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P&A Analysis
Key Take Aways from USFDA CDER Report

FDA Fiscal Year 2023 Report on the State of Pharmaceutical Quality

The FDA's Fiscal Year 2023 Report on the State of Pharmaceutical Quality provides essential insights that Regulatory Affairs (RA) and Quality Assurance (QA) teams in the pharmaceutical industry should closely monitor. As we navigate an increasingly complex regulatory environment, these key takeaways emphasize critical focus areas and highlight the necessity of proactive quality management.

Key Highlights from the Report:

- **Global Oversight**: The FDA oversees **4,819 manufacturing sites** worldwide, with approximately **42% located in the U.S.**, marking a **14% increase** over the past five years. Notably, **40% of these sites** fall within the "no applications sector," which includes over-the-counter (OTC) monograph products, homeopathic drugs, and new drugs not yet approved by the FDA.
- **Inspection Activity**: The FDA conducted **776 drug quality assurance inspections** in FY2023, representing an increase of over **40%** compared to the **548 inspections** in FY2022.
- **Manufacturing Landscape**: The top five countries supplying the U.S. market include:
    - **U.S.**: 2,009 sites
    - **India**: 585 sites
    - **China**: 484 sites
    - **Germany**: 195 sites
    - **Italy**: 151 sites
      A chart in the report illustrates the growth of facilities by country from FY 2019 to FY 2023, revealing that only Canada and the UK experienced a decline in the number of sites (4% and 1%, respectively).
- **Mutual Recognition Agreements (MRAs)**: Inspections under MRAs rose from **144 in FY2022** to **187 in FY2023**, the highest recorded to date. This trend indicates a growing reliance on foreign inspectorates, which reduces redundant inspections and optimizes the use of limited FDA resources, benefiting the industry by minimizing repetitive inspections from various regulatory authorities.
- **Inspection Coverage**: In 2023, **25% of Indian facilities** in the site catalog were inspected, compared to only **6% of Chinese facilities**. The Office of Pharmaceutical Quality (OPQ) noted that the higher inspection rate in India was largely due to for-cause inspections, while travel restrictions hindered inspections in China.

- **Product Catalog Growth**: By the end of FY2023, CDER's Product Catalog included **17,519 application products** (up from **16,698** in FY2022) and **131,367 non-application product National Drug Codes** (up from **123,532** in FY2022). This extensive array of products necessitates rigorous quality metrics evaluations, keeping the OPQ and inspectorate actively engaged.
- **Quality-Related Reports**: In FY2023, CDER received:
    - **12,549 quality-related MedWatch reports** (a **1.6% increase** from FY2022)
    - **3,792 Field Alert Reports** (an **8.3% increase**)
    - **347 Biological Product Deviation Reports** (a **77% increase**)
    - **398 quality-related Consumer Complaints** (a **53.7% increase**)
      The report attributes these increases to specific product events, including recalls of ophthalmic products with quality issues.
- **Import Alerts and Recalls**: FY2023 saw **93 new drug quality-related import alerts**, surpassing the combined total of **77** from FY2021 and FY2022. This rise was partly linked to issues in hand sanitizer manufacturing. Additionally, **674 drug products were recalled**, a **26% decrease** from the peak of **912 recalls** in FY2022, involving **158 sites** and generating **225 recall events**. Notably, **35% of recalled products** were tied to five specific events detailed in the report.
- **Warning Letters**: The FDA issued **94 warning letters** to drug manufacturing sites in FY2023, addressing concerns related to drug quality.

These insights underscore the importance of maintaining high standards of quality and compliance within the pharmaceutical industry. RA and QA teams should leverage this information to enhance their quality management practices and ensure adherence to regulatory expectations.

Breakdown of the FDA Report Findings and Strategic Recommendations for Quality Assurance

1. **Increased Global Manufacturing Sites and Inspections** The FDA significantly enhanced its drug quality assurance inspections, rising from **548 inspections in FY2022** to **776 in FY2023**. The CDER Site Catalog now lists **4,819 drug manufacturing sites** globally, with nearly **42% located in the U.S.** This increase in inspections reflects heightened regulatory scrutiny, driven by the agency's efforts to address its pandemic backlog.

Why This Matters: More inspections mean greater pressure to maintain a state of readiness for audits. Many firms still operate under the assumption that the FDA's inspection frequency has not changed, but this data confirms the increased scrutiny. If your organization is not prepared for an FDA inspection, consider scheduling an audit or mock inspection with former FDA professionals.

Our Recommendations:

- **Bi-Monthly Compliance Reviews**: Regularly update all documentation, procedures, and training materials to ensure they are current.
- **Quarterly Internal Audits**: Develop a comprehensive checklist covering all manufacturing aspects, from raw material sourcing to final product testing, to proactively identify and address compliance issues.
- **Mandatory Staff Training**: Conduct training sessions focused on FDA inspection readiness, including expectations during inspections and proper interactions with inspectors. We often incorporate this training into our mock inspection services.
- **Bi-Annual Mock Inspections**: Engage third-party consultants to simulate FDA inspections, helping to identify gaps and areas for improvement.

2. **Increased MRAs and Foreign Inspections** FY2023 marked a record high for Mutual Recognition Agreement (MRA) partner inspections, with **187 conducted**. Foreign inspections now account for approximately **59% of all drug quality assurance inspections**, highlighting the FDA's focus on global supply chain integrity and the necessity for compliance across all manufacturing sites.

Why This Matters: MRAs and foreign inspections are crucial for ensuring that drugs manufactured internationally meet U.S. quality standards. As pharmaceutical supply chains globalize, maintaining oversight becomes increasingly complex. If you rely on suppliers, when was your last audit of them?

Our Recommendations:

- **Schedule Supplier Audits**: If you haven't conducted thorough supplier audits recently, prioritize them for 2024. The demand for supplier auditing services is at an all-time high, reflecting the expanding complexity of global supply chains. Consider bundling audits for cost efficiency.
- **Review Quality Agreements**: Establish or review detailed quality agreements with foreign manufacturing partners, specifying quality standards, documentation requirements, and inspection protocols. We can assist in drafting robust agreements.
- **Utilize Collaborative Technology**: Implement platforms like Microsoft Teams or Google Workspace for real-time communication and document sharing with international partners, ensuring transparency and swift resolution of quality issues.

3. **Progress in the Quality Management Maturity (QMM) Program** The QMM program aims to cultivate a quality culture among pharmaceutical manufacturers, promoting proactive quality management practices to enhance product quality and regulatory compliance. The FDA has developed a prototype assessment protocol for evaluating the quality management maturity of manufacturing sites, as detailed in an August 2023 white paper.

Throughout 2023, the FDA engaged with over ten stakeholder groups to gather input on the QMM program, resulting in a public docket that received **23 submissions**. In January 2024, the FDA announced a voluntary Quality Management Maturity Prototype Assessment Protocol Evaluation Program, inviting select manufacturers to participate and provide feedback.

Why This Matters: Internal quality teams must adopt a continuous improvement mindset, enhancing risk management practices and integrating the QMM principles outlined by the FDA. If you haven't reviewed the FDA's QMM white paper, now is the time to do so.

Our Recommendations:

- **Establish a Quality Metrics Program**: Implement a robust program to monitor quality control systems and processes, gathering data on key metrics to drive continuous improvement and support risk-based inspection scheduling.
- **Implement ICH Q10 Principles**: Thoroughly apply the concepts of ICH Q10 to manage and improve the Pharmaceutical Quality System (PQS), including quality risk management to address product availability risks.
- **Cultivate a Quality Culture**: Prioritize oversight and control in manufacturing, ensuring that quality objectives are directly aligned with business goals.

By following these strategic recommendations, organizations can enhance their quality assurance practices and better prepare for the evolving regulatory landscape.

4. Drug Shortages: A Persistent Challenge

Drug shortages continue to be a significant concern, primarily driven by quality issues and rising demand. The FDA's report identifies several factors contributing to these shortages and highlights the risks associated with natural hazards and supply chain vulnerabilities that can exacerbate the situation:

- **Quality Issues**: Problems such as contamination, manufacturing defects, and non-compliance with regulatory standards frequently lead to drug shortages. These challenges often arise from inadequate quality management practices and insufficient investment in quality control systems.
- **Increased Demand**: Surges in demand for specific medications—prompted by public health emergencies, new therapeutic indications, or rising disease prevalence—can exceed supply capacity.
- **Natural Hazards**: Events like hurricanes, floods, and earthquakes can disrupt manufacturing facilities and supply chains. The report notes that the frequency and severity of these natural disasters are increasing due to climate change.
- **Global Supply Chain Vulnerabilities**: The international nature of pharmaceutical supply chains introduces multiple points of risk. Dependencies on single-source suppliers, geopolitical tensions, transportation disruptions, and regulatory changes can all adversely affect supply continuity.

Why This Matters: Drug shortages have serious implications for patient care, making it crucial to address the root causes.

Our Recommendations:

1.Develop Comprehensive Risk Management Plans: Identify potential risks to the supply chain, including quality issues, natural hazards, and demand fluctuations. Conduct thorough risk assessments at each stage of the supply chain and prioritize risks based on their potential impact.

2.Create Contingency Plans: Prepare for potential supply chain disruptions by establishing backup manufacturing sites and alternative logistics routes.

3.Enhance Quality Management Systems: Strengthen your quality management systems to prevent issues that could lead to production halts or recalls. Companies with resilient QMSs often utilize advanced quality control technologies, such as real-time monitoring and predictive analytics, to detect and address quality issues proactively.

5. Increase in Post market Quality Defect Reports

The volume of post market quality defect reports has risen significantly, as evidenced by notable increases in MedWatch reports, Field Alert Reports (FAR), and Biological Products Deviation Reports (BPDR). These trends indicate widespread challenges in maintaining product quality after market release.

Context:

- **MedWatch Reports**: These voluntary submissions from healthcare professionals, patients, and consumers regarding product quality issues—such as contamination and defective components—showed a significant rise in FY2023, reflecting ongoing quality concerns.
- **Field Alert Reports (FAR)**: Mandatory reports that drug manufacturers must submit to the FDA within three working days of discovering significant quality defects. The increase in FARs highlights challenges in quality assurance during manufacturing and distribution.

- **Biological Product Deviation Reports (BPDR)**: Reports of deviations from current Good Manufacturing Practices (cGMP) or unexpected events affecting the safety, purity, or potency of biological products. The rise in BPDRs in FY2023 suggests potential issues in biologics production.
- **Recalls**: The increase in recalls in FY2023 indicates persistent problems in product quality management and the need for more robust preventive measures.

Why This Matters: Postmarket quality defects and recalls can severely impact a company's reputation and incur significant costs, diverting resources from product innovation.

Our Recommendations:

1. **Enhance Postmarket Surveillance Systems**: Implement systems to detect quality issues early. Consider using software platforms like MedDRA or Oracle Argus Safety for effective pharmacovigilance, enabling real-time tracking of adverse events and product performance.
2. **Utilize Analytics Platforms**: Leverage tools like Tableau or Qlik to visualize quality metrics and identify trends. Set up dashboards to monitor key performance indicators (KPIs) such as defect rates and complaint trends, allowing for early detection of emerging issues.
3. **Implement Data Integration Solutions**: Use solutions like Apache NiFi or Talend to consolidate data from various sources, including electronic health records (EHRs), product returns, and customer feedback. This integration facilitates comprehensive analysis and informed decision-making.
4. **Upgrade Your Quality Management System (QMS)**: Invest in a comprehensive QMS platform, such as Master Control or Veeva Systems, to effectively manage quality issues and ensure that post market problems are identified and addressed promptly.
5. **Schedule Regular Internal Audits**: Create an audit calendar covering all critical areas, including manufacturing processes, supply chain management, and post market surveillance. Regular audits (quarterly or bi-annually) conducted by trained auditors can help identify potential quality issues early. Contact us to access top pharmacovigilance consultants and auditors for your needs.

6. Increase in Drug Quality-Related Import Alerts and Warning Letters

In FY2023, the FDA issued **93 drug quality-related import alerts**, marking a significant rise from previous years. This increase is primarily attributed to issues such as non-compliance with record requests and deficiencies in current Good Manufacturing Practices (cGMP). Additionally, the FDA sent out **94 warning letters** to drug manufacturing sites, reflecting ongoing challenges in adhering to FDA standards.

Why This Matters: Import alerts and warning letters indicate serious quality lapses that can prevent products from entering the U.S. market. The rising numbers likely result from the FDA conducting more inspections and uncovering additional compliance issues during these evaluations.

Our Recommendations:

1. **Implement a Comprehensive Audit Plan**: Regular and thorough auditing is one of the most effective strategies for RA/QA teams to mitigate non-compliance risks. Develop a detailed audit plan that encompasses all critical areas, including manufacturing processes, documentation practices, and supplier management. Focus on key areas highlighted in recent FDA reports, such as cGMP compliance and record-keeping.
2. **Utilize Standardized Audit Tools**: Employ standardized audit checklists and methodologies, such as the FDA's Quality System Inspection Technique (QSIT) guidelines, to ensure consistency and thoroughness in the audit process. Review audit findings with senior management and create corrective action plans to address identified issues promptly. Utilize a Corrective and Preventive Action (CAPA) system to track and resolve these issues effectively.

3. **Establish Clear Quality Agreements with Suppliers**: Develop detailed quality agreements that outline specific FDA compliance requirements, including testing specifications and documentation standards. Implement incoming inspection procedures to verify the quality of imported products before they enter the supply chain. Consider using sampling plans based on standards like ANSI/ASQ Z1.4 for acceptance sampling.
4. **Adopt a Robust Document Management System (DMS)**: Implement a DMS that features version control, access controls, and audit trails. Consider validated electronic systems such as Veeva Vault QualityDocs or MasterControl to enhance document management capabilities.

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7. Emphasis on Developing Risk Management Plans (RMPs) for Natural Hazards

The report highlights the increasing necessity for pharmaceutical companies to conduct thorough risk assessments focused on natural hazards. These assessments should consider the rising frequency and severity of extreme weather events, including hurricanes, floods, and earthquakes. The FDA urges the industry to ensure that manufacturing and distribution facilities are resilient enough to withstand such disasters, incorporating structural reinforcements, backup power systems, and comprehensive emergency response plans.

Why This Matters: RA/QA teams must ensure that facilities and processes are resilient to natural hazards to maintain continuous operations.

Our Recommendations:

1. **Conduct Comprehensive Risk Assessments**: Identify potential natural hazards that could impact manufacturing and distribution. Utilize tools like Geographic Information Systems (GIS) to analyze location-specific risks, incorporating historical data and predictive modeling for extreme weather events. Identify critical infrastructure and assets vulnerable to these hazards, prioritize risks based on their potential impact, and document findings in the RMP.
2. **Enhance Physical Resilience**: Strengthen the physical infrastructure of manufacturing and distribution facilities to withstand extreme weather events. Install backup power systems, such as generators and uninterruptible power supplies (UPS), to ensure operational continuity during power outages. Regularly test and maintain these systems.
3. **Develop Detailed Contingency Plans**: Create contingency plans to ensure operational continuity and supply chain logistics during and after natural disasters. Establish alternative manufacturing sites and backup suppliers to mitigate supply chain disruptions, ensuring they meet the same quality standards and regulatory requirements. Consider implementing inventory management strategies, such as safety stock and buffer inventory, to maintain adequate supplies of critical raw materials and finished products.

Overall, the Office of Pharmaceutical Quality (OPQ) is actively engaged in ensuring the quality of the drug supply and compliance within the pharmaceutical industry through its various responsibilities and activities. We encourage a thorough review of the full report to gain deeper insights into the FDA's quality priorities.