

Engineering Management
Field Project

GMP Compliance for Pharmaceutical Excipients in the Glycerin Industry

By

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Executive Summary

After the events of September 11, 2001, the United States enacted the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (the Bioterrorism Act) to protect the public from terrorist attacks on the U.S. food supply. The Food and Drug Administration (FDA) tightened its regulations on manufacturers, including those of excipients, or processing aids used in many food and pharmaceutical products. One common excipient, glycerin, now faced stricter regulations.

Unfortunately, there was a lack of resources available for excipient manufacturers until recent years. The need for guidance documents became evident as incidents involving counterfeit glycerin were linked to widespread illness and death across the globe. The International Pharmaceutical Excipients Council joined forces with the Pharmaceutical Quality Group and published *The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients*. IPEC-PQG divides excipient GMP's into five sections: quality management systems – excipient quality systems, management responsibility, resource management, product realization, and measurement, analysis and improvement.

Company XYZ sells refined glycerin to customers for use in pharmaceutical and food applications; therefore, the site needs to ensure full compliance with excipient GMP's. Because of the number and depth of topics outlined in IPEC-PQG's GMP's, this project will focus on excipient GMP training, management commitment, annual product review, and significant change notification. Recommendations for maintaining compliance in these areas will be shared with Company XYZ.

Acronyms

API – Active Pharmaceutical Ingredient

cGMP's – Current Good Manufacturing Practices

COA – Certificate of Analysis

DEG – Diethylene Glycol

FDA – Food and Drug Administration

FMEA – Failure Mode and Effects Analysis

GMP'S – Good Manufacturing Practices

GRAS – Generally Recognized as Safe

HACCP – Hazard Analysis and Critical Control Point

IPEA – International Pharmaceutical Excipients Auditing, Inc.

IPEC – International Pharmaceutical Excipients Council

ISO – International Organization for Standardization

JP – Japanese Pharmacopeia

JPEC – Japanese Pharmaceutical Excipient Council

OOS – Out-of-Specification

PhEur – European Pharmacopeia

PQG – Pharmaceutical Quality Group

QA – Quality Assurance

R&D – Research and Development

SOP – Standard Operating Procedure

USP – United States Pharmacopoeia

Introduction

Following the terrorist acts of September 11, 2001, the United States enacted the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, otherwise known as the Bioterrorism Act. Its purpose is to protect the public from terrorist attacks on the U.S. food supply. The Food and Drug Administration (FDA) then tightened its regulations on food manufacturers. Many excipients also became subject to such regulations because excipients are food additives, dietary ingredients, or raw agricultural commodities used for food (Falk 2004, 78). An excipient is “any substance other than the active drug or prodrug that is included in the manufacturing process or is contained in a finished pharmaceutical dosage form” (Chang 2007, 56). This means suppliers and users of excipients are now required to comply with FDA regulations.

Glycerin is one of the pharmaceutical excipients subject to the newer regulations. Company XYZ operates the world’s largest glycerin refinery and sells glycerin to many customers who use it in pharmaceutical and food applications. It’s imperative that XYZ ensure full FDA and United States Pharmacopoeia (USP) compliance in order to continue to compete in the glycerin industry.

Quality has long been a focus of industries, but now more than ever, it has become a key concern of customers. The past couple of years have been filled with numerous news stories concerning quality, or lack thereof, of several consumer products. Recall after recall has been reported and consumers’ awareness and concern over the quality of the goods they’re purchasing has sky rocketed. Themes have surfaced from these stories. China appears to be the front runner when it comes to countries producing and exporting low quality products that may carry health and safety concerns with them. For example,

there was the case in which a Chinese pet food manufacturer exported wheat gluten containing an industrial chemical melamine, which then resulted in pet deaths in the United States (*New York Times* 6 May 2007). There have also been cases in which toys from Chinese manufacturers were found to contain lead. Such news stories have caused consumers to have a heightened awareness of product quality.

The glycerin industry has not escaped this increased scrutiny. Many cases have occurred the past few years in which manufacturers of glycerin were selling counterfeit glycerin, including poisonous diethylene glycol (DEG), in efforts to increase their profits. This toxic chemical ended up in various medicines and was linked to at least eight mass killings around the world in the past two decades, during which an estimated thousands died (*New York Times* 6 May 2007). Such episodes beg the question, what must be done to build confidence in the quality of excipients used in several food and pharmaceutical products worldwide?

Literature Review

Introduction

A literature review was completed to determine the amount of guidance material available for manufacturers of pharmaceutical excipients. Research was conducted using online science and engineering databases, such as Compendex, Web of Science and Proquest. The University of Kansas Library assisted in obtaining full text journal and magazine articles. Because the Bioterrorism Act and resulting regulations are relatively new, most research was completed using publications from the past five to ten years. Articles explaining regulations imposed by the FDA on excipient manufacturers were found. Also, recent events around contamination or counterfeit of excipients were reviewed to understand the importance of the regulations, Good Manufacturing Practices (GMP's), and facility audits. By gaining a thorough understanding of the concerns around excipient quality, Company XYZ will better understand how to meet its customers' needs.

The Need for Standards

According to Rafidison and Ulman, authors of "Critical Good Manufacturing Practice Aspects to Consider for Pharmaceutical Excipients," excipients often make up 99% of a finished drug product and their role varies from noncritical to highly functional. Excipients typically have a generally recognized as safe (GRAS) status because they originated in the food industry (Rafidison and Ulman 2003, 118). International Organization for Standardization (ISO) quality standards, which many companies are familiar with, were listed as a useful resource, but they were noted for explaining what

quality systems should exist versus providing guidance on how to implement such systems. At the time of Rafidison's and Ulman's article, current legislation and guidance documents were still focused mainly on active pharmaceutical ingredients (API's) or finished drug manufacturers. Control of excipient manufacturers was still not a top priority; however, incidents occurring across the globe illustrated the need for improved control. The low accessibility of excipient guidance, even as recent as 2003, has slowed progress in this area though.

The need to regulate excipients became evident as cases continued to surface in which manufacturers of glycerin sold counterfeit glycerin, including poisonous DEG, in efforts to increase their profits. Rarely is the origin of the DEG confirmed, but recent cases have been traced back to manufacturers in China. In one high profile case referred to in a 2007 New York Times article, "Syrup Killer in Medicine Bottle," a Chinese manufacturer named Wang Guiping was looking to earn extra money and decided to substitute industrial-grade syrup for the pharmaceutical-grade syrup approved for human consumption. He swallowed a small amount of the syrup and when nothing happened to him, he decided it would be a safe substitute for glycerin. Yet, he knowingly forged licenses and laboratory reports. Later, while looking for an even cheaper substitute, he decided to sell DEG as glycerin since DEG was an odorless syrup he deemed to be a reasonable substitute. Only he didn't perform his taste test on the DEG, which is an indication that even he knew how dangerous it could be (*New York Times* 6 May 2007). Another case mentioned in the same article was that of the Taixing Glycerine Factory, which claimed to be located in Hengxiang, China. The factory's web site showed pictures of a beautiful, tall structure; however, no such facility exists in the city. The

Glycerine Factory purchased its DEG from the same manufacturer as Wang and then proceeded to make and sell the toxic syrup with certificates of analysis (COA's) that claimed it was 99.5% pure glycerin. Also disturbing is the fact that nearly all shipping papers accompanying the toxic syrup contained the name "TD" glycerin. TD stands for the Chinese word "tidai," which means "substitute," almost giving away the secret that product was not pure glycerin (*New York Times* 6 May 2007). The amazing thing is that the barrels of toxic syrup passed through many hands without anyone once testing or questioning the contents. This eventually led to an epidemic in Panama – a mysterious illness with a 50% death rate.

What went wrong in these cases? Documents were forged, buyers were not familiar with their suppliers, labels were taken at face value (contents were assumed to be accurately labeled), names of suppliers were removed from shipping papers as the syrup passed through various distributors (to eliminate fear of being cut out of the supply chain), original COA's were not passed onto to each buyer, and each buyer/distributor failed to test the product upon receipt (*New York Times* 6 May 2007). The public now realized how critical excipient quality could be.

Resources Available Today

Slowly, industry recognized the need to provide regulatory guidance for excipient manufacturers. In "Excipient GMP Quality Standards: One is Enough," Irwin Silverstein describes the formation of the International Pharmaceutical Excipients Council (IPEC) in 1991 and its purpose. This council consists of representatives from various excipient manufacturers and pharmaceutical companies. Its first focus was to

create GMP guidelines for the manufacture and use of excipients. A committee worked for four years to develop a GMP standard, which was based on the widely known ISO 9001 standard for quality management. The draft standard was shared with IPEC-Europe and the Japanese Pharmaceutical Excipient Council (JPEC). After their review, the edited document became the globally accepted standard and in 1995 the *Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients* was published. It was later updated in 2001 to incorporate ISO 9000:2000 requirements (Silverstein 2002, 46-48). In 2006, the standard was again updated to incorporate ISO 9001 and the Pharmaceutical Quality Group's (PQG) PS 9100:2002 Pharmaceutical Excipients into a guide called *The Joint IPEC-PQG Good Manufacturing Practices guide for Pharmaceutical Excipients* (IPEC 2006, i). This standard helps ensure excipients are produced safely and appropriately as required by the Food, Drug, and Cosmetic Act. Through it all, IPEC has kept the FDA informed of its GMP guide as well as other guides it's published, such as *The Joint IPEC-PQG Good Manufacturing Practices Audit Guide for Pharmaceutical Excipients* and *Significant Change Guide for Bulk Pharmaceutical Excipients*. IPEC even shared its GMP standards with the World Health Organization to help develop guidelines for excipient manufacturers in less developed countries (Silverstein 2002, 48).

Further expectations for pharmaceutical grade materials are outlined in Victoria Shaheen's article, "Objectives, Challenges, and Progress in the Global Harmonization of Excipient Monographs." She explains that pharmaceutical grade materials are manufactured according to current good manufacturing practices (cGMP's) and must meet specifications for use in pharmaceutical products, as outlined by the (USP)

(Shaheen 2003, 40). Products must also meet Japanese and European Pharmacopeia (JP and PhEur) requirements if they will be sold in those markets. Because it can be difficult for excipient manufacturers to complete the required testing for all three compendia, efforts are underway to harmonize excipient monographs to satisfy USP, JP, and PhEur.

Balance Between Regulation and Investment

Another theme was evident in the journal articles “Emerging Trends in the Use of Pharmaceutical Excipients,” “Critical Good Manufacturing Practice Aspects to Consider for Pharmaceutical Excipients,” and “Why Audit Pharmaceutical Excipient Manufacturers.” While authors agreed that manufacturers of excipients were in need of regulatory guidance, some also pointed out that it’s important not to lose sight of the fact that excipients do not need to be regulated to the same degree as active drug products. Ralph Shangraw, author of “Emerging Trends in the Use of Pharmaceutical Excipients” pointed out that while excipients can be the cause of more issues than previously thought, they do not cause as many issues as some people claim they do. Shangraw stressed the need to increase regulatory focus, but not to the extent of active drug products. Issues related to one excipient are not an indication that all excipients are subject to those issues (Shangraw 1997, 36). All types of excipients do not need to demonstrate the same performance qualities (Shangraw 1997, 38). When implementing actions to address regulatory compliance, excipients must be handled on a case by case basis.

In their article, “Critical Good Manufacturing Practice Aspects to Consider for Pharmaceutical Excipients,” Rafidison and Ulman also recognized the need for excipient manufacturers to meet pharmaceutical companies’ GMP expectations and to provide the

supply chain confidence needed to meet the increased demand for safe products (Rafidison and Ulman 2003, 118). The authors emphasized four GMP areas of focus for excipient manufacturers – traceability, change control, notification, and contamination. While the authors felt these four areas were essential, they ultimately suggested excipient manufacturers must determine what level of controls is needed. The authors suggested excipient manufacturers consider factors such as the use of their product, open versus closed systems, nature/type of product, complexity of processing, degree of environmental control/exposure, and cleaning procedures (Rafidison and Ulman 2003, 122-123). While excipient manufacturers want to provide the appropriate level of confidence to pharmaceutical buyers of their materials, they also want to avoid unnecessary investments.

Facilities need to balance regulatory compliance with the amount of investment they're willing to make. One decision excipient manufacturers must make is whether or not they will allow facility audits. In "Why Audit Pharmaceutical Excipient Manufacturers," Marshall Steinberg explains there are two groups of excipient manufacturers – those who manufacture almost exclusively for the pharmaceutical industry and those who have major customers outside the pharmaceutical industry (Steinberg 2003, 150). The first group obviously needs to allow facility audits, but there are strong reasons for the second group to consider audits as well. If a company labels its products "USP," then it must meet the USP GMP guidelines, "<1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients" (Steinberg 2003, 152). While audits may feel like an inconvenience to the second group of excipient manufacturers, these manufacturers must meet quality standards if they choose to supply

USP excipients (Steinberg 2003, 152). They must decide either they will or they won't offer USP products, and no matter how small the volume of such customers may be, the supplier has to demonstrate it can meet the USP GMP's. By allowing audits, excipient manufacturers are not only demonstrating they meet the GMP requirements, but are also giving themselves an advantage over their competitors. After all, USP products can be sold to customers who don't necessarily require USP and the extra effort put towards following standards and allowing audits will be seen as an added bonus. It may even become mandatory for suppliers of USP products to allow customer audits in the future.

Good Manufacturing Practices for Excipients

Purpose

This field project will attempt to outline some of the regulations that now apply to pharmaceutical excipients and suggest actions to help ensure compliance. First, an understanding of the standards is needed before an excipient manufacturer can evaluate its compliance. Then, the manufacturer should evaluate what must be done to meet excipient regulations, demonstrate compliance to regulatory groups, build confidence in its customers, and succeed in regulatory, third party, and customer audits.

According to IPEC & PQG, “The objective of excipient GMP is to ensure that the manufacture of an excipient results in a consistent material with desired quality characteristics. The emphasis of GMP for excipients is to assure product integrity, avoid product contamination and ensure that records are maintained” (IPEC-PQG 2006, 3). To support this objective, the excipient manufacturers must maintain quality systems that meet the intent and help deliver GMP requirements.

Overview of IPEC-PQG GMP’s

IPEC-PQG divides excipient GMP’s into five sections: quality management systems – excipient quality systems, management responsibility, resource management, product realization, and measurement, analysis and improvement. A brief overview of each section will be provided here. To learn and fully understand the GMP’s, the site quality assurance (QA) manager should consider attending one of the GMP workshops offered by International Pharmaceutical Excipients Auditing, Inc. (IPEA), an independent subsidiary of IPEC-Americas.

Quality Management System – Excipient Quality Systems

The first section, quality management systems – excipient quality systems, provides guidelines for site quality management processes that will help assure quality product (IPEC-PQG 2006, 4). This section provides guidelines for:

- General Requirements
- Documentation Requirements
 - General
 - Quality Manual
 - Control of Documents
 - Control of Records
- Change Control

The excipient manufacturer should demonstrate responsibility for excipient quality and have appropriate control measures in place. This requires a quality manual that describes the quality management system, quality policy, and the manufacturer's commitment to GMP's. A system for document control must exist. This includes documented procedures, a numbering system for procedures, a review and approval process that includes QA, and guidelines for distributing current versions of procedures throughout the site. While the GMP's do not specify a timeline for reviewing procedures, IPEC-PQG recommends every 2-3 years. Along with document control, control of records should be established. The site needs a procedure that defines retention guidelines for records. Site employees also need to be trained on appropriate record keeping practices, such as making legible entries, signing and dating entries, and following guidelines for making corrections to entries. For change control, the site needs a documented procedure that explains how changes are reviewed, includes QA review and approval, and documents follow ups to changes (i.e. customer notification).

Management Responsibility

The second section, Management Responsibility, includes:

- Management Commitment
- Customer Focus
- Quality Policy
- Planning
 - Quality Objectives
 - Quality Management System Planning
- Responsibility, Authority and Communication
 - Responsibility and Authority
 - Management Representative
 - Internal Communication
- Management Review
 - General
 - Review Input
 - Review Output

Site management must demonstrate commitment to the customer, demonstrate awareness and commitment to the site quality policy, set and measure objectives for GMP compliance in the organization, ensure adequate staffing to meet objectives, clearly define responsibilities and reporting relationships, and communicate GMP and regulatory requirements to the rest of the organization via newsletters, emails, or meetings.

Management should also complete management reviews, which are periodic reviews of the site's quality systems. During this time, management would discuss site quality results, identify corrective actions and additional resources needed, and document recommendations.

Resource Management

Resource Management looks at personnel and material resources needed to support the quality management system:

- Provision of Resources

- Human Resources
 - General
 - Competence, Awareness and Training
 - Personnel Hygiene
- Infrastructure
 - Buildings and Facilities
 - Equipment
 - Equipment Construction
 - Equipment Maintenance
 - Computer Systems
 - Utilities
 - Water
- Work Environment
 - Air Handling
 - Controlled Environment
 - Cleaning and Sanitary Conditions
 - Pest Control
 - Lighting
 - Drainage
 - Washing and Toilet Facilities

The site must have sufficient staffing and provide adequate training for skills needed on the job, as well as GMP overview and personal hygiene training. Personnel performing work that could affect the quality of excipients must have appropriate training and experience for their tasks (IPEC-PQG 2006, 8). All training should be documented. Buildings and facilities must be adequately designed and maintained in a way that helps prevent contamination. Equipment must be designed and maintained in a manner that minimizes contamination. This can be done by requiring adherence to maintenance SOP's, keeping records of maintenance activities, and establishing guidelines for returning equipment back to service after maintenance is completed. There should be procedures for maintaining a clean facility and disposing of waste properly. A pest control program is needed to keep the facility free of bugs and rodents. Guidelines should be established and followed for computer systems, utilities, water, air handling,

controlled environments, lighting, drainage, and washing/toilet facilities as each of these can affect product quality. Overall, the site must follow design standards and documented procedures for each of these systems to maintain excipient quality.

Product Realization

Product realization is an extensive section of the GMP's that encompasses several topics critical in the production of excipients:

- Planning of Product Realization
- Customer-related Processes
 - Determination of Requirements Related to the Product
 - Review of Requirements Related to the Product
 - Customer Communication
- Design and Development
- Purchasing
 - Purchasing Process
 - Purchasing Information
 - Verification of Purchased Product
- Production and Service Provision
 - Control of Production and Service Provision
 - Production Instructions and Records
 - Equipment Cleaning
 - Residual of Solvents, Mother Liquors and Second Crop Crystallizations
 - In-process Blending or Mixing
 - In-process Control
 - Packaging and Labeling
 - Records of Equipment Use
 - Validation of Processes for Production and Service Provision
 - Identification and Traceability
 - Traceability
 - Inspection and Test Status
 - Labeling
 - Customer Property
 - Preservation of Product
 - Handling, Storage and Preservation
 - Packaging Systems
 - Delivery and Distribution
- Control of Measuring and Monitoring Devices

This section covers processes and controls needed for the manufacture of the excipient. Not all of these items are owned by plant personnel; in fact, several are owned by resources outside of the manufacturing site. For example, purchasing and research and development (R&D) resources are often responsible for identifying and qualifying raw material suppliers. The manufacturing site needs to be aware of any processes owned and implemented outside the plant walls. For other items in this section, the site needs to demonstrate ownership and implementation. It needs to maintain dedicated equipment and process areas when possible and take all change requests through the site change control process. Customers need to be notified of significant changes. Employees must follow procedures for brand changeovers, cleaning and sanitization, raw material receiving, material quarantine, production, and product storage and handling. Complete and accurate production records are expected to be kept. In-process inspection and testing must be conducted as defined in documented standards. The site should complete and maintain validations for the process and equipment. A calibration program is expected to be defined and followed for equipment and instruments critical to product quality. The site and its employees need to follow documented procedures and take other measures necessary to protect product traceability.

Measurement, Analysis and Improvement

Finally, guidelines are provided for Measurement, Analysis and Improvement:

- General
- Monitoring and Measurement
 - Customer Satisfaction
 - Internal Audit
 - Monitoring and Measurement of Processes
 - Monitoring and Measurement of Product

- Laboratory Controls
 - Finished Excipient Testing and Release
 - Out-of-Specification Test Results
 - Retained Samples
 - Certificates of Analysis
 - Impurities
 - Stability
 - Expiry/Retest Periods
- Control of Nonconforming Product
 - Reprocessing
 - Reworking
 - Returned Excipients
- Analysis of Data
- Improvement
 - Continual Improvement
 - Corrective Action
 - Preventive Action

This is another detailed section covering several topics important to excipient quality. It focuses on monitoring and measurement of the quality management system. It also focuses on identifying actions for improvement. The site is expected to have systems to address customer complaints, internal quality audits, and monitoring and measurement of process conditions. Product must also be monitored and measured through lab controls, finished product testing and release, out-of-specification (OOS) procedures, retained samples, COA's, identification of and limits for known impurities, and a stability program. The manufacturer should also communicate guidelines for expiry or retest periods to customers purchasing the excipient. It's critical for site employees to understand and follow procedures for nonconforming product – they should know how to verify OOS results, quarantine product, and contact QA resources. Clear guidelines for reprocessing or reworking product must also be provided to employees. In order to understand how effective the site's quality management system is, the site needs

periodic reviews of key quality measures. Corrective and preventive actions should be identified when needed to help drive continual improvement.

Summary

The above is only a summary of the five sections of GMP guidelines provided by IPEC-PQG. For further details, excipient manufacturers should consult *The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients*. Because of the number and depth of topics outlined in IPEC-PQG's GMP's, this project will focus on only a handful of GMP requirements. Specifically, excipient GMP training, management commitment, annual product review, and significant change notification will be explored. Recommendations for maintaining compliance in these areas will be shared with Company XYZ.

Excipient GMP's at Company XYZ

Background

Company XYZ refines crude glycerin and has grown to be the largest glycerin refinery in the world. Over the years, the site has built a solid pharmaceutical and food customer base. Serving customers of this nature requires a higher level of standards than those typically applied for industrial customers. Because refined glycerin is purchased for use in food and pharmaceutical applications, it meets the definition of an excipient. Again, excipients are often used as supplements with API's to produce finished drug products. As an excipient, refined glycerin must demonstrate compliance with excipient GMP's. Company XYZ must understand what is necessary to fully comply with regulations for pharmaceutical excipients so it can remain competitive in the glycerin industry. In order to do this, a solid understanding of the excipient GMP's is a must. The plant must also be able to demonstrate compliance to customers when requested via documentation, audits, and other visits. As a starting point, recommendations will be given to the site for four key areas – excipient GMP training, management commitment, annual product review, and significant change notification.

Beginning of Excipient GMP Compliance

The first step for Company XYZ is to clearly define the point at which GMP compliance begins in the glycerin refining process. From this point forward, GMP's outlined in IPEC's *The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients* are expected to be followed. It's not always obvious where to define the starting point for GMP's – it varies with manufacturing processes. According to

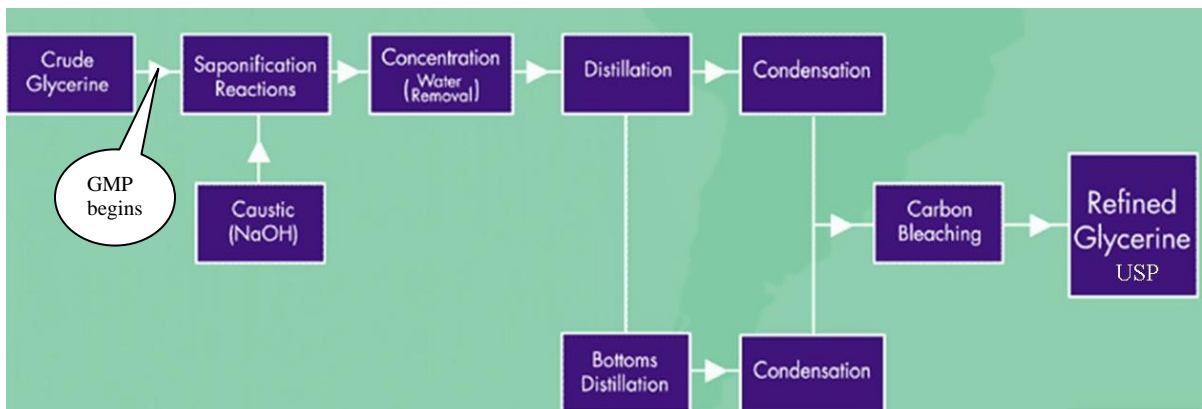
USP’s “<1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients,” “To determine the processing step at which these manufacturing practices should be implemented, good judgment and a thorough knowledge of the process are required.”

Excipient manufacturers must review their processes and the transformation points that are involved. To determine which processing step GMP’s should be implemented, a detailed process flow diagram should be referenced and methods such as HACCP (Hazard Analysis and Critical Control Point) or FMEA (Failure Mode and Effects Analysis) may be used to help identify critical process points. (IPEC-PQG 2006, 3).

Excipient manufacturers must review their processes and the transformation points that are involved. To determine which processing step GMP’s should be implemented, a detailed process flow diagram should be referenced and methods such as HACCP (Hazard Analysis and Critical Control Point) or FMEA (Failure Mode and Effects Analysis) may be used to help identify critical process points. (IPEC-PQG 2006, 3).

For XYZ’s glycerin refining process (see Figure 1), the starting point of GMP compliance should be the point at which crude glycerin receipts are combined to create glycerin blends that feed the refinery. There are already supplier qualification systems in place to ensure crude glycerin receipts meet standards required by XYZ. After the crude shipments are received, the next step is to blend them together. Since this is the first processing step, it is suggested as the beginning of excipient grade GMP’s.

Figure 1: Overview of the Glycerin Refining Process.



GMP Training for Company XYZ

IPEC-PQG GMP training must be developed and conducted at Company XYZ. All site employees must understand that glycerin is an excipient and should comply with IPEC-PQG's GMP guidelines. They also need a basic understanding of the GMP's. Site QA resources will of course be expected to develop more in-depth knowledge of excipient requirements and will coach other site employees as needed. A suggested excipient GMP overview training is in Appendix A. This training should be deployed to XYZ's entire organization. It is only the start of improving excipient GMP understanding. Further excipient GMP training topics should be prioritized and rolled out to the organization to continue building their knowledge base. The more employees know and understand, the better equipped they will be to identify and support business needs. By understanding the criticality of their work, employees will be able to increase their contribution to quality management systems. This will better position Company XYZ as the leading supplier of excipient grade glycerin.

Management's Commitment

Company XYZ also needs to highlight management's commitment to GMP's. Not only should management support site GMP training, but management also needs to clearly define the site's quality policy and objectives. Management should be leading the efforts to improve quality systems that support excipient GMP compliance, so it's important for employees to see its commitment to quality and customers. The quality policy will set the tone for the organization. It should be a brief summary of the goals involved in improving the quality management systems and increasing employee

awareness. Perhaps even more importantly, the policy should be something employees can relate to. It will be difficult for employees to work towards quality improvement if they aren't able to see the connection between their work and product quality. The connection must be obvious between actions occurring during the manufacturing process, excipient GMP compliance, and customers' confidence in glycerin. In order for a quality program to really succeed, every employee must feel the responsibility of his/her actions.

Along with establishing the quality policy, management should help define measurable quality objectives for the site. Historically, Company XYZ has tracked quality measures on a site scorecard and reviewed these results with leadership during monthly and quarterly reviews. To further clarify/improve GMP compliance, it would be to the site's benefit to differentiate between compliance measures and internal improvement measures. Some measures must be met to ensure GMP compliance is maintained, while other measures are simply stricter targets the site chooses to impose on itself as it works towards continual improvement. GMP compliance is not affected if the site falls short of meeting the improvement targets.

After assessing existing quality measures for Company XYZ, a recommendation was made to revise the site scorecard to clarify which measures demonstrate compliance. The following items were proposed to track compliance:

- Quality incidents - off-quality material shipped to customers
- Centerlines critical to product quality
- Validations completed versus validation masterplan
- QA critical corrective actions completed on time
- Internal quality audits completed
- Customer complaints received
- Cost of off-quality rework

The site will continue to track progress against internal improvement goals. Such goals do not affect compliance; rather, they keep the site focused on continual improvement.

Examples of improvement goals include:

- Quality near misses (items caught before escalating to incidents)
- Quality incidents – off-quality internal (product not shipped to customers)
- Centerlines not critical to product quality
- QA minor/improvement corrective actions completed on time
- Internal quality audits completed on time

Annual Product Review

According to IPEC-PQG's GMP's, excipient manufacturers should review key quality measures periodically to assess the need for improvements (IPEC-PPQG 2006, 26). This assessment should include measures such as quality incidents, customer complaints, process failures, and product nonconformities. Although no time period is defined in the GMP's, it is suggested that the review be completed annually.

XYZ's glycerin refinery already reviews quality measures on the site scorecard monthly and quarterly with site leadership. To further assess potential gaps and improvements needed, the glycerin refinery should also complete an annual product review. This review would give the site the opportunity to see trends that have developed throughout the year. Measures not currently discussed on a monthly basis could also be included to better understand process capability. Corrective actions can then be identified to bring measures trending outside of desired limits back into control.

The recommendation is to complete and document this product review in early July, after the fiscal year has ended. The data will be pulled together by the site QA manager, department QA resources, and department process engineers. The following measures should to be trended and summarized in the report:

- Quality incidents - off-quality material shipped to customers
- Centerlines critical to product quality
- Validations completed versus validation masterplan
- QA critical corrective actions completed on time
- Internal quality audits completed
- Customer complaints received
- Cost of off-quality rework
- Quality near misses (items caught before escalating to incidents)
- Quality incidents – off-quality internal (product not shipped to customers)
- Centerlines not critical to product quality
- QA minor/improvement corrective actions completed on time
- Internal quality audits completed on time
- Deviations from process centerlines/targets
- Process failures
- Equipment breakdowns
- Calibrations completed
- Product nonconformities
- Customer audit feedback
- Production history

Any trends seen in the data, as well as outages for the year, should be addressed.

Findings and recommendations should be documented. First, any measures not currently meeting the defined limits must be addressed immediately. Corrective actions should be identified by site QA and department resources and implemented within 30 days. The site QA manager will track progress towards corrective actions. At the end of those 30 days, the measures need to be reviewed to determine the effectiveness of the corrective actions. Second, measures trending towards the limits will be addressed next. Corrective and preventive actions must be identified and implemented for these measures within 90 days. Again, the site QA manager will track progress against these actions on the site QA action plan. A draft SOP has been created for Company XYZ and is in Appendix B. It outlines the suggested procedure the site should follow for annual product review. It is recommended that the site review this SOP with employees and implement the annual product review beginning with the fiscal year July 2007 – June 2008.

Definition of Significant Change

The IPEC-Americas *Significant Change Guide for Bulk Pharmaceutical Excipients* can be used to coach manufacturers of excipients in the development and execution of significant change notification procedures. This guide was developed by representatives of several companies that participate on the International Pharmaceutical Excipients Council of the Americas. It attempts to define significant change, provide guidance on evaluating the impact of the change, explain types of changes, and outline reporting requirements. Because of the thoroughness of the guide, it was a logical reference for Company XYZ. The guide will assist the plant as it develops and maintains robust significant change procedures and communicates those procedures to its glycerin customers.

It's important for plant employees to understand exactly what a significant change is. According to IPEC-Americas, "any change by the manufacturer of an excipient that alters an excipient physical or chemical property outside the limits of normal variability, or that is likely to alter the excipient performance in the dosage form is considered significant" (IPEC-Americas 2005, 2). Changes can be categorized into the following types (IPEC-Americas 2005, 8):

- Site
 - Change to manufacturing site or Quality Control lab
- Scale
 - Scale up from pilot to production, optimize to increase capacity
- Equipment

- Replacement in kind versus new
- Change to equipment included in the process validation
- Manufacturing Process
 - Change to processing instructions (i.e. centerline conditions), raw materials, sequence of operating steps, and the operation to be performed (i.e. processing steps)
- Packaging and Labeling
 - Any change to packaging components
 - Any change to labeling content (i.e. site of manufacture or testing, biological origin, additives, or storage and handling conditions)
- Specification
 - Changes to raw material, Quality Control , or finished product specifications

If there is any doubt as to whether or not the change meets the definition of significant, IPEC-Americas recommends leaning towards the conservative side and notifying pharmaceutical customers. In some cases, regulatory agencies may require notification as well. When evaluating changes and their impacts to excipient quality, manufacturers must consider the point at which full GMP compliance begins. From this point forward in the process, the excipient manufacturer is really obligated to evaluate the impact of changes in order to maintain GMP compliance.

Significant Change Criteria

The basis of a robust significant change program is the set of objective criteria to be used when evaluating changes. IPEC-Americas provides an outline of criteria that are likely to affect the excipient's performance (IPEC-Americas 2005, 3). If the manufacturer answers "yes" to the following questions provided by IPEC-Americas, then the manufacturer should further investigate the change to determine its significance:

1. Has there been a change in the chemical properties of the excipient as a result of the change?
 - At a minimum, include all monograph and manufacturer specification parameters. Is there a statistically significant difference between pre-change and post-change test results?
2. Has there been a change in the physical properties of the excipient as a result of the change?
 - Will a mutually agreed upon specification be altered (i.e. particle shape, surface area, pH or viscosity)?
3. Has there been a change in the impurity profile for the excipient as a result of the change?
 - An impurity profile contains identified organic impurities, unidentified organic impurities at or above 0.1% whether specified or not, residual solvents, and inorganic impurities.
 - Not all excipient manufacturers have impurity profiles because impurities can sometimes be difficult to quantify in excipients (IPEC-Americas 2005, 4).

- Compare the impurity profiles of the pre-change and post-change products. Has a new impurity been introduced at 0.1% concentration?
Has an impurity previously present at or above 0.1% disappeared?
 - Were there changes in the residual solvents level?
4. Has there been a change in the functionality of the excipient as a result of the change?
- IPEC is not able to provide objective criteria for evaluating functionality because it varies with the type of excipient, its application, and the manufacturer's capability (IPEC-Americas 2005, 5). If the manufacturer believes the functionality may be affected, it should notify customers.
5. Where applicable, has the moisture level changed?
- Has the moisture level changed beyond the range of production?
6. Where applicable, has the bioburden changed?
- Has the control of microorganisms in the excipient been affected?
7. Has there been a change in the origin of any raw materials or contact packaging?
- A change in origin can cause a change in the first six criteria. Has the country of origin, geological origin, or species of origin for the raw material changed?

Even when using the above criteria, it may not always be obvious whether or not a change is significant to excipient quality. IPEC-Americas understands this and recommends manufacturers use the following classification of change risk levels (IPEC-Americas 2005, 6):

- Level 1, Minor Change

- Minor changes unlikely to affect excipient chemical or physical properties, impurity profile, or functionality. Customer notification is not required, but the change should be documented.
- Level 2, Might be Significant
 - Changes may be significant to excipient quality and should be evaluated against criteria 1, 2, and 3 above to determine potential impact. Changes to biological origin of raw material need to be considered (may impact TSE or GMO). Such changes do not require notification or approval from the customer; however, IPEC-Americas strongly suggests notifying customers.
- Level 3, Always Significant
 - Changes are almost always significant. If the manufacturer determines excipient functionality will be impacted, then it must notify customers of the change and receive their approval prior to shipping the changed product. It may require up to 6-12 months to receive a customer's approval if stability data is required to be updated.

IPEC-Americas even provides a Decision Tree, which can help manufacturers classify changes into level 1, 2, or 3 (see Appendix C).

Significant Change Notification Procedures

Company XYZ's glycerin refinery should verify it has a robust significant change process. It needs a SOP (Standard Operating Procedure) for significant changes. The SOP should explain where GMP compliance and significant change evaluation begins,

what criteria are expected to be referenced when evaluating changes, who will be responsible for evaluating changes, and how customers will be notified. The site's employees should then be trained on the significant change SOP.

As defined earlier, GMP compliance for XYZ's glycerin refinery will begin at the point at which receipts of crude glycerin are combined to make a crude blend. From the blend tank forward, GMP compliance is expected and any changes must be documented and evaluated to determine if they require customer and/or regulatory agency notification. The site's existing change request process will be used to identify and evaluate significant changes. There are weekly change control meetings, during which site area experts meet to discuss change requests brought by other employees. There are experts for areas such as environmental, quality, safety, etc. Any time a change will affect one of these areas, the area expert must provide approval before the change can be executed. Approval may not be granted the first time a change is brought to the change control meeting. It may be necessary for employees to follow up on questions and to return to a future meeting.

The site quality assurance manager already participates in the site change control meetings. Company XYZ can easily incorporate significant change procedures into this process by modifying the "quality" section of the existing change control form so that it includes the criteria IPEC-Americas recommends using to determine if changes are significant. Currently, the form has a checklist with questions pertaining to quality. The person requesting the change is expected to complete the checklist, and then the checklist is reviewed by the site QA manager for concurrence. To better meet the guidelines for significant change, this checklist could be modified so that it consists of three sections.

The first section should still be completed by the change request owner. The owner would provide preliminary information about how the change could affect existing quality systems. The second section would then be completed by the site QA manager. Since the QA manager has a more in-depth knowledge of quality systems and GMP requirements, she is better equipped to determine which quality systems may require follow up. Finally, the third section will address significant change identification and notification. Several XYZ technical resources will need to pool their expertise together to properly evaluate the change request against IPEC-Americas' significant change criteria. The suggested resources for this section are site QA, regional QA, analytical, R&D, and regulatory resources. If this group decides the change is in fact significant, it must also identify which customers and regulatory bodies should be notified. The site QA manager will then draft a letter communicating the change. Regional QA and regulatory will review and approve the letter before a final copy is sent. A draft significant change SOP and modified QA section for the change control form can be found in the Appendix D and E respectively.

Recommendations

An excipient is not the same as an active drug; therefore, it does not necessarily require the same level of regulations. Because excipients were not clearly regulated in the past, some auditors work under the impression that excipients must meet the extensive regulations finished drug products are expected to. Customers may try to impose these regulations on their excipient manufacturers, so it's important for excipient manufacturers to understand what really is required of them. Organizations such as IPEC and IPEA offer workshops to help educate both the manufacturers and customers on excipient GMP audits. IPEA is an independent subsidiary of IPEC-Americas and it was founded in 2000 to audit facilities who manufacture pharmaceutical excipients to ensure they are meeting USP's "<1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients" and *The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients*. IPEA even shares a comparison of GMP requirements for API's versus excipients to help educate the industry.

Company XYZ should continue to develop knowledge of GMP's for excipient manufacturers. It should also evaluate its compliance, or how well the site is meeting these GMP requirements. This can be done through third party audits or thorough internal audits.

FDA and USP Compliance are now critical for manufacturers of excipients because of changes implemented with the Bioterrorism Act. Excipient suppliers must learn and abide by the FDA's regulations in order to remain competitive in pharmaceutical and food industries. Navigating such regulations is not an easy task, especially since guidance documents for excipient suppliers are relatively new. An in-depth

understanding of excipient GMP's is necessary for Company XYZ to maintain strong relationships with its customers and to become the undisputed supplier of refined glycerin.

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- United States Pharmacopeia. "<1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients."

Appendix

- A. Excipient GMP Overview Training
- B. Annual Product Review SOP
- C. IPEC-Americas Decision Tree
- D. Significant Change Notification SOP
- E. Quality/GMP section of Change Control Form

A. Excipient GMP Overview Training



Excipient GMP
Overview Training.pp

B. Annual Product Review SOP

TITLE	Annual Product Review		
DOC #		REVISION #	PAGE # of #

1. PURPOSE and SCOPE

Purpose: This procedure outlines expectations for the annual product review, which will include a review of key measures that impact quality and will be used to assess the need for additional improvements.

Scope: This process applies to Company XYZ's glycerin refinery and related systems and facilities.

2. REFERENCES

- 2.1 *The International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) Significant Change Guide for Bulk Pharmaceutical Excipients*
- 2.2 *The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2006*
- 2.3 *<1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients*
- 2.4 Management Review SOP
- 2.5 Quality Review SOP
- 2.6 Quality Records SOP

3. ROLES and RESPONSIBILITIES

- 3.1 Site Quality Assurance Manager is responsible for compiling and summarizing data, identifying areas needing improvement, and leading departments in their work to identify appropriate corrective actions.
- 3.2 Department Quality Assurance resources are responsible for compiling and summarizing data and coaching departments in their work to identify appropriate corrective actions.
- 3.3 Department process engineers (PE's) are responsible for compiling and summarizing data and for helping to identify appropriate corrective actions.

4. PROCEDURES

See the following page(s).

5. ATTACHMENTS and DEFINITIONS

- 5.1 n/a

6. REASON FOR CHANGE

Revision #	Date	Change

TITLE	Annual Product Review		
DOC #		REVISION #	PAGE # of #

7. APPROVALS

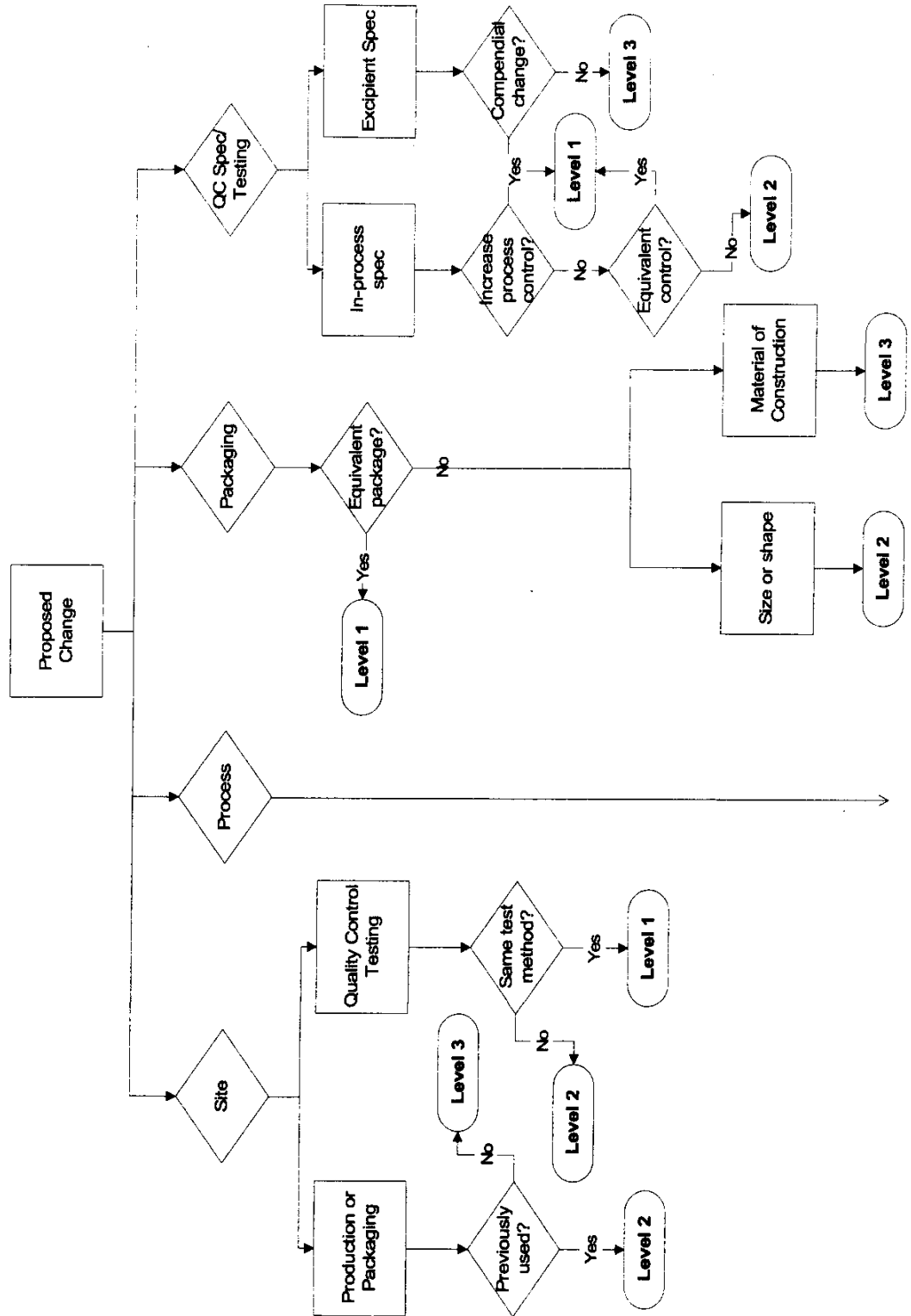
Process Owner		Date	
QA Approver		Date	
Site Approver		Date	

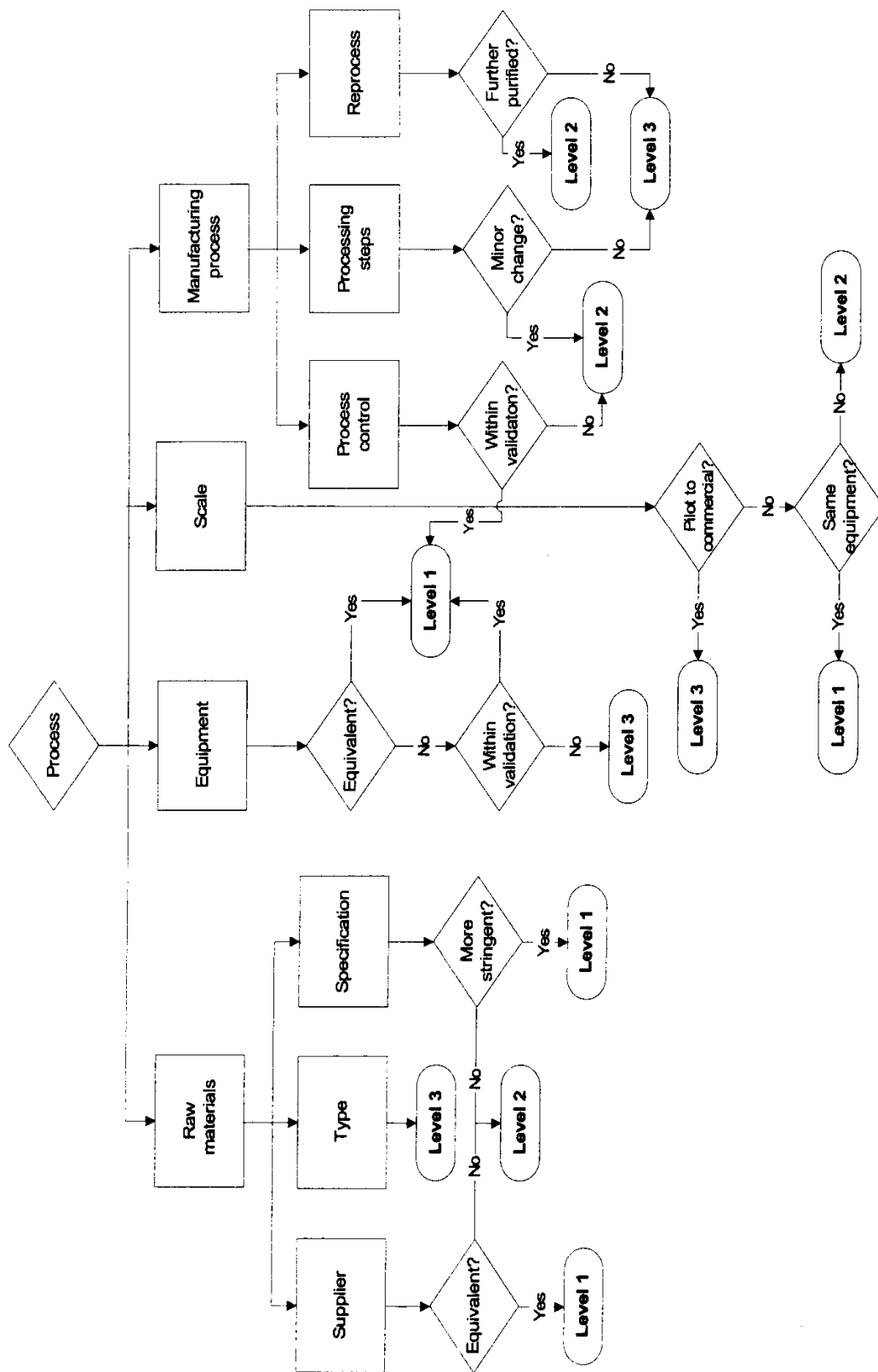
TITLE	Annual Product Review		
DOC #		REVISION #	PAGE # of #

4. PROCEDURES

- 4.1 This procedure outlines the annual product review process as it applies to Company XYZ's refined glycerin.
- 4.2 The annual product review will be completed at the end of the fiscal year, in July. Data will be collected and summarized for the previous July through June.
- 4.3 The site QA manager, QA department resources, and department PE's will compile data for the measures they are responsible for. Each measure will be trended and summarized for the year.
- 4.4 The following measures should to be trended and summarized in the report: QA capability, SQL's, quality incidents - off-quality material shipped to customers, primary Q-factors, validations completed versus masterplan, QA critical follow ups completed on time, SIP (internal) audits completed, customer complaints received, cost of off-quality rework. off-quality internal (product not shipped to customers), secondary Q-factors, QA minor/improvement follow ups completed on time, SIP, process centerline data, deviations from centerlines, process failures, breakdowns, calibrations completed, product nonconformities, and customer audit feedback. Production history should also be reviewed.
- 4.5 Any measures showing changes or gaps for the year will be identified.
- 4.6 For the measures with data outside of their defined targets, corrective actions must be identified and implemented within 30 days. The site QA manager will lead the effort to identify corrective actions and will require the assistance of the department QA resources and department PE's.
- 4.7 All corrective actions will be added to the site QA action plan and tracked by the site QA manager. Owners for each action must provide updates to the site QA manager.
- 4.8 At the end of 30 days, the measure must be reevaluated to determine whether or not improvement was seen.
- 4.9 For measures trending towards limits (but currently meeting limits), the site QA manager will lead the effort to identify corrective and preventive actions to prevent these measures from exceeding limits. These actions must be identified and implemented within 90 days.
- 4.10 Again, all corrective actions will be added to the site QA action plan and tracked by the site QA manager. Owners for each action must provide updates to the site QA manager.

C. IPEC-Americas Decision Tree





D. Significant Change Notification SOP

TITLE	Significant Change Process		
DOC #		REVISION #	PAGE # of #

1. PURPOSE and SCOPE

Purpose: The significant change process is intended to outline procedures for evaluating the impact changes will have on QA/GMP, identifying significant changes, and communicating significant changes to customers and regulatory agencies.

Scope: This process will be followed for all changes that apply to Company XYZ’s glycerin refinery and related systems and facilities. This includes changes managed by other XYZ divisions and contractors.

2. REFERENCES

- 2.7 *The International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) Significant Change Guide for Bulk Pharmaceutical Excipients*
- 2.8 *The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2006*
- 2.9 *<1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients*
- 2.10 Documentation System Description SOP
- 2.11 Quality Records SOP
- 2.12 Change Control Process SOP
- 2.13 Change Request Form (found on the XYZ Homepage)

3. ROLES and RESPONSIBILITIES

- 3.4 Change Originator is responsible for completing the change control form and introducing the change in the site’s weekly change control meeting.
- 3.5 Site Quality Assurance Manager is responsible for evaluating change requests against quality/GMP requirements and significant change criteria.
- 3.6 Regional Quality Assurance is responsible for evaluating change requests against significant change criteria.
- 3.7 Analytical is responsible for evaluating change requests against significant change criteria.
- 3.8 R&D is responsible for evaluating change requests against significant change criteria.
- 3.9 Regulatory is responsible for evaluating change requests against significant change criteria.

4. PROCEDURES

See the following page(s).

5. ATTACHMENTS and DEFINITIONS

- 5.1 Quality/GMP section of the Change Control Form
- 5.2 IPEC-Americas Decision Tree

6. REASON FOR CHANGE

Revision #	Date	Change

TITLE	Significant Change Process		
DOC #		REVISION #	PAGE # of #

7. APPROVALS

Process Owner		Date	
QA Approver		Date	
Site Approver		Date	

TITLE	Significant Change Process		
DOC #		REVISION #	PAGE # of #

4. PROCEDURES

- 4.1 This procedure outlines the significant change process as it applies to the Company XYZ's refined glycerin. It is to be followed in accordance with the site's change control process.
- 4.2 All change requests and evaluations of changes will be documented and archived for defined retention periods for refined glycerin.
- 4.3 The change originator completes the site's change request form and brings the request to the site change control meeting, held every Wednesday at 2pm. The request will be reviewed by the change control team, which consists of qualified members from site QA, Health and Safety, Facilities Management, Power and Controls, and Storeroom.
- 4.4 The following types of changes must be evaluated at change control:
 - 4.4.1 Site
 - 4.4.2 Scale
 - 4.4.3 Equipment
 - 4.4.4 Process
 - 4.4.5 Packaging and Labeling
 - 4.4.6 Specification (including raw materials)
- 4.5 When evaluating the impact of changes in the Glycerin Department, the point at which full GMP compliance begins is defined as the crude glycerin blend tank. From the blend tank forward, full GMP compliance is required. Any changes made from the blend tank forward must be evaluated against the significant change criteria to determine if customer notification is required.
- 4.6 The change request owner will begin the evaluation of the change by answering the questions in section 1 of the Quality/GMP portion of the change control form.
- 4.7 The site change control team will review the change request. The team will discuss the change and either provide approval by signing the change request form, decline the change request, or request follow up.
- 4.8 Site QA will answer the questions in section 2 of the Quality/GMP portion of the change control form.
- 4.9 If directed by section 2, site QA, regional QA, analytical, R&D, and regulatory will review section 3 to determine whether or not the change requires significant change notification and which customers will be affected. IPEC-Americas Decision Tree can be used as a guide when classifying types of changes.
- 4.10 All changes determined to be significant require customer notification. If required, regulatory authorities will be notified as well.
- 4.11 If notification is required, the site QA manager will draft a letter explaining the change to the customer and/or agency. The regional QA and regulatory resources will review and approve the letter before a final copy is sent to the customer and/or agency.
- 4.12 Customers must be given appropriate advance notification of changes. Reminder: some customers may require up to 6-12 months to collect stability data prior to approving Level 3 changes and accepting refined glycerin made after the change.
- 4.13 Documentation of the customer and/or regulatory agency notification will be filed by site QA and archived according to the Quality Records SOP.

E. Quality/GMP Section of Change Control Form

<input checked="" type="checkbox"/>	Quality Assurance / GMP	No	Yes
1	Change Owner - If you answer yes to any of the following questions, include the QA Manager on the review and approval routing checklist.		
	Will the process operate outside the parameters listed as critical to product quality in the Manufacturing Standards?	<input type="checkbox"/>	<input type="checkbox"/>
	Will the process operate outside validated ranges?	<input type="checkbox"/>	<input type="checkbox"/>
	Is there a change in the production site of the finished product?	<input type="checkbox"/>	<input type="checkbox"/>
	Is there a change in the size or material of construction of any packages (totes, drums) used to ship the finished product?	<input type="checkbox"/>	<input type="checkbox"/>
	Are there any new ingredients or raw materials? Are there changes to existing ingredients or raw materials?	<input type="checkbox"/>	<input type="checkbox"/>
	Will any new chemicals be introduced at any step of the process (from raw material receipt to finished product loadout)?	<input type="checkbox"/>	<input type="checkbox"/>
	Will there be a new supplier or a change to an existing supplier's manufacturing location, process, or material specifications?	<input type="checkbox"/>	<input type="checkbox"/>
	Are there any changes to current analytical methods for raw materials, in-processing testing, or finished product?	<input type="checkbox"/>	<input type="checkbox"/>
	Are there any changes to existing raw material, in-process, or finished product specifications?	<input type="checkbox"/>	<input type="checkbox"/>
	Is there a change to the order of addition of materials during processing?	<input type="checkbox"/>	<input type="checkbox"/>
	Is there a change of equipment that is not a replacement in kind or is different than its original validation description?	<input type="checkbox"/>	<input type="checkbox"/>
	Is there a change to current reprocessing procedures?	<input type="checkbox"/>	<input type="checkbox"/>
	Is there a change to current cleaning procedures?	<input type="checkbox"/>	<input type="checkbox"/>
	Is there a change to current brand changeover procedures?	<input type="checkbox"/>	<input type="checkbox"/>
	Will finished product storage conditions be affected?	<input type="checkbox"/>	<input type="checkbox"/>
	Will any support systems (HVAC, steam, water, etc.) be changed?	<input type="checkbox"/>	<input type="checkbox"/>
2	Site QA – Answer the following questions to determine impact of change.		
	Are any technical standards affected (manufacturing standards, formula cards, RMS's, and analytical methods)?	<input type="checkbox"/>	<input type="checkbox"/>
	Does the change require confirmatory stability testing?	<input type="checkbox"/>	<input type="checkbox"/>
	Does the change impact any product registrations with external regulatory authorities?	<input type="checkbox"/>	<input type="checkbox"/>
	Is a validation/re-validation protocol required?	<input type="checkbox"/>	<input type="checkbox"/>
	Are any quality control or quality assurance procedures affected by the change?	<input type="checkbox"/>	<input type="checkbox"/>
	Are there any special product protection systems needed to protect other products while the change is being made?	<input type="checkbox"/>	<input type="checkbox"/>
	Does the change affect the site's compliance with <i>The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients</i> (are any GMP requirements affected)?		
	What level is this change classified as? Could notification of a customer or regulatory agency be required as per <i>The IPEC-Americas Significant Change guide for Bulk Pharmaceutical Excipients</i> ? If yes, answer the questions in section 3.	<input type="checkbox"/>	<input type="checkbox"/>
	Could the status of finished product be affected (i.e. Kosher for Passover)?	<input type="checkbox"/>	<input type="checkbox"/>

<input type="checkbox"/>	Significant Change Evaluation Criteria (IPEC-Americas Significant Change Guide 2005)	No	Yes
3	The following questions should be discussed and answered by Site QA, Regional QA, Analytical, MPO/R&D, and PS&RA.		
	1. Will there be a change in the chemical properties of the excipient as a result of the change?	<input type="checkbox"/>	<input type="checkbox"/>
	- Will there be a statistically significant difference between pre-change and post-change test results for monograph and manufacturer specification parameters?	<input type="checkbox"/>	<input type="checkbox"/>
	2. Will there be a change in the physical properties of the excipient as a result of the change?	<input type="checkbox"/>	<input type="checkbox"/>
	- Will a mutually agreed upon specification between the manufacturer and customer be altered (i.e. density, particle shape, surface area, pH or viscosity)?	<input type="checkbox"/>	<input type="checkbox"/>
	3. Will there be a change in the impurity profile for the excipient as a result of the change?	<input type="checkbox"/>	<input type="checkbox"/>
	- Compare the impurity profiles of the pre-change and post-change products. Has a new impurity been introduced at 0.1% concentration? Has an impurity previously present at or above 0.1% disappeared?	<input type="checkbox"/>	<input type="checkbox"/>
	- Were there changes in the residual solvents level?	<input type="checkbox"/>	<input type="checkbox"/>
	4. Will there be a change in the functionality of the excipient as a result of the change?	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>
	5. Where applicable, will the moisture level change?	<input type="checkbox"/>	<input type="checkbox"/>
	- Has the moisture level changed beyond the range of production?	<input type="checkbox"/>	<input type="checkbox"/>
	6. Where applicable, will the bioburden change?	<input type="checkbox"/>	<input type="checkbox"/>
	- Has the control of microorganisms in the excipient been affected?	<input type="checkbox"/>	<input type="checkbox"/>
	7. Will there be a change in the origin of any raw materials or contact packaging?	<input type="checkbox"/>	<input type="checkbox"/>
	- A change in origin can cause a change in the first six criteria. Has the country of origin, geological origin, or species of origin for the raw material changed?	<input type="checkbox"/>	<input type="checkbox"/>
	Is notification of a customer or regulatory agency required as per <i>The IPEC-Americas Significant Change guide for Bulk Pharmaceutical Excipients</i> ? What level change is this classified as?	<input type="checkbox"/>	<input type="checkbox"/>