Life & Health

Medical Device Communiqué

Q1 2014

CDRH UPDATES THE CASE FOR QUALITY

In late February, Steven Silverman, Director of CDRH's Office of Compliance, spoke before the Food and Drug Law Institute's Medical Device Conference on Key Legal and Regulatory Requirements. Silverman launched his presentation with two questions: "Why a quality strategy?" and "How does quality differ from compliance?" The subsequent answers updated CDRH's oft-discussed Case for Quality, giving CCOs a 2014 look at FDA's focus and initiatives.

Silverman quickly identified FDA's quality initiatives going forward:

- The Case for Quality
- The Voluntary Compliance Improvement Pilot (VCIP)
- The reorganization of the Office of Compliance

(continued...)

CDRH UPDATES THE CASE FOR QUALITY *(Continued)*

Here's a deeper look at Silverman's comments and related information about CDRH's regulatory activities and trends for medical devices.

Why Focus on A Quality Strategy?

Inspections and Official Action Indicated outcomes (OAI) by CDRH between 2005 and 2013 are once again showing a sharp increase after a dip in 2008 and 2009. Noted Silverman, "We are consistently seeing a high volume of the same issues year after year." Although he did not identify those issues, other data from FDA along with our own experience, points to these common violations at medical device facilities that produced nearly 1100 Form 483s issued by FDA in 2013. At the top of the list of "most common" violations are inadequate or nonexistent CAPA procedures; inadequate or nonexistent procedures for receiving, reviewing and evaluating complaints; inadequate documentation of CAPA activities and/or results; inadequate or nonexistent process validation; and absence of written MDR procedures. Beyond the regulatory actions taken, there were 331 medical device recalls in the fourth quarter of 2013 alone, with one company responsible for 9% of the quarter's total activity.

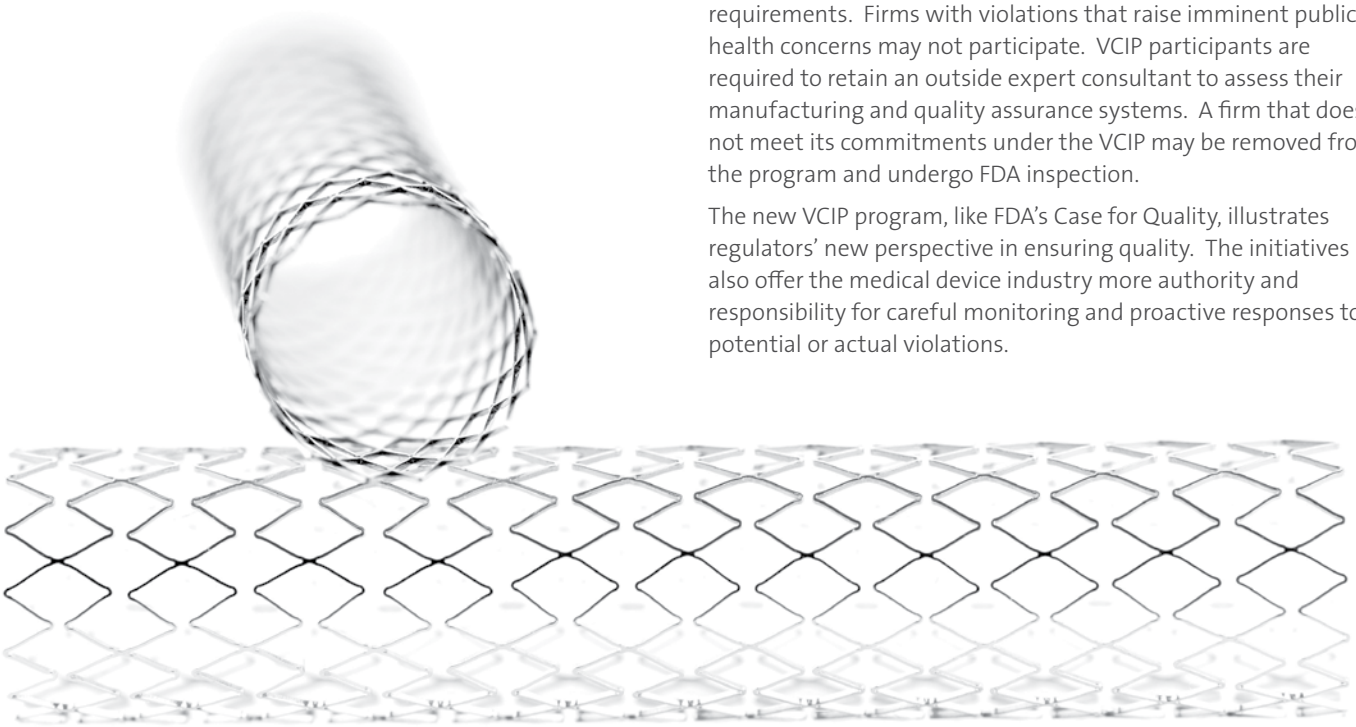
Quality vs. Compliance

FDA has consistently emphasized its focus on quality rather than simple compliance with regulatory requirements. According to Silverman, the current state of the quality vs. compliance paradigm completely separates business objectives from quality objectives and compliance, which just barely overlap. FDA's objective for the future state of quality vs. compliance has the three – business objectives, compliance and quality objectives firmly overlapping.

Why aim for quality instead of simple compliance? FDA's Case for Quality makes the case that a culture of quality yields benefits – and that achieving that culture requires support and ownership of quality that goes beyond quality and compliance units.

Among the initiatives CDRH has launched to promote its quality vs. compliance perspective is the Voluntary Compliance Improvement Pilot. CDRH proposed participation with up to five manufacturers to demonstrate an alternative to surveillance inspections. Firms voluntarily self-identify and correct possible regulatory violations instead of undergoing FDA inspection. The types of problems identified by these participants could range from quality system violations to failure to satisfy device clearance or approval requirements or adverse event reporting requirements. Firms with violations that raise imminent public health concerns may not participate. VCIP participants are required to retain an outside expert consultant to assess their manufacturing and quality assurance systems. A firm that does not meet its commitments under the VCIP may be removed from the program and undergo FDA inspection.

The new VCIP program, like FDA's Case for Quality, illustrates regulators' new perspective in ensuring quality. The initiatives also offer the medical device industry more authority and responsibility for careful monitoring and proactive responses to potential or actual violations.



GLOBAL REGULATORY TRENDS

Countries from India to Canada, and from Russia to Japan, are intensifying their scrutiny of medical device development, manufacturing, importation and distribution. Until recently, medical devices have not been as tightly regulated as pharmaceuticals. That is changing, however, as the market for medical devices escalates and the production of those devices becomes ever more global.

According to Expert Recall, there were 331 medical device recalls in the fourth quarter of 2013, with 49% of those affecting at least two countries. The recalls, along with FDA's increasingly aggressive inspection strategy for non-US medical product facilities, point to something well-known by compliance professionals: the development and manufacturing of medical products is a process that is increasingly global in nature.

While global harmonization of medical product regulation has yet to be achieved, increasing cooperation among national governments and regulatory agencies promotes a convergence of regulations and quality standards. Unfortunately, CCOs are still required to address multiple, often overlapping and sometimes contradictory, regulations. Achieving that objective requires knowing regulatory trends and changing laws in countries with which the CCO's company operates or has suppliers. Here's a brief look at some of the most significant 2013 developments:

CHINA

China's Food and Drug Administration (CFDA) has undertaken a number of actions geared toward improving the quality and reputation of its medical products.

- Among the actions is CFDA's Guide for Regular Site Inspections of Medical Device Manufacturers, which not only details all aspects of an inspection but also sets standards for inspectors. Although the Guide does not change existing good manufacturing practice regulations for medical devices, it does set out government expectations for inspectors and the inspected.
- A second CFDA initiative is the release of a draft Good Supply Practices (GSP) for Medical Devices. The draft GSP rule lays out a number of requirements for quality activities in the distribution of medical devices. Those requirements include the appointment of corporate officers primarily responsible for overall quality of distribution; appointment of specialized quality control personnel; qualification of employees in quality management, inspections and sales of implantable devices; complete and accurate records of procurement, inspection, storage, sales, inventory management, return and replacement, inspections and disposal of nonconforming products; and key steps of the distribution process including procurement, receiving, storage, sales, stock in and out, and transportation.

BRAZIL

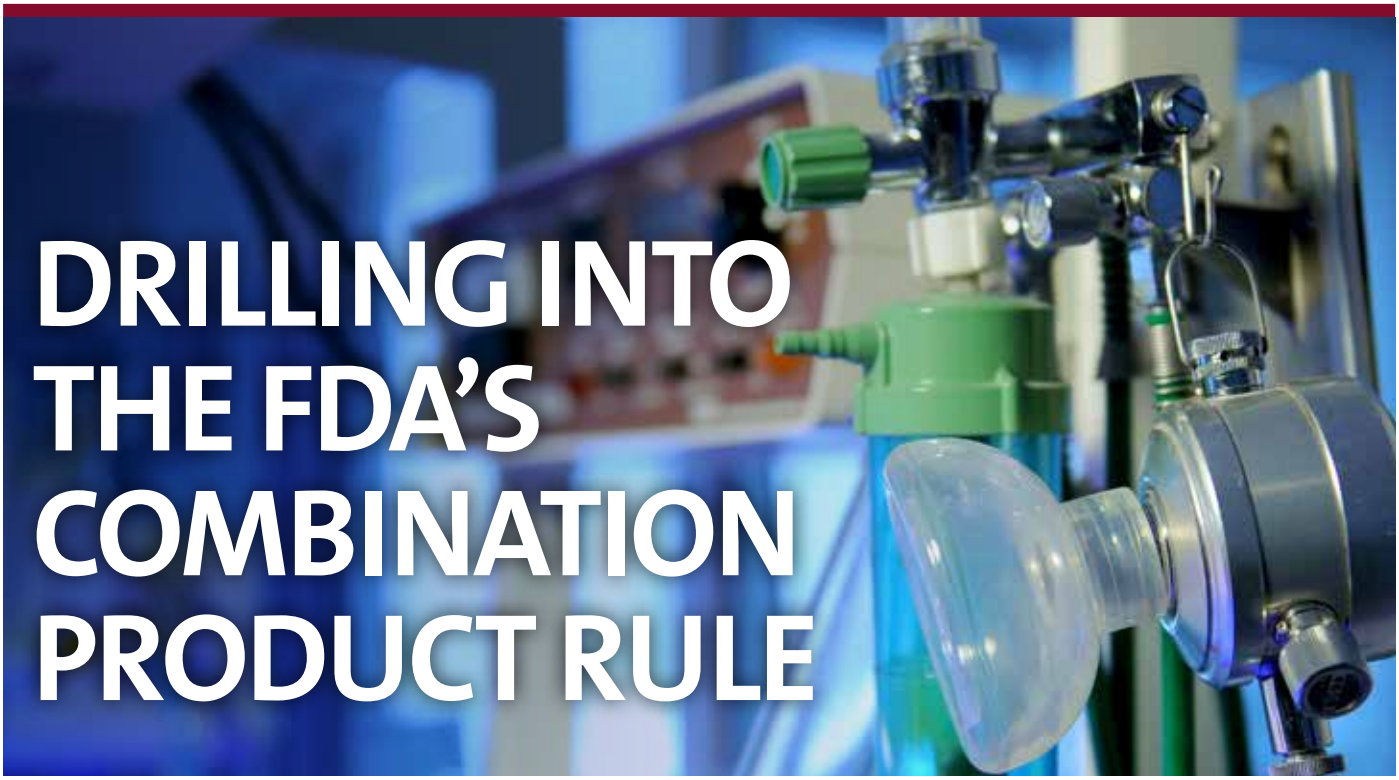
Brazil's medical device regulator (ANVISA) has introduced changes to Brazil's Good Manufacturing Practice quality management system. Companies are required to comply with Brazilian Good Manufacturing Practices (BGMP) for each product line when more than one device is produced in a single facility.

SOUTH KOREA

Bucking the trend in most countries, South Korea has eased compliance requirements for medical devices. Manufacturers of Class II and III medical devices are allowed greater use of third-party auditors to verify compliance with Korean Good Manufacturing Practices (KGMP). In some cases, Class I medical device manufacturers may be exempt from KGMP, needing only to submit premarket notifications electronically.

EUROPE

On July 22, 2014, medical devices will be regulated under the RoHS requirements in Europe. In vitro diagnostic medical devices must comply with RoHS requirements as of July 22, 2016. Medical devices had, until now, been exempt under RoHS. Under RoHS, manufacturers, importers and distributors must notify Member State regulators if they know or have reason to believe that one of their products does not conform to RoHS requirements and must take corrective action.



DRILLING INTO THE FDA'S COMBINATION PRODUCT RULE

When the US Food and Drug Administration (FDA) issued its final rule for current Good Manufacturing Practice (cGMP) Requirements for Combination Products, the rule was *"... intended to promote the public health by clarifying which cGMP requirements apply when drugs, device, and biological products are combined to create combination products. In addition, the rule sets forth a transparent and streamlined regulatory framework for firms to use when demonstrating compliance with cGMP requirements for 'single-entity' and 'co-packaged' combination products."* The final rule contained few changes to the draft version released several years earlier.

The FDA seemed to recognize that its intentions might have been too ambitious, promising to issue additional guidance. That guidance has not yet been released, leaving medical device manufacturers to pore over the rule itself for clarification of the cGMP requirements for their individual combination products. Some of the most significant provisions of the final rule relate to definitions of different types of combination products and their cGMP requirements:

- A manufacturer of a single-entity or co-packaged drug/device combination product may comply with the cGMP or QSR requirements that apply to each constituent part.
- A manufacturer of a single-entity or co-packaged drug/device combination product may comply with the requirements of one constituent part under conditions defined in the rule. A manufacturer may comply with either drug cGMPs or medical device QSRs, for example, but under the final rule it would also be required to comply with additional quality regulations contained in the rule.
- A manufacturer of a combination product that includes biological or human tissue components must comply with all cGMP and QSR requirements for each constituent part.
- A manufacturer of a "convenience kit" has no cGMP requirements beyond those that apply to the assembly, packaging, labeling or sterilization of the kit. The final rule's new requirements do apply [if] any of the kit's components is repackaged, relabeled or otherwise modified in order to be included in the kit.

DRILLING INTO THE FDA'S COMBINATION PRODUCT RULE *(Continued)*

FDA Answers Industry Questions

Although the final rule provides the "letter of the law," the Federal Register notice includes comments about the proposed rule that highlight a number of industry concerns and FDA responses. Absent from FDA's promised guidance, these comments and answers provide some insight into the final rule and its individual components. Some of the most significant of those comments and FDA responses:

- Question: ***Clarification of what manufacturers must do to "demonstrate" compliance with the new rule.*** FDA's response: "We confirm that the term 'demonstrate' is not intended to have new meaning for purposes of the rule. The Agency intends for it to be interpreted in the same manner as it would be for purposes of the CGMP regulations listed in § 4.3." FDA further added, "... depending on the circumstances and requirements at issue, appropriate means by which to demonstrate compliance with these CGMP requirements may include development of written procedures and maintenance of records documenting use and verification of CGMPs."
- ***Are products already on the market prior to the establishment of OCP considered combination products by the Agency and subject to the final rule?*** FDA answered "Compliance with all applicable CGMP requirements is required for all products and appropriate to ensure consistent manufacture of products that meet the safety and effectiveness and quality standards that form the basis for product marketing authorization, regardless of when a product was first marketed or approved."
- ***How will the new rule apply to "convenience kits?"*** Several questions related to the topic of convenience kits and their regulation. FDA repeated, "This rule is not intended to create new CGMP requirements, and instead seeks to clarify how to apply them to combination products. A kit that includes two or more types of medical products (e.g., a device and a drug), is a combination product and subject to this rule. Accordingly, the manufacture of the products in the kit would also be subject to this rule." FDA continued to address questions of how to define the term "convenience kit." FDA said, "For purposes of this rule, we define the term to include only kits that solely include products that are: (1) also legally marketed independently and (2) included in the kit as already packaged for independent marketing and with the same labeling as for independent marketing." According to FDA, "... the only additional CGMP requirements that would generally apply to such a convenience kit would be those applicable to the assembly, packaging, labeling, any sterilization, or further processing of the kit itself."
- ***What activities are included in the definition of "manufacture" under the new rule?*** FDA responded, "The term 'manufacture' for purposes of the rule is intended to encompass all activities defined as manufacturing under the drug CGMPs and QS regulation and also under the biological product and HCT/P regulation listed in § 4.3. Both specification developers and contract manufacturers 'manufacture' and are considered manufacturers for purposes of these underlying CGMP regulations and are, therefore subject to this rule if they manufacture combination products or constituent parts of combination products."
- ***Comment #8 asked for confirmation that container and closures, which they asserted are currently treated as drug components, would continue to be treated as such.*** FDA responded, "The suggestion that containers and closures are treated as drug components for purposes of CGMPs is incorrect. Components are defined under §210.3 as 'any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.' FDA further noted, "While some CGMP requirements apply to both drug components and containers/closures, containers/closures are separately addressed in the drug CGMPs, and distinct CGMP requirements apply to them (see § 211.84)."

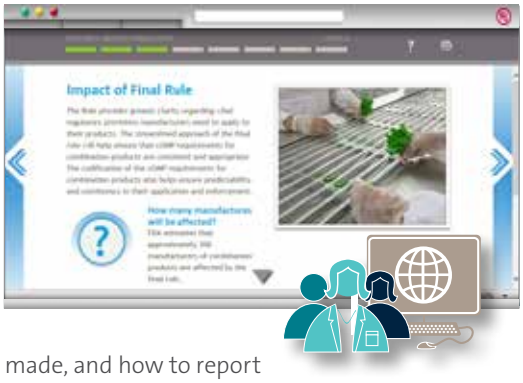
FDA responded to additional questions and comments and reiterated one of the constant compliance refrains from the agency, "All manufacturers are responsible for ensuring compliance with all CGMP requirements applicable to the manufacturing activities at their facilities. In addition, the applicant is responsible for ensuring compliance with all of the CGMP requirements applicable to the product, taking into account all of the activities occurring at all facilities involved in the manufacturing process."

Manufacturers of combination products are already required to comply with the final rule. While compliance officers undoubtedly have examined and studied the rule itself, it may be worthwhile to review the questions/comments submitted by the industry and the responses from FDA.

NEW COMBINATION PRODUCTS COURSE
Now Available

In 2013, the US Food and Drug Administration (FDA) issued a new regulation (Final Rule) on cGMP requirements applicable to combination products. While this rule does not create new cGMP requirements, it does clarify which cGMP requirements apply for combination products, while also providing a streamlined regulatory framework for firms to use when demonstrating cGMP compliance for combination products.

To help your quality and manufacturing teams understand this regulation, UL has developed a new course, Combination Products – cGMP Requirements (PHDV93). This course is now available to annual GMP library subscribers.



This course focuses on the four different types of combination products as well as the scope of the new regulation in 21 CFR Part 4. Learners will also understand how post-marketing modifications are made, and how to report post-marketing adverse events. The course, which can be taken on a PC or iPad, was authored by Dave Peterson, renowned GMP expert and member of the UL EduNeering Advisory Services team.

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Minor updates will not be included, as they are typically grammatical or aesthetic changes. In addition, new courses will be listed as well.

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