Compliance Hot Topics

Allyson B. Mullen, Hyman, Phelps, & McNamara PC

AMDM 2022 Annual Meeting

Agenda

- Overview of post-market compliance requirements
- Updates to Quality System Regulations
- Key post-market guidances
- Notable compliance actions

Post-Market Compliance

- Labeling 21 C.F.R. Parts 801, 809 & 830
  - Unique Device Identification
- Registration and listing 21 C.F.R. Part 807
- Quality System Regulation 21 C.F.R. Part 820
- MDR Reporting 21 C.F.R. Part 803
- Corrections and Removals/Recalls 21 C.F.R. Parts 7 & 806

Quality System Regulation

Quality System Regulation

- Requires manufacturers to establish a “quality system” for the design and production of devices
- Manufacturers are required to have
  - Detailed quality policy, plan, and management oversight
  - Specifications and controls be established for devices
  - Devices be designed and manufactured under a quality system and meet these specifications
  - Devices be correctly installed, checked, and serviced
  - Quality data be analyzed to identify and correct quality problems
  - Complaints be processed

QSR/ISO 13485 Harmonization

- February 23, 2022, FDA published in the Federal Register a proposed rule that would replace the Quality System Regulation (QSR), 21 C.F.R. Part 820, with a newly named Quality Management System Regulation (QMSR)
- So what's the plan?
  - FDA is accepting comments until May 24, 2022
  - After that, FDA will review the comments, make any necessary amendments to the proposed rule, and then it will undergo internal review before publication of the final rule
- What's the timing?
  - Unknown but by way of example
    - De novo proposed rule issued December 2018 and final rule issued October 2021
  - If finalized, the proposed rule includes a one-year transition period

Harmonization

- Does not necessarily mean its identical
- QMSR omits many of the specific QSR requirements and instead incorporates by reference ISO 13485:2016
  - QMSR retains definitions of some terms that do not appear in ISO 13485 (e.g., component, finished device, design validation, remanufacturer, and nonconformity)
  - Some existing terms have also been revised for better alignment with ISO 13485 (e.g., replacing the defined term “management with executive responsibility” with “top management”)
- Some FDA-specific requirements retained (e.g., control of records and device labeling and packaging controls)
- Risk management is a key component of ISO 13485

What can we do now?

- Carefully consider the proposed rule and how it would affect your operations
  - AND submit comments
- Become compliant with ISO 13485: 2016 (if not already)
- Bring your risk management system into compliance with ISO 14971: 2019 (if not already)
  - 2007 version is only being accepted by FDA through December 25, 2022
  - ISO 13485: 2016 relies heavily on risk management and makes reference to ISO 14971 specifically
  - FDA's plan for revisions focuses specifically on risk management
- Consider participating in the Medical Device Single Audit Program (MDSAP)
  - Benefits of a single audit for multiple jurisdictions
  - Become accustomed to audit technique that is more focused in ISO 13485 than QSIT

Medtronic Warning Letter

- "While you implemented your [CAPA] procedure, we disagree with your characterization of the risk threshold which led to a conclusion of a lower risk than was appropriate."
  - Justified not doing a recall based on a low likelihood of the event occurring
  - FDA stated that their CAPA procedure under estimated the level of risk because it uses "the number of products shipped include[ing] devices not in use by patients (e.g., devices shipped to distributors that have not yet been distributed to customers)."
- Failed to properly verify effectiveness
  - Compared complaint rate post-design change to pre-design change.
  - Number of complaints redacted but FDA says the company "received 322 complaints during the . . . effectiveness check period" and "did not re-evaluate the effectiveness of your corrective and preventive actions to determine whether" the corrective action should be re-evaluated
- Failure to investigate complaints
  - Complaint of insulin delivery not programmed by the patient. Escalated to cybersecurity team. Complaint investigation included a review of downloaded data but did not "include reviewing the actual pump history"
- December 2021: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/medtronic-inc-617539-12092021

MDR Reporting

MDR Reporting

- MDRs are intended to alert FDA to potential product issues
- MDRs are required when (i) a user facilities become aware of an event that reasonably suggests that a device has or may have caused or contributed to a death or serious injury; or (ii) a manufacturer or importer receives or otherwise becomes aware of information, from any source, that reasonably suggests that one of its marketed devices may have:
  - Caused or contributed to a death or serious injury
  - Malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to death or serious injury, if the malfunction were to recur
- A “serious injury” is one that:
  - Is life-threatening;
  - Results in permanent impairment of a body function or permanent damage to body structure; or
  - Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure
- Typically must be reported within 30 days

Notable MDRs

- According to the MAUDE database there were 8 complaints related to Syphilis tests from January 1, 2021 – December 31, 2021
  - As compared to 1 from January 2016 – December 2020
- December 2021 – FDA issued a letter to clinical laboratory staff and healthcare providers
  - Alerted them to the possibility of false positive results on the Rapid Plasma Reagin (RPR; non-treponemal) test, when using the Bio-Rad Laboratories BioPlex 2200 Syphilis Total & RPR kit, in some people who received a COVID-19 vaccine
  - The letter noted that, "Health care providers should make patients who received a reactive RPR result using the Bio-Rad BioPlex 2200 Syphilis Total & RPR test kit aware that they may need to be retested for syphilis with another test to confirm results"

- Letter: https://www.fda.gov/medical-devices/letters-health-care-providers/possible-false-rpr-reactivity-bioplex-2200-syphilis-total-rpr-test-kit-following-covid-19-vaccine#:~:text=The%20U.S.%20Food%20and%20Drug,in%20some%20people%20who%20received

Recalls

Recalls

- 21 C.F.R. Parts 7
- Two types: Mandatory and Voluntary
- Three classes:
  - Class I: there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death
  - Class II: the use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences, or the probability of serious adverse health consequences is remote
  - Class III: the use of or exposure to a violative product is not likely to cause adverse health consequences

Corrections and Removals

- 21 C.F.R. Part 806
- Manufacturers must report “corrections” and “removals” of devices that pose or may pose a “risk to health” to FDA within 10 days of initiating action
  - Correction: the repair, modification, adjustment, relabeling, destruction, or inspection of a product without its physical removal
  - Removal: the physical removal of a product from its point of use for repair, adjustment, relabeling, destruction, or inspection
- Recalls are corrections and removals of violative product
- Class III recalls, by definition, do not involve a “risk to health” and do not have to be reported to FDA
  - Records still must be maintained

New Recall Guidance

- Final Guidance: Initiation of Voluntary Recalls Under 21 C.F.R. Part 7, Subpart C (March 2022)
- Companies should be “recall ready”
- Provides practical guidelines for both firms and direct accounts
  - E.g., train appropriate personnel and created a recall communication plan, identify specific points for contact for communications (internal, with FDA, and to accounts)
- Encourages use of electronic means to notify the public about recalls
- Emphasizes that recalls firms do not need to wait for the completion of an investigation before initiating a recall
- https://www.fda.gov/media/123664/download

Noteworthy Recalls – ACON Laboratories

- January 2022 – ACON initiated a recall after identifying U.S. distribution of unauthorized “counterfeit product” using its trade name “Flowflex SARS-CoV-2 Antigen Rapid Test”
- The product is CE marked and only available in the European market
- ACON was noted to be working with FDA and other law enforcement agencies to ensure that only EUA-authorized Flowflex tests are commercialized in the U.S.

Noteworthy Recalls – Philips Respironics

- "On March 10, 2022, the FDA issued a notification order to Philips Respironics requiring the company to notify patients and others of the company's June 14, 2021, recall of certain Philips Respironics ventilators, continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) machines, and the unreasonable risk of substantial harm to the public health posed by the degradation of the polyester-based polyurethane (PE-PUR) sound abatement foam used in those products. The FDA has determined that this order is necessary to eliminate the unreasonable risk of harm posed by the recalled products, *because the company's notification efforts to date have been inadequate*."
  - Press release: "The FDA has heard the frustration expressed by patients and durable medical equipment suppliers who are unaware of the recall and have received insufficient information on their next steps regarding the recall process," said Jeff Shuren, M.D., J.D."
  - "Since the initiation of the recall, the FDA has engaged with Philips on several fronts about the effectiveness of its communications with the public regarding the recall and the risks presented by the recalled products and has expressed concern that it is likely a significant portion of patients and consumers using the recalled products are unaware of the health risks presented by those products."
- November 12, 2021 – FDA issued an updated safety communication on the Philips Respironics recalled ventilators, BiPAP, and CPAP machines
- Since April 2021, FDA states that it "has received over 3,000 MDRs related to foam breakdown (degradation). A wide range of adverse events have been reported to the FDA, including cancer, pneumonia, asthma, other respiratory problems, infection, headache, cough, dyspnea (difficulty breathing), dizziness, nodules, and chest pain."
- June 2021 – Philips performed a recall of certain ventilators, BiPAP, and CPAP machines
- Between 2014-April 2021, 30 MDRs related to foam breakdown (degradation) – no reports of injury

Notable Compliance Actions

NIPT Warning to Patients & Providers

- Warning regarding potential for false results
- While widely used, the letter notes that none have been cleared/approved
- No actual evidence presented to support the warning
  - "FDA is aware of reports that patients and health care providers have made critical health care decisions based on results from these screening tests alone and without additional confirmatory testing. Specifically, pregnant people have ended pregnancies based only on the results of NIPS tests. Without confirming the results with a diagnostic test, there is no way to know whether the fetus actually had the genetic abnormality reported by the screening test. The FDA is aware of cases where a screening test reported a genetic abnormality and a confirmatory diagnostic test later found that the fetus was healthy."
- "The scientific literature generally report high negative predictive values, greater than 99.9% when calculated, for the NIPS tests studied. . . . However, the literature confirms that the reliability of positive screening results is limited, particularly for microdeletions."
- Interesting timing:
  - Comes after a January 2022 NY Times article regarding potential for erroneous results
  - Discussions of VALID and MDUFA are happening

April 19, 2022 Letter: https://www.fda.gov/medical-devices/safety-communications/genetic-non-invasive-prenatal-screening-tests-may-have-false-results-fda-safety-communication

Imaging Software Letter to HCPs

- "Reminding health care providers about the intended use of radiological computer-aided triage and notification (CADt) devices for intracranial large vessel occlusion (LVO)"
- "Information from real-world use suggests that providers may not be aware of the intended use of these devices. If LVO CADt devices are not used as intended, there is the potential for misdiagnosis resulting in patient injury or death."
  - "These devices should not be relied on when making any diagnostic decisions. In addition, health care providers should ensure that they understand which vessels the device was designed and tested to evaluate."
- Letter notes that FDA is working with manufacturers to ensure that healthcare providers are informed of the intended use and design

April 11, 2022 Letter: https://www.fda.gov/medical-devices/letters-health-care-providers/intended-use-imaging-software-intracranial-large-vessel-occlusion-letter-health-care-providers?utm_medium=email&utm_source=govdelivery

Questions & Discussion

Contact Information

Allyson B. Mullen
Hyman, Phelps & McNamara, P.C.
700 Thirteenth Street, NW
Suite 1200
Washington, DC 20005
(202) 737-9639
amullen@hpm.com
www.hpm.com
www.fdalawblog.net