design through to post market surveillance. The solution must serve as a central, electronic repository for all quality data, enabling the manufacturer to quickly access the information they need, when they need it.

2. **Communication and collaboration:** Achieving enterprise-wide quality requires all parties to the process to effectively and openly communicate at every step in the process. This includes individuals across different business sites, and even external collaborators and business partners. A quality management solution must facilitate this broad level of collaboration—serving as a single communication platform for all quality-related processes and information.
3. **Robust, yet not cumbersome:** Faced with more complex and stringent regulations, mid-sized and emerging manufacturers need a quality management solution that is robust enough to meets their complex needs, but at the same time is easy to use. The solution must feature user-friendly interfaces tailored to the various collaborators who will use it throughout the enterprise. The system must leverage best practice processes that align with regulatory standards and industry guidelines. Automated and standard workflows are another critical component, guiding users through the various steps necessary to achieve high quality outcomes.

4. **Access to meaningful business insights:** As regulatory requirements related to quality become more stringent and the risk for noncompliance increases, manufacturers must be able to quickly uncover and address potential issues. A quality management solution should feature data segmentation, dashboards and reporting that allows users at all levels of the organization to gain meaningful insights into their operations for data-driven decision making.

5. **Track and trace abilities:** An extended focus beyond compliance to quality requires a manufacturer to demonstrate to regulators how it is achieving quality throughout its operations. This includes the ability to track the full cycle of corrective and preventative actions (CAPAs)—from the identification of root cause, to actions to address it, and through to verification that the actions were effective. A quality management solution must provide a full audit trail of critical actions, and enable users to store supporting documentation.

6. **Flexibility and scalability:** Global regulations are constantly changing, as are a manufacturer's operations. A manufacturer that invests in its quality management capabilities today does not want to have to reinvent the wheel in the future. A quality management system must be both flexible to adapt to changing demands, and scalable to meet growing needs.

Conclusion

Facing growing pressures from payers, clinicians, and patients to improve product quality and safety, regulators are shifting more responsibility on manufacturers to instill quality throughout their operations and throughout their product lifecycles. Fundamental to this shift is a growing focus on electronic processes, data driven decisions and increased transparency to information.

In the past, mid-sized and emerging life sciences companies might have functioned sufficiently with manual processes and disconnected systems, but moving forward will be unable to satisfy the requirements of regulators and business partners who increasingly want quick access to in-depth information on their quality operations.

Manufacturers can either react to this changing environment—and risk falling behind—or proactively address their systems and processes based on the changes they know are happening in the industry. Those that implement an enterprise-wide quality management system can meet current needs, prepare for future regulatory changes and scale their quality operations to support their growing businesses.

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