Consider the following hypothetical situation: The US Food and Drug Administration (FDA) has informed the clinical investigator of a routine inspection. The clinical investigator, in turn, notifies investigational pharmacy senior leadership of an impending inspection to begin within five business days. Anxiety and tension levels rise. During the inspection, FDA requests and inspects investigational pharmacy policies and procedures as well as product accountability and handling. Were investigational products accounted for and stored appropriately? Does the investigational pharmacy have a quality management system or risk management policy? How are corrective and preventive actions tracked? Will the investigational pharmacy be cited with a Form 483?

These questions could be answered quickly and inspection anxiety reduced if the investigational pharmacy implemented a quality management system (QMS) approach to conducting clinical research prior to the notification of inspection.

As FDA continues to promote risk mitigation and a systematic procedural approach to clinical research, the investigational pharmacy (also known as research pharmacy) is reconfiguring policies and procedures to meet the changing regulatory landscape. Senior pharmacy management is challenged to “think within the landscape” and transform the research pharmacy into an operationally efficient and regulatory-compliant service center utilizing the eight quality management principles approach.

**Research Pharmacy Overview**

Research pharmacies are diverse in physical size, staff, staff composition and location. These pharmacies may be located within academic medical centers, private practice offices and/or research-only sites. The research pharmacy staff is primarily responsible (as delegated by the clinical investigator) for receipt, accountability, preparation, dispensing and destruction for investigational products, including biologics, devices, combination...
therapeutic products, vaccines and pharmaceuticals. Many academic medical institutions will dispense investigational products to inpatients via a clinical trials unit or general clinical research center and/or directly to the medical center floor or emergency room. The clinical trials units may be supported by funding from federal grants (as general clinical research centers are no longer funded by clinical and translational science awards grants) and/or industry-sponsored clinical research trials.

Research pharmacies (U.S. only) are governed by several federal regulators, including FDA, European Medicine Agency (EMA) for European research pharmacies, Drug Enforcement Agency (DEA), Center for Medicare Services (CMS) and Health and Human Services (HHS). Specifically, FDA governs the research operations of the research pharmacy. The research pharmacy’s operations must comply with International Conference on Harmonisation E6, Good Clinical Practice guidelines, research-specific 21 Code of Federal Regulations, and the Common Rule. In addition to clinical research regulations, the research pharmacy must comply with other medical center accreditation standards, such as The Joint Commission, Center Medicare Services, Drug Enforcement Agency and HHS regulations, and any applicable state and local laws.

Research pharmacies are highly regulated and require standard operating procedures and/or work instructions to streamline operations and enable effective supply chain operations while meeting the standards and federal and state regulations. The research pharmacist or pharmacy technician should be trained on clinical research regulations and Good Clinical Practice (GCP) guidelines. Furthermore, research pharmacy staff members should be required to train on each clinical trial protocol to gain clinical understanding of the investigational product(s) and risks involved in dispensing the investigational product.

Noncompliance Issues in the Research Pharmacy

As a result of increased regulations and complex clinical trial protocols, the research pharmacy is increasingly at risk for being cited for investigational product noncompliance issues. Without well-documented standard operating procedures, this risk for noncompliance citations further increases. Citations can vary from incomplete investigational product accountability to incorrect dosing. Other issues may include:

- Overutilized or underutilized policies and procedures
- Incomplete regulatory documentation (e.g., non-trained/unauthorized pharmacy staff dispensing the investigational product)
- Lack of management oversight, decentralized research pharmacy locations
- Lack of clinical research training
- Lack of clinical trial protocol training
- Incomplete record keeping (lack of good documentation practices)
- Inappropriate investigational product access

If a noncompliance incident does occur, the issue should be documented and the matter should be investigated to expose the root cause of the incident. After the root cause is determined, corrective and preventive actions should be implemented to correct the noncompliance and prevent it in the future. Unfortunately, the QMS approach is not known or adopted by many research pharmacies and corrective and preventive actions are sometimes not tracked, corrected and/or mitigated.

Noncompliance citations can impact the research pharmacy and clinical research program as a whole. The clinical investigator is ultimately responsible for all aspects of the clinical trial and authorizes or delegates specific clinical trial duties to qualified and trained staff members. If the research pharmacy fails to perform its responsibilities as required by the clinical trial protocol and the aforementioned regulations, then the clinical investigator could face FDA or Office of Inspector General sanctions. The severity of the
sanctions varies depending on the noncompliance incident. Sanctions can include one or many of the following: medical license disbarment, federal imprisonment, exclusion from new clinical trial protocols (blacklisted), termination of current clinical trial protocols and monetary restitution.

**Risk Mitigation and QMS in the Research Pharmacy**

To mitigate risk and stiff noncompliance penalties for clinical investigators and the organization, senior investigational pharmacy leadership should consider using a systematic approach to conducting clinical trials by following eight principles of quality management systems:

- Principle 1: Customer focus
- Principle 2: Leadership
- Principle 3: Involvement of people
- Principle 4: Process approach
- Principle 5: System approach to management
- Principle 6: Continual improvement
- Principle 7: Factual approach to decision-making
- Principle 8: Mutually beneficial supplier relationships

QMS principles are designed to be customer-centric, inclusive of senior management and process owners, and built with quality metrics and controls. By adopting and implementing a QMS program-wide approach, senior investigational pharmacy leadership can identify noncompliance issues as they happen, while investigating, correcting or preventing noncompliance issues in real time. Senior investigational pharmacy leadership should reference Lean Six Sigma to further develop robust value-add controls when streamlining research pharmacy operational program management.

As the research pharmacy is reorganized to mitigate risk and meet the needs of the current and future state of the regulatory environment, senior leadership and the clinical investigator should consider revising staffing structures and current program management, such as policies, procedures, work instructions and templates. The revised program management structure and policy changes should leverage FDA’s current position on risk mitigation strategies and quality-by-design. The best approach to risk mitigation and customer-centric total quality management is with the QMS approach. The QMS principle is simple: Lead with “quality,” and your product should always meet customer expectations and, in the case of the research pharmacy, should always meet compliance regulations.

Operational efficiency is another important aspect of the QMS approach that should be incorporated within the research pharmacy. Specifically, operational efficiency within the research pharmacy should streamline all research pharmacy policies into one “quality policy.” All standard operating procedures (SOPs), work instructions, templates and working documents fall under the quality policy and should be easily accessible to all applicable staff members. The documents are revised as needed and stored according to good documentation practices.

**Research Pharmacy Operations Transformation**

To begin the transformation process of developing a centralized QMS structure, senior investigational pharmacy leadership should engage an independent team to conduct a current state assessment of the research pharmacy. The assessment should include a gap analysis including Suppliers, Inputs, Producers, Outputs and Customers (SIPOC) analysis tool if necessary to identify channels, metrics, vendor interaction, inputs, process and customers and to identify research pharmacy deficiencies and noncompliance issues. Once the deficiencies are identified, program management, recommendations are made and the future state of the research pharmacy mapped out. Recommendations and future state mapping include appropriate process owner and change agents, program management metrics, staffing changes or alignment, high-level process approach, and corrective and preventive actions. Additional SOPs and work instructions are mapped to all processes identified in the gap analysis and SIPOC. If the assessment, recommendations and future state mapping are successful, the future state of the research pharmacy design is robust...
and flexible enough to absorb changes in regulatory policy with minimal impact to the research pharmacy and research pharmacy staff.

The next activity in program management includes developing a centralized QMS structure, designing an implementation phase (based on project management principles) and developing a training program and manual. Other activities include quality control testing (to enable consistent application of SOPs and work instructions) and timely touch points with research pharmacy staff to level set changes in research pharmacy program management. Program management implementation should also include regularly scheduled training days and or sessions to review regulatory policy and/or changes in research pharmacy SOPs/work instructions, as well as, design and implement an on-boarding training program to mitigate SOPs/work instruction application errors. As the research pharmacy is undergoing a QMS transformation, it should consider the following SOPs, work instructions and templates when mapping and redesigning program management:

- Clinical trials start-up
- Regulatory administration and maintenance
- IT
- IP storage
- IP access (staff and physical)
- IP accountability/label requirements
  - IP preparation
  - IP destruction
- Quality control/root cause/corrective and preventive actions
- Risk management
- Training
  - International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP)
  - Protocol
  - Pharmacy

By utilizing the QMS approach to restructure program management, the academic medical center, private practice or research-only site research pharmacy can produce a customer-centric operational efficient product that is highly adaptable and constantly reproducible while meeting regulatory policy. Furthermore, the QMS approach enables research pharmacy staff to remain well-trained in clinical research policy and clinical trial protocol procedures, which leads to increased productivity, the delivery of the highest safety standards and quality research pharmacy services.

References

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