THE FDA GROUP LLC

Insider Newsletter — Issue #3

Item #1 –

Regulations on CGMPs specific to outsourcing facilities—proposed new rule for Compounding Facilities

Item #1: Unified Agenda

- **Where:** The FDA's most recent unified agenda (December 2021)
- **What:** Spring 2021 agenda is regulations on CGMPs specific to outsourcing facilities
- **When:** The proposed rule is expected to be published in July of 2022
- **Detail:** To establish minimum CGMP requirements for human drugs compounded by outsourcing facilities

Item #1: The Rule

HHS/FDA **RIN:** 0910-AH61 **Publication ID:** Fall 2021

Title: Current Good Manufacturing Practice for Outsourcing Facilities

Abstract: This rule would set forth the minimum current good manufacturing practice (cGMP) requirements for human drug products compounded by an outsourcing facility.

Agency: Department of Health and Human Services(HHS) Priority: Other Significant

RIN Status: Previously published in the Unified Agenda Agenda Stage of Rulemaking: Proposed Rule Stage

Major: No Unfunded Mandates: Undetermined

CFR Citation: 21 CFR 216

Legal Authority: 21 U.S.C. 351 21 U.S.C. 371

Legal Deadline: None

Item #1: Commentary for Compounding Facility Leadership

- Minimum requirements for the processes associated with compounding should increase consistency with control for the components manufactured to be consistent and controlled.
- Quality System implementation, Records and Investigations of Deviations (with CAPA), Training and Quality oversite of Compounding Activities may represent significant gaps.
- Preparation for the rule should be to discuss Quality System implementation with an experienced cGMP Quality consulting professional.
  - Include a Gap Analysis
  - Quality System design and implementation
  - A strong Training program

Item #2 –

Software as a Service (SaaS) and Software as a Medical Device (SaaMD)—Harmonizing Quality System Regulation (21 CFR part 820) with IEC62304

Item #2: SaaS 101

- **What is SaaS and why is it important to you?** SaaS (Software as a Service) is a cloud-based software delivery model hosted on third-party servers; Applications may be accessed on demand from your devices anywhere and anytime. SaaS is typically subscription based. Your applications reside on a remote cloud network accessed through the web or an API, and it works like a rental.
- **Two SaaS models: Single tenant and Multi-tenant**
  - **Single-tenant** SaaS is an architecture where the SaaS client is the tenant. In the Single-Tenant SaaS environment, each team has a dedicated server and supporting infrastructure. Single-tenant products can't be shared between users and the buyer can customize the software according to their requirements.
  - **Multi-tenant SaaS** is a business structure where many organizations share the same software to save and store data. Multi-tenant SaaS also implies that a single instance of the software and its supporting information is used by multiple customers. Each customer shares the same database and application.
  - An example of this multi-tenant structure is where a single instance of an application hosted in the cloud where it can be accessed by many authorized individuals and be used to analyze anonymized PHR to determine the effectiveness of certain treatments and patient outcomes.
- **SaaS frees you from the need of having your own internal computer systems and support.**
- **SaaS is cloud computing at its best.** Cloud computing is a term referred to storing and accessing data over the internet. Data that is not your local person computer's hard drive.

Item #2: SaaS Cloud Vendors

- **Amazon: Amazon Web Services (AWS) —** AWS is a platform that offers flexible, reliable, scalable, easy-to-use and, cost-effective cloud based services. AWS helps growing companies to become more agile, innovate faster, lower operating costs, and speed up product introductions to capture market share.
- **IBM Cloud Computing —** Cloud computing transforms IT infrastructure into a utility: It lets you 'plug into' infrastructure via the internet, and use computing resources without installing and maintaining them on-premises. Cloud computing is on-demand access, via the internet, to computing resources—applications, servers (physical servers and virtual servers), data storage, development tools, networking capabilities, and more—hosted at a remote data center managed by a cloud services provider (or CSP). The CSP makes these resources available for a monthly subscription fee or bills them according to usage.
- **Microsoft Azure –** Microsoft's cloud-computing infrastructure and platform is an ideal tool for building, deploying, and managing applications through a global network of Microsoft-managed datacenters.
- **Some other hosted services to consider**: IaaS (Infrastructure-as-a-Service), PaaS (Platform-as-a-Service) , and SaaS (Software-as-a-Service) are the three most common models of cloud services, and it's not uncommon for an organization to use all three.

Item #2: Deployment of SaaS

- Customers can deploy SaaS in one of ***three different models***, as defined by the National Institute of Standards Technology (NIST):
  - **Private Cloud:** Cloud software is built on infrastructure that is provisioned for exclusive use by a single organization comprising multiple consumers. The infrastructure may be owned, managed and operated by the organization, a third party or some combination, and it may exist on or off premises.
  - **Public Cloud:** Cloud software is built on infrastructure that is provisioned for open use by the public. The infrastructure may be owned, managed and operated by a business, academic or government organization, or some combination. It exists on the premises of the cloud provider.
  - **Hybrid Cloud:** Cloud software is primarily built on one type of infrastructure but has the ability to switch to another in times of high demand. Standardized or proprietary technology enables data and application portability.

Item #2: SaaS Benefits

- **Accessibility:** Ability to run via an internet browser 24/7 from any device
- **Operational Management:** No installation, equipment updates or traditional licensing management
- **Cost Effective:** No upfront hardware costs and flexible payment methods such as pay-as-you-go models
- **Scalability:** Easily scale a solution to accommodate changing needs
- **Data Storage:** Data is routinely saved in the cloud
- **Analytics:** Access to data reporting and intelligence tools
- **Increased Security:** SaaS providers invest heavily in security technology and expertise

Item #2: SaaMD

- **Software as a Medical Device** (FDA) ranges from software that allows a smartphone to view images obtained from a magnetic resonance imaging (MRI) medical device for diagnostic purposes to Computer-Aided Detection (CAD) software that performs image post-processing to help detect breast cancer.
- The International Medical Device Regulators Forum (IMDRF) Software as a Medical Device Working Group (WG) published a possible risk categorization framework for Software as a Medical Device (SaaMD):
  - The Software as a Medical Device risk categorization has four categories (I, II, III, and IV). These categories are based on the levels of impact on the patient or public health where accurate information provided by the Software as a Medical Device to treat or diagnose, drive or inform clinical management is vital to avoid death, long-term disability or other serious deterioration of health, mitigating public health. The Level IV category is Software as a Medical Device with the highest impact on the patient or public health and Level I is the lowest.

Item #2: SaaMD of SaMD

- Software which is connected to a hardware medical device (rather than being an accessory) but isn't needed to achieve that medical device's intended medical purpose is considered SaMD.
- Two of the biggest advantages include improved health outcomes through more accurate data as well as quicker production and feedback, leading to faster innovation.
- A great, tangible example of SaMD is a product like Omron's HeartGuide. This is a blood pressure monitor that works with a smartwatch. Healthcare Weekly has a great review of the product but the general idea is that it is a smartwatch with many of the features you will find in most smartwatches on the market today.

Item #2: Software Types

- **Software as a medical device (SaMD):** Standalone medical software without an associated hardware device.
- **Software in a medical device (SiMD):** Software that is integrated into medical equipment or smart medical devices
- **Software as an accessory to a medical device (SaAMD):** The software here functions as an adjuvant to an existing medical device.

Item #2: What *is* SaMD?

- According to the international medical devices regulator's forum (IMDRF), software as a medical device is defined as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device."
- Any software that is an entity on its own without an associated hardware device can be classified as SaMD.
- For example, the software that computes the drug dosage based on patient data can be classified as a SaMD whereas a software within a device that dispenses medication is not SaMD.

Item #2: Quality System Regulation (21 CFR part 820)

Applicability. (1) Current good manufacturing practice (CGMP) requirements are set forth in this quality system regulation. The requirements in this part govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. The requirements in this part are intended to ensure that finished devices will be safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act (the act). This part establishes basic requirements applicable to manufacturers of finished medical devices. If a manufacturer engages in only some operations subject to the requirements in this part, and not in others, that manufacturer need only comply with those requirements applicable to the operations in which it is engaged. With respect to class I devices, design controls apply only to those devices listed in §820.30(a)(2).

Item #2: QSR Review — Overview

- Quality system
- 820.20 Management responsibility
- 820.25 Personnel
- 820.30 Design Controls
- Subpart M—Records (very important)
- 820.180 General requirements
- 820.181 Device Master Record (DMR)
- 820.184 Device History Record (DHR)
- 820.186 Quality System Record

Item #2: QSR Review — Subpart M – DHF records

- Organization of all the files and documents comprising the development of your medical device is contained here for reference.
- You should have no trouble navigating and finding files for an FDA inspector, if you have an efficient and well-organized document file structure.
- The DHF contains the following records:
  - Design Inputs – references to all of your development processes
  - Design Outputs – references to build the device
  - Design Reviews – meeting minutes, consensus reports, etc. (Does the design make sense)
  - Design Transfer – often considered technology transfer to manufacturing
  - Design Verification / Validation – GAMP V Model based

Item #2: QSR Review — Subpart M – DMR records

- All the instructions, schematics, drawings, charts, etc. are contained in this directory. Everything need to build and test your device is located here. Again, organization is the key, as well as document version control.
- The DMR includes references to:
  - (a) Device specifications including appropriate drawings, composition, formulation, component specifications, and software specifications;
  - (b) Production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications;
  - (c) Quality assurance procedures and specifications including acceptance criteria and the quality assurance equipment to be used;

Item #2: QSR Review — Subpart M – DMR records (cont.)

- For the device, the FDA only requires you to reference the required documents, not duplicate them. A lot of the documents required for the DMR should already exist in the DHF.
- A good trace matrix would help to easily map where reference files are located. This would keep you from stumbling through an audit trying to find DHF and DMR reference files.

Item #2: QSR Review — Subpart M – Device History Record (DHR)

- The DHR contains references for:
  - (a) The dates of manufacture;
  - (b) The quantity manufactured;
  - (c) The quantity released for distribution;
  - (d) The acceptance records which demonstrate the device is manufactured in accordance with the DMR;
  - (e) The primary identification label and labeling used for each production unit; and
  - (f) Any unique device identifier (UDI) or universal product code (UPC), and any other device identification(s) and control number(s) used.
- Each manufacturer shall establish and maintain procedures to ensure that DHR's for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the DMR and the requirements of this part.
- The DHR contains all the information, history, of the Device and all the details that went into making it according to the DMR.
- The DHF contains all the information, history, of the Design process.

Item #2: QMS Thoughts for the QSR

- ❑ Keep it ***simple***
- ❑ Keep it the ***right size***
- ❑ Build ***value*** into it
- ❑ Keep it well ***organized and navigable***
- ❑ Don't forget about ***Change Management***
- ❑ Do have a ***Quality Manual***
- ❑ Use it to ***develop your procedures***
- ❑ Remember, it's ***all about records management!***

Item #2: FDA QSIT—Very Helpful

Item #2: QSIT

- This process for performing subsystem inspections is ***based on a "top-down" approach to inspecting***.
- The subsystem approach is designed to provide you with the key objectives that can help determine a firm's state of compliance.
- The process was designed to account for the time constraints placed on field investigators when performing device quality system inspections. If you can focus your effort on key elements of a firm's quality system, you can efficiently and effectively evaluate that quality system.

Item #2: QSIT (cont.)

- The “top-down” approach begins each subsystem review with an evaluation of whether the firm has addressed the basic requirements in that subsystem by defining and documenting appropriate procedures. This is followed by an analysis of whether the firm has implemented the requirements of that subsystem.
- The four major subsystems are Management Control; Corrective and Preventive Actions (CAPA) (with satellites Medical Device Reporting, Corrections and Removals, and Medical Device Tracking); Design Controls; and Production and Process Controls (P&PC) (with satellite Sterilization Process Controls).

Item #2: QSIT Checklist

- ❑ The firm must have a written quality policy.
- ❑ The definition of quality policy is provided in the Quality System Regulation. It means the overall intentions and directions of an organization with respect to quality.
- ❑ The firm is responsible for establishing a clear quality policy with achievable objectives then translating the objectives into actual methods and procedures.
- ❑ Management with executive responsibility (i.e., has the authority to establish and make changes to the company quality policy) must assure the policy and objectives are understood and implemented at all levels of their organization.
- ❑ The policy does not need to be extensive.
- ❑ Personnel are not required to be able to recite the policy but they should be familiar with it and know where to obtain it.

Item #2: ISO 13485:2016

- ISO 13485:2016 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.
- Medical devices under the new Rules “Medical Devices Rules, 2017”are classified as per Global Harmonization Task Force (GHTF) based on associated risks, Class A (low risk) Class B (low moderate risk) Class C (moderate high risk)
- ISO 13485 Medical devices -- Quality management systems -- Requirements for regulatory purposes is an International Organization for Standardization (ISO) standard published for the first time in 1996; it represents the requirements for a comprehensive quality management system for the design and manufacture of medical devices.

Item #2: IEC-62304

- **What IEC 62304?** IEC 62304 is a functional safety standard that covers safe design and maintenance of software. It provides processes, activities, and tasks to ensure safety. It applies to the development and maintenance of medical device software when: The software is itself a medical device.
- IEC 62304 defines software lifecycle processes for medical device software. Regulatory practitioners understand that the FDA sees this as a consensus standard.

Item #2: IEC-62304 Software Development

- Engineering
  - Requirements definition
  - Specifications
  - Programming standards
  - Design / Build (Code) / Test – an iterative model either agile or waterfall
  - FAT
- Qualifications
  - IQ
  - OQ
  - TMX
  - VSR
- Software deemed fit for use – software release

Item #2: IEC-62304 Software Development

Software documentation	Class A	Class B	Class C
Software development planning	X	X	X
Software requirements analysis	X	X	X
Software architectural design		X	X
Software detailed design			X
Software unit implementation	X	X	X
Software unit verification		X	X
Software integration and integration testing		X	X
Software system testing	X	X	X
Software release	X	X	X
X - required			

Item #2: IEC-62304 Alignment with 820

- Quality Management System
- Risk Management Process
- Software safety classification (A, B, or C)
- Software development plan – SDLC model
- Software integration and integration testing planning
- PROBLEM REPORT — a record of actual or potential behavior of a software device
- SOFTWARE SYSTEM inputs and outputs
- Software Verification

Item #2: IEC-62304 Alignment with 820

- Software Maintenance PROCESS
- Change Control PROCESS
- SOFTWARE PRODUCT Problem Report
- Feedback from a user or other interested person who believes software product to be unsafe, inappropriate for the intended use or contrary to specification

Item #3 –

Large medical device manufacturer is cited for failing to investigate over 800 complaints of defective components (plus CAPA and MDR problems)

Item #3: A Few Warning Letter Excerpts

21 CFR 820.198(c)

- "Your firm ***failed to investigate over 800 complaints*** of defective black retainer rings."
- "You began releasing the re-designed pump with black retainer ring in August 2019, and you closed CAPA (b)(4)#299677 as effective October 2020. From December 2019 to May 2021, you received 887 complaints of defective black retainer rings; in 772 of the 887 complaints your firm referenced CAPA (b)(4)#299677 as the "Formal Investigation Reference Number" ***even though this CAPA was an investigation of the previous clear retainer ring design***."
- On January 21, 2020, you received a complaint (CASE-2020-00056605) from a customer reporting a crack on their insulin pump reservoir compartment, and damage to the retainer ring. Your product analysis on the returned device confirmed the device had a "partially broken retainer, cracked reservoir tube lip, missing reservoir tube lip O-ring, and broken reservoir tube lip." On April 24, 2020, you determined no formal investigation was necessary due to existing/previous formal investigation and referenced CAPA (b)(4)#299677. ***You closed this complaint on April 24, 2020.***

Item #3: A Few Warning Letter Excerpts

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Item #3: Two Takeaways

- Some companies misunderstand regulations and how to comply with it.
- Also, they fail to understand what is expected from them in term of what needs to have written evidence and what doesn't.
- Here's a huge piece of advice: ***"If there is no written evidence of it happening, it NEVER happened."*** In addition, to more likely than not, always make conservative decisions when it comes to data supporting the form, fit and function of your final product.
- It's helpful to periodically review citations and warning letters from the industry to learn from other companies' shortcomings and to better understand expectations.
- Quality Teams should put themselves on the situations that lead to these and do an introspective analysis of their company's Quality Systems to make sure they are not the next warning letter holder.
- In this way they are taking a preventative approach and making sure they institute a culture of continues improvement and active prevention.

Thank you