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Leveraging Existing Management Systems to Comply with both cGMP and Process Safety Requirements

For Active Pharmaceutical Ingredients

An ioMosaic White Paper

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Abstract

Many companies who are regulated by current Good Manufacturing Practices (or cGMP) are discovering that they are also required to comply with process safety management regulations such as PSM in the US or Seveso or COMAH in Europe. And chemical and petrochemical companies who have been regulated for years under PSM are now starting to produce pharmaceutical products that are regulated under cGMP.

While cGMP and PSM regulate different hazards, the management systems that are needed to comply with each regulation are often the same. This paper will address the elements of the US PSM regulation and compare those requirements to the US cGMP regulations to show how the same management systems can be used to simultaneously comply with both regulations.

Introduction

Process safety regulations protect people, assets, and the environment by managing hazards associated with the release of hazardous chemicals and other energy sources.

Current Good Manufacturing Practices (or cGMP) regulations protect people and animals from the adulteration of food and drugs that makes the product impure, unsafe, or unwholesome. 21 US Code 342 & 351 define adulterated food and drugs in detail.

While the goals of the two regulations are different, they both contain similar requirements that can utilize the same management systems to comply with both regulations simultaneously. This paper will compare the key elements from the US Process Safety Management (PSM) requirements from 29 CFR 1910.119 with the International Conference on Harmonization (ICH) Q7 which is cGMP for Active Pharmaceutical Ingredients (APIs).

The cGMP requirements for food, dietary supplements, drugs, and excipients have similar requirements, but the related references will not be detailed in this paper. For more information on these topics, please reference 21 CFR 110 for cGMP for human food; 21 CFR 111 for cGMP for dietary supplements; 29 CFR 210 for drugs; 21 CFR 211 for finished pharmaceuticals; and the International Pharmaceutical Excipient Council (IPEC) for cGMP excipient guidelines.

Purpose of regulations

Event

Both the PSM regulation and cGMP strive to mitigate or eliminate catastrophic incidents. For PSM, these incidents often involve the loss of containment of flammable or hazardous chemicals. For cGMP, these incidents cause drug or food contamination causing production issues and recalls.

Consequence

Both types of incidents can result in injuries or fatalities to the public. For PSM incidents, the incident can, and often does, impact the workers at the facility. PSM can also impact the company's physical assets and the environment while cGMP incidents do not.

Both types of incidents can result in lawsuits and fines. For PSM in the US, the fines would originate from the Occupational Safety and Health Administration (OSHA) while fines for cGMP would typically originate from the Food and Drug Administration (FDA).

Both types of incidents can result in the company losing business and experiencing damage to their reputation in the industry.

Benefits of Compliance

Both PSM and cGMP regulations have similar requirements for management systems to prevent catastrophic events. In some cases, the separate PSM and cGMP management systems can be combined to improve efficiency.

Adhering to the requirements of both the PSM and cGMP regulations will allow your company to remain compliant with the required regulations, protect human health, avoid fines, and maintain your company's reputation and customer base.

Process Descriptions, hazard information, and equipment design have to be documented

PSM

Section 1910.119(d) requires that information about the covered process be documented. This includes hazards associated with the chemicals that are used, a process block flow diagram, safe upper and lower limits for parameters such as temperature, pressure, or chemical composition,

consequences of deviations, design information on the equipment in the process, and documentation that Recognized and Generally Accepted Good Engineering Practices (RAGAGEP) were used when designing the process equipment.

cGMP

ICH Q7 lists the requirements for documenting a cGMP process for APIs. Section 2.12 requires a system for managing quality that encompasses the organizational structure, procedures, processes, and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality related activities should be defined and documented. This is essentially managing the hazards that could impact the quality of the product. This includes the requirements for the buildings and process equipment that must be designed and constructed to facilitate adequate cleaning, maintenance, and operations. Building requirements include plumbing, ventilation, and sanitation. The design requirements for buildings and process equipment are outlined in ICH Q7 sections 4 and 5, respectively.

ICH Q7(6.4) requires a detailed production plan to manage quality as the API is produced. And ICH Q7(8.32) requires the documentation of critical control points in the process that ensure the quality and reproducibility of the product.

Documentation system

Both PSM and cGMP require that the hazards of the process, process control points or safe limits, and the appropriate design of the relevant equipment are documented. While PSM addresses hazardous chemicals and cGMP manages possible impacts to quality, the same documentation system that your company utilizes to document these hazards now can be used for both regulations. Your established workflow for creating and approving documentation, managing and approving changes, and determining who must approve these steps can be utilized.

Risk Analysis Required to Manage Hazards

PSM

1910.119(e) requires the employer to perform an initial process hazard analysis (hazard evaluation) on new or modified processes covered by this standard and to revalidate the analysis at least every 5 years.

cGMP

ICH Q7(8.30) requires in-process controls and that the acceptance criteria be defined based on the information gained during the development stage or using historical data. Section 2.50 requires that the quality personnel perform routine reviews of the in-process control points and critical API test results to determine if they are adequately controlling the quality of the product. Changes are required if the controls are not adequate. Any deviations or non-conformances must also be reviewed and acted upon.

ICH Q9 outlines the quality risk management system that should be utilized to determine the critical control points within the process.

Managing Risk

Though the exact process of conducting process hazard analyses for PSM and determining the critical control points within a cGMP process is not be the same, the philosophies are the same. The possible hazards of the process must be identified, the risks must be assessed, and then actions must be taken to eliminate the risk or mitigate the risk to an acceptable level. Assessments must be completed again when changes are made that could introduce additional hazards and the process must be periodically reviewed to ensure that the actions taken are still sufficiently managing risk. This overall approach can be applied to both PSM and cGMP while using different risk analysis tools. Both regulations specify similar risk assessment methodologies such as:

- HAZOP
- Preliminary Hazard Analysis (checklist)
- FMEA

Training for risk assessment for both regulations can be done simultaneously to minimize cost.

Employees must be Included

PSM

PSM 1910.119(c) requires employers to develop a written plan of action for the implementation of employee participation. This section also requires that employers consult with employees and their representatives on the conduct and development of process hazard analyses and the other elements within the PSM standard.

cGMP

ICH Q7 2.11 states that each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

Managing the quality of the product includes design of the facility, production, quality control, procedures, processes, and cleaning and maintenance of the equipment and buildings.

Ensuring Employee Participation

PSM specifically calls for employee participation on process hazard analysis (and other PSM elements) while cGMP requires employee participation when managing the quality of the API. Both are seeking to include employees where the largest risk exists for impacting health.

Your current practices for ensuring that qualified and impacted employees are part of hazard analysis or managing the quality of a cGMP product can be utilized to ensure that the appropriate personnel are engaged as you implement both regulations.

Employees must be Trained

PSM

Training is required by PSM 1910.119(g). This section states that training is required for each employee working in a covered process and if an employee changes roles within that process. An overview of the process is required with emphasis on the safety and health hazards, emergency response, and safe work practices applicable to their job. Section (g)(2) requires refresher training and section (g)(3) requires that the training and proof that the employee understood the training is documented.

cGMP

cGMP regulations require that employees who manufacture, process, package or hold the regulated product and their supervisors are qualified and trained. ICH Q7 3.12 requires that training be regularly conducted by qualified individuals and that the training covers, at a minimum, the specific operations that the employee performs and GMP as it relates to the employee's functions. Records of training are required to be maintained and training needs to be periodically assessed.

Training System

Both regulations require training your employees, retraining as needed, and documenting that training. Your current management system for training on either PSM or cGMP can be extended to both regulations. The topics that are trained upon will be different, but establishing qualified trainers, training new employees or employees who move into new roles, testing that those employees understand the training material and can execute their required responsibilities, and documenting that training will all follow the same process that you have already established.

Contractors Must be Managed

PSM

1910.119(h) requires that employers evaluate a contractor's safety performance and program before hiring them. The employer is required to inform the contractor of the hazards of the process and to periodically evaluate the contractor while they are on-site.

cGMP

ICH Q7 3.3 requires that consultant qualifications, which can include sufficient education, training, or experience, be documented.

Section 2.22(8) requires that quality personnel approve contract manufacturers before using them to produce APIs for the company and section 16 details all the requirements for using contract manufacturers (or tollers).

Managing contractors

Your current system for vetting contractors to ensure they are qualified and that they will operate safely can be used for both PSM and cGMP contractors. The specific qualifications that you are investigating will differ, but the process to check those qualifications can be the same.

Approval Required Before Start-up

PSM

1910.119(i) requires that the employer perform a pre-startup safety review (PSSR) for new and modified facilities when the modification is significant enough to require a change in the process safety information. The review must ensure construction and equipment is designed and installed in accordance with design specifications, that safety, operating, maintenance, and emergency

procedures are in place and are adequate; that a process hazard analysis (PHA) has been performed and recommendations have been resolved or implemented before startup, where required, and that training of each employee involved in operating the affected process has been completed.

cGMP

ICH Q7 12 requires that processes are qualified and validated before full production begins and that these activities are documented. Qualification activities are covered in section 12.3 and verify that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose, that the equipment or systems comply with the approved design, that the equipment or systems perform as intended throughout the anticipated operating ranges and that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly.

After the qualifications are completed, then a process validation is required per section 12.40. Process Validation is the documented evidence that the process can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

Procedures are required per section 6.10 and training is required per section 3.12. Risk assessments are required per ICH Q9 as changes are made.

Managing approval for start-up

PSM requires a PSSR while cGMP requires qualification and validation of the new or modified process. The approval for start-up is different, but the management systems you utilize to conduct these activities will be the same. You will create a team of qualified individuals who will follow the established procedures for conducting the PSSR or Qualification/Validation requirements. The team will ensure that the equipment has been designed and installed properly, that relevant procedures are created or modified, that the hazards have been addressed with the PHA or Quality Risk Assessment, and that personnel are trained on the changes that have been made.

Maintenance Required to reduce equipment failures

PSM

1910.119(j) requires that the employer perform maintenance on the process equipment. This includes creating written procedures, establishing appropriate inspection, testing, and preventive maintenance (ITPM) based on Recognized and Generally Accepted Good Engineering practices (RAGAGEP), addressing equipment deficiencies, training maintenance employees, and quality

assurance for designed and installed equipment and spare parts to ensure they are suitable for the intended use.

cGMP

ICH Q7 also requires maintenance of the buildings, equipment, and computer systems. Section 4.7 requires that buildings be maintained, repaired, and kept in a clean condition. Written procedures are required that assign responsibilities for these tasks.

Section 5.20 requires that schedules and procedures be created for the maintenance of equipment and section 5.44 requires that procedures be created for the maintenance of computer systems. Training is addressed in section 3.12.

Maintaining equipment

Both PSM and cGMP require that equipment be maintained. cGMP also stresses maintenance of the buildings and the computer systems. If your company is using a computerized maintenance management system (CMMS) or a more manual system, this system can be used to maintain the equipment for both PSM and cGMP. And buildings and computer systems can be added to this system as well. Establishing maintenance procedures and training personnel will also follow your established processes.

Specific procedures required to manage hazards

PSM

1910.119(f) requires that operating procedures be created for activities in the covered process for each operating phase including startup, normal and emergency shutdown, and normal, temporary, and emergency operations.

1910.119(k) requires that the employer issue a hot work permit for hot work operations conducted on or near a covered process. The permit must document that the fire prevention and protection requirements in 29 CFR 1910.252(a) have been implemented prior to beginning the hot work operations, it must indicate the date(s) authorized for hot work and identify the object on which hot work is to be performed. The permit must be kept on file until completion of the hot work operations.

cGMP

ICH Q7 (5.12) requires that written procedures be created for the cleaning of equipment, specifying how often the equipment must be cleaned, establishing acceptance criteria of residue levels and cleaning agents, keeping the equipment clean while it waits to be used, and then verifying its cleanliness right before it is used in production.

Managing specific hazards

Both PSM and cGMP require specific hazards be managed. PSM is managing hot work that can occur in areas where combustible and flammable materials are located. cGMP manages the cleanliness of the equipment to ensure the quality of the end product. As we discussed for operating procedures, your existing documentation system can be used regardless of the procedures that needs to be created, reviewed, approved, and distributed to your employees. And your current training practices can be used to ensure that the impacted employee are properly trained and understand the procedures to be followed.

Control of change requires independent approvals

PSM

1910.119(l) requires that the employer establish and implement written procedures to manage changes (except for "replacements in kind") to process chemicals, technology, equipment, and procedures; and changes to facilities that affect a covered process.

The procedures must address the technical basis for the proposed change, the impact of change on safety and health, modifications to operating procedures, the necessary time period for the change, and authorization requirements for the proposed change. All impacted employees must be trained prior to start-up of the impacted process.

cGMP

ICH Q7 (13.10 & .11) require a formal change control system to evaluate all changes that may affect the production and control of the intermediate or API. Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling, and packaging materials, and computer software.

Section 13.13 allows the employer to manage the change depending upon how major or minor the change is relative to its impact on quality. 13.14 requires that all documents that are impacted by the change be updated. Training is required by section 3.12.

Managing change

Both PSM and cGMP require that change be managed. PSM requires management of change (MOC) when the change is not replacement in kind. cGMP requires MOC to the degree that it impacts quality. Both regulations require that a written MOC procedure is used and that the change is authorized by people who are independent of the ones making the change. Impacted personnel must also be trained on the changes before the start-up of the impacted process or equipment. The existing MOC system can be used for either regulation as long as the system is set up to adapt the specific questions depending upon whether the change involves a PSM covered process, the quality of a cGMP product, or both. Proper approvals must also be identified.

Investigations required for near misses and incidents

PSM

1910.119(m) requires that the employer investigate each incident which resulted in, or could reasonably have resulted in, a catastrophic release of a highly hazardous chemical in the workplace. A team must be created and consist of at least one person knowledgeable in the process involved and other persons with appropriate knowledge and experience to thoroughly investigate and analyze the incident. A report must be written after the investigation is completed that includes specific information.

The employer must establish a system to promptly address and resolve the incident report findings and recommendations. Resolutions and corrective actions must be documented and shared with impacted employees.

cGMP

ICH Q7 (2.22)(11) requires quality personnel to ensure that quality related complaints are investigated and resolved. Section 2.3 requires that quality personnel ensure that all production deviations are reported and evaluated, that critical deviations are investigated, and that the conclusions are recorded as they occur.

Section 2.5 requires regular quality reviews be completed and documented at least annually for all quality incidents. The results of the reviews must be evaluated, and an assessment made as to

whether any corrective actions are required. If so, the corrective actions must be completed in a timely manner.

Investigating Near Misses and Incidents

Both PSM and cGMP require that investigations occur for near misses and incidents. For PSM, these investigations are related to potential or actual releases of hazardous materials while cGMP is managing potential or actual impacts to quality. Both regulations require that the defined incidents be reported and that qualified personnel investigate the incident. Documentation is required and corrective actions must be identified and addressed in a timely manner. The process that the company currently uses to investigate incidents can be used for both regulations.

Crisis Management Required to Handle Catastrophic Events

PSM

1910.119(n) requires that the employer document and implement an emergency action plan for the entire plant in accordance with the provisions of 29 CFR 1910.38. That regulation requires an action plan be developed for possible fires or other emergencies, responsibilities are designated for the response team, and drills are conducted so employees can practice executing the plan.

cGMP

ICH Q7 (15.13) requires a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered. (A recall is required when a product is found to be in violation of the governing regulations or specifications for that product.) Section 15.14 requires the recall procedure to designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated. Section 15.15 requires that in the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed, and their advice sought.

Managing Crises

Both PSM and cGMP require that an employer prepare a crisis management plan in the event of an emergency. For PSM, this plan includes evacuating the premises due to a fire or other emergency, while cGMP addresses product that is potentially in violation of the required regulations or specifications for that the product. In both cases, written procedures are required that outline the plan of action if a crisis occurs. Both require designated personnel to take responsibility for the action plan and to involve local authorities as needed to resolve the issue.

Both regulatory bodies require that training exercises are conducted. This would include a response to a simulated incident for PSM or a mock product recall for cGMP.

Audits Required to Assess Management Systems

PSM

1910.119(o) requires that the employer certify that they have evaluated compliance with the provisions of this section at least every three years to verify that the procedures and practices developed under the standard are adequate and are being followed. The compliance audit must be conducted by at least one person knowledgeable in the process and a report of the findings of the audit must be documented. The employer must promptly determine and document an appropriate response to each of the findings of the compliance audit, and document that deficiencies have been corrected.

cGMP

ICH Q7 (2.22)(7) requires that quality personnel perform internal audits. Section 2.4 requires that regular internal audits be conducted per the established schedule to verify compliance with the principles of cGMP for APIs. Section 2.41 requires that audit findings and corrective actions be documented and brought to the attention of responsible management of the firm. Corrective actions must be completed in a timely and effective manner.

Conducting Audits

Both PSM and cGMP require that compliance audits be conducted on a regular basis and that a knowledgeable person is part of the audit team. Both require that the audit, findings, and corrective actions be documented and that corrective actions be addressed in a timely manner. While the audit protocols will be different for PSM and cGMP, the process of establishing procedures, conducting the audit per the schedule, documenting the findings, establishing corrective actions, and addressing those corrective actions in timely manner will follow the same management system.

Summary

PSM and cGMP are both regulations for managing risk. PSM focuses on the risks associated with hazardous chemicals while cGMP focuses on the risk of adulterated products. While the focus is different, companies can comply with both regulations with their existing management systems. As a company introduces either PSM or cGMP, they will need to document the new hazards while ensuring employee participation, write new procedures to address the new requirements, update existing procedures to include the new requirements. and modify the existing management systems.

The maintenance system will be expanded to include new equipment and ITPM, the contractor management system will include more vendors with different requirements and specifications, the document control system will include more documents, management of change will include different people and processes, and the incident investigation and auditing systems will include the new regulation. The philosophy of the current risk analysis system will be leveraged to create the new process required by either PSM or ICH Q9. As changes are being made, the training system will be used to create and deliver the training that is needed.

PSM and cGMP are both regulations that manage risk, and companies can use their existing management systems to comply with both.

Appendix A – Glossary of Acronyms

API - Active Pharmaceutical Ingredients

CFR – Code of Federal Regulations (United States)

CMMS – Computerized Maintenance Management System

FMEA – Failure Mode and Effects Analysis

cGMP – current Good Manufacturing Practices

FDA – Food and Drug Administration (United States)

HAZOP – Hazard and Operability Study

ICH - International Conference on Harmonization

IPEC - International Pharmaceutical Excipient Council

ITPM – Inspection, Testing, and Preventive Maintenance

MOC – Management of Change

OSHA - Occupational Safety and Health Administration (United States)

PHA – Process Hazard Analysis

PSM – Process Safety Management

PSSR – Pre Start-up Safety Review

RAGAGEP - Recognized and Generally Accepted Good Engineering Practices

APPENDIX B –PSM vs cGMP at a Glance

PSM Reference 29 CFR 1910.119	API cGMP Reference ICH Q7	Common Requirements
Section d - Document process and equipment information	*Sections 2.12, 4, 5, 6.4 and 8.32* - Document all quality related activities including design	Utilizes same systems for document control and change management
Section e - Conduct process hazard analysis	*Sections 2.50, 8.30 and ICH Q9* - Conduct risk assessment	Utilizes similar processes to identify the possible hazards and implement corrective actions
Section c - Include employees during process hazard analysis and other PSM elements	*Section 2.11* - Quality system includes the active participation of employees	Both require creation of a plan to include impacted employees
Section g - Train employees and document training	*Section 3.12* - Train impacted employees, and document	Utilizes same training process
Section h – Contractor approval and management system	*Sections 2.22(8), 3.3 and 16* - Approve process for consultants and tollers	Both use same contractor approval system
Section l – Pre start-up safety reviews	*Section 12 primarily (12.3 & 12.40) and 6.10 and ICH Q9* – Validation for new or modified processes	Similar teams used to ensure that new or modified processes meet the specified requirements before start-up
Section j - Maintain process equipment	*Sections 4.7, 5.20 and 5.44* - Maintain process equipment and buildings	Both use the same maintenance management system
Section f & k - Procedures required for operations and hot work	*Section 5.12* - Procedure required for equipment cleaning	Utilizes similar processes for minimizing incidents
Section l – Management of change process	*Sections 13.10, 13.11, 13.13, and 13.14* - Formal change program is required	Can utilize the same management of change process if the questions and approvals are adapted for each regulation
Section m – Investigate and resolve incidents	*Sections 2.22(11), 2.3 and 2.5* - Investigate and resolve complaints and production deviations	Both use the same incident investigation process
Section n - Document an emergency action plan	*Sections 15.13, 15.14 and 15.15* - Document all possibilities that could result in a recall	Utilizes the same process to create an emergency action plan
Section o – Audit management system every 3 years and resolve deficiencies	*Sections 2.22(7), 2.4 and 2.41* - Perform internal audits and address corrective actions	Utilizes the same process of auditing with a protocol and corrective action system