5.3 Good Manufacturing Practices and Product Safety

Material Topic

Throughout the value chain, from R&D and clinical trials to commercial production and distribution for patient use after launch, PharmaEssentia adheres to standardized operating procedures, quality management systems, and product traceability systems. We examine potential factors that may affect the stable supply of medication to patients and seek solutions to ensure safe, stable and timely delivery of our products in order to meet the needs of patients.

Early Stage	Medium Stage	Late Stage
Demand Integration and Planning	**High-Quality Production**	**Safe Product Transportation**
Periodic cross-functional meetings to integrate clinical and commercial demands and establish safety stock and second source.	Approved and inspected to comply with GMP certifications from the US FDA, EU EMA, Taiwan TFDA, etc., and strictly supervised by the quality control unit to ensure quality, safety, and product release standards.	The warehouse management unit arranges the shipment operation according to the shipment instructions, coordinating and arranging transportation operations in compliance with the temperature requirements of the drugs and GDP regulations.

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Management Policy

Internal Policies

- Developed more than 20 quality Management Policy that comply with international standards such as those in Europe and the United States
  - Examples of these policies include Quality Management Policy, Raw Material Management Policy, Production and Process Control Policy, Validation Policy, and Complaints and Recalls Policy
- Regarding pharmacovigilance
  - Pharmacovigilance Policy
  - Post-Marketing Adverse Event Reporting Standard Operating Procedures
  - Product Quality Complaint Reporting Standard Operating Procedures
  - Global Post-Marketing Safety Data Collection Standard Operating Procedures
  - Global Product Safety and Risk Management Mechanism Standard Operating Procedures

External Guidelines

- Regulations issued by local regulatory authorities in various countries, such as European Pharmacopoeia, US Pharmacopeia, and guidelines issued by the US FDA
- "Medical Law," "Pharmaceutical Affairs Law," "Pharmaceutical Affairs Law Enforcement Regulations," "Pharmaceutical Good Manufacturing Practice Regulations," "Drug Safety Surveillance Regulations," and "Serious Adverse Drug Reaction Reporting Regulations"

Management Commitment

We are committed to following the relevant regulations of the regulatory authorities in various countries for quality management at each stage, complying with the local standards for drug application and strictly controlling the packing process and transportation. We will carefully track adverse drug events and reporting channels, instill the concept of "quality first, keep patients safe" in our daily operations and the minds of every employee, and implement drug risk management to ensure the safety of the medication we produce.

Accountable Units

- The Product Safety & Risk Management (PSRM) Team composed of pharmacovigilance personnel from PharmaEssentia Headquarters and subsidiary companies in various countries, as well as pharmacovigilance quality assurance personnel
- The quality assurance department and quality control department of the Headquarters are responsible for the quality of marketed drugs and clinical drugs, and cooperate with the clinical trial quality assurance and Pharmacovigilance Taskforce
- ECCS - Product Quality and Patient Safety Taskforce
- The Product Safety & Risk Management (PSRM) team composed of pharmacovigilance personnel from PharmaEssentia Headquarters and subsidiary companies in various countries, as well as personnel responsible for pharmacovigilance and quality assurance
- The Quality Assurance department and Quality Control department at PharmaEssentia Headquarters are responsible for the quality of marketed drugs and clinical drugs, and collaborate with the teams responsible for clinical trial quality assurance and pharmacovigilance
- ECCS - Product Quality and Patient Safety Taskforce

Input Resource

- Invested more than NT$15 million in global pharmacovigilance
- Hired a Global Vice President of Pharmacovigilance and an Global Executive Director of Pharmacovigilance to oversee the work
- Established an independent pharmacovigilance department at Headquarters of PharmaEssentia, and set up dedicated pharmacovigilance personnel in each subsidiary or office
- Commissioned a pharmacovigilance CRO company to form a project taskforce to manage and maintain the BESREMi® drug safety database, assist in drug safety information collection/processing/exchange, and report to regulatory authorities in each country
- Held 11 education and training sessions for new employees on pharmacovigilance throughout the year
- Regularly confirmed and tracked the notification items and quantities of safety incidents from external research institutions and subsidiaries
- Regularly evaluated drug safety cases, submited periodic safety reports in accordance with regulatory authorities' requirements, and produced quarterly safety reports

Targets

Short-term Targets for 2023

- Update and revise standard operating procedures related to pharmacovigilance in accordance with regulations, and revise quality assurance-related clinical operation SOPs and pharmacovigilance SOPs
- Develop a pharmacovigilance plan in accordance with regulatory requirements
- Achieve a 100% completion rate for new employee's pharmacovigilance training
- Implement all required items of the pharmacovigilance plan in accordance with legal compliance requirements
- Achieve a 100% execution rate for the reporting of drug safety information by PharmaEssentia's Headquarters and subsidiaries within the designated timeframe
- Conduct a demonstration drug safety inspection under the TFDA program
- Continuously retrieve and analyze academic literature on drug safety, continuously perform drug and adverse reaction identification and analysis, and regularly produce safety reports
- Establish independent personnel dedicated to pharmacovigilance quality assurance, develop a pharmacovigilance quality assurance annual plan, and conduct quality assurance activities
- Complete the response procedure to PMDA plant inspections in Japan, pass FDA follow-up plant inspections for raw materials and injection plants, and pass follow-up plant inspections by Taiwan's FDA
- Introduce an electronic equipment management system to optimize the quality management system process

Medium-term Targets for 2024-2026

- Maintain or update the PharmaEssentia's global pharmacovigilance standard operating procedures, and assist subsidiary companies in developing standard operating procedures that comply with local regulations
- Continuously revise and implement the pharmacovigilance plan so as to comply with various legal requirements
- To have the execution rate of drug safety information notification by PharmaEssentia Headquarters and subsidiary companies within the prescribed timeframe reach 100%
- To continuously search global academic literature for information related to the safety of PharmaEssentia products, and to have the execution rate of adverse drug reaction identification and analysis reach 100%
- Expand the PharmaEssentia Headquarters pharmacovigilance department by 1-2 staff members, and continuously provide the pharmacovigilance training to new employees
- Establish the responsibilities and information sharing of quality assurance for PharmaEssentia's subsidiaries/branches in various countries, and hold global meetings on quality

Long-term Targets (2026 and beyond)

- Continuously review, update, or revise pharmacovigilance management regulations and pharmacovigilance standard operating procedures
- Develop and construct a self-managed drug safety database for PharmaEssentia
- Increase the number of employees on the PharmaEssentia Headquarters' pharmacovigilance department, and continuously train new pharmacovigilance personnel so that the department can independently manage the collection, analysis, and notification of drug safety around the world in the future
- Pass the periodic Good Clinical Practice (GCP) and pharmacovigilance audits by regulatory agencies in countries where PharmaEssentia has obtained drug licenses
- Continuously improve the level of drug quality management

Evaluation of Management Policy

Management Evaluation Mechanism

- Post-market safety monitoring: Timely notification according to regulatory requirements of various countries and maintaining normal operation of real-time reporting mechanism
- Regular safety reports: Regular submission of drug development safety reports and periodic safety reports to regulatory authorities in various countries
- Internal auditing: Auditing conducted by the Quality Assurance department or an independent third-party unit commissioned for this purpose
- External inspections: Inspections by international and domestic drug safety regulatory authorities
- Assessment of the operation status of the real-time reporting mechanism
- Assessment of the operation of drug safety reporting hotlines (Taiwan, USA, South Korea, Japan)
- GMP certificate renewal or extension according to plan

2022 Evaluation Results

- Compliance with regulations to report the third PSUR after the launch of BESREMi®
- 100% completion rate of new staff training in pharmacovigilance. No drug safety regulatory authority conducted inspections related to pharmacovigilance in 2022
- The Taichung Plant successfully completed the GMP inspection by the PMDA of Japan
- No occurrence of serious violations of relevant drug quality regulations or health and safety laws and regulations in official inspections conducted by external organizations
- No incidents related to product quality requiring official reporting occurred in 2022; a total of 103 customer complaints were received, with a complaint rate of 0.86%

High-Standard Production Certification

We are committed to providing high-quality pharmaceuticals to patients, and in 2022 we invested over NT$30 million on maintenance, calibration, verification, and new equipment purchases. Considering the physical risks caused by climate change, we also insured our plants to reduce possible property losses and added preventive measures to prevent flooding. Our Taichung Plant is Taiwan's first biologics plant to pass the European Medicines Agency (EMA) audit and receive Good Manufacturing Practice (GMP) certification. Since 2020, we have also obtained GMP certification from Taiwan's TFDA, South Korea's MFDS, and the FDA of the United States. In addition to passing external inspections by the EMA and Japan's PMDA in 2022, we also completed 12 internal audits, during which no serious deficiencies were found, and improvement plans were submitted within the deadlines.

During the 2022 internal quality audit at the Panco Healthcare Logistics Center, only non-critical quality assurance system deviations were identified, and all were properly handled. With these actions, PharmaEssentia vertically integrates its supply chain from production to quality control, filling and shipping, and global market layout in steps to realize its blueprint for international pharmaceutical production certification.

PharmaEssentia's Taichung Biopharmaceutical Plant is the first protein drug plant in Taiwan to pass the European Medicines Agency (EMA) inspection and obtain GMP certification

2022 No major deficiencies were confirmed after a PMDA plant inspection in Japan.

2021 Passed GMP audit by Korea MFDS and FDA plant inspection in the United States and obtained drug licenses

2020 Newly established injection plant obtained TFDA evaluation approval for GMP and "Good Distribution Practice (GDP)" certification in Taiwan

2018 Became the first protein drug manufacturer in Taiwan to pass the EMA audit and obtain GMP certification

2013 GMP certification obtained for the Taichung Biotech Manufacturing Plant

2012 Completion of the construction of the Taichung Biotech Manufacturing Plant

3 Main Facilities of PharmaEssentia

- DS Manufacturing Plant
- PEG Production Factory
- Sterile Agent Filling Plant

Internal Audit

- Conduct at least 1 internal audit per month
- Each department should receive at least 1 internal audit per year
- For any non-conformities found during the audit, corrective and preventive action (CAPA) plans must be submitted and completed within the specified time frame based on the severity level.

External Audit

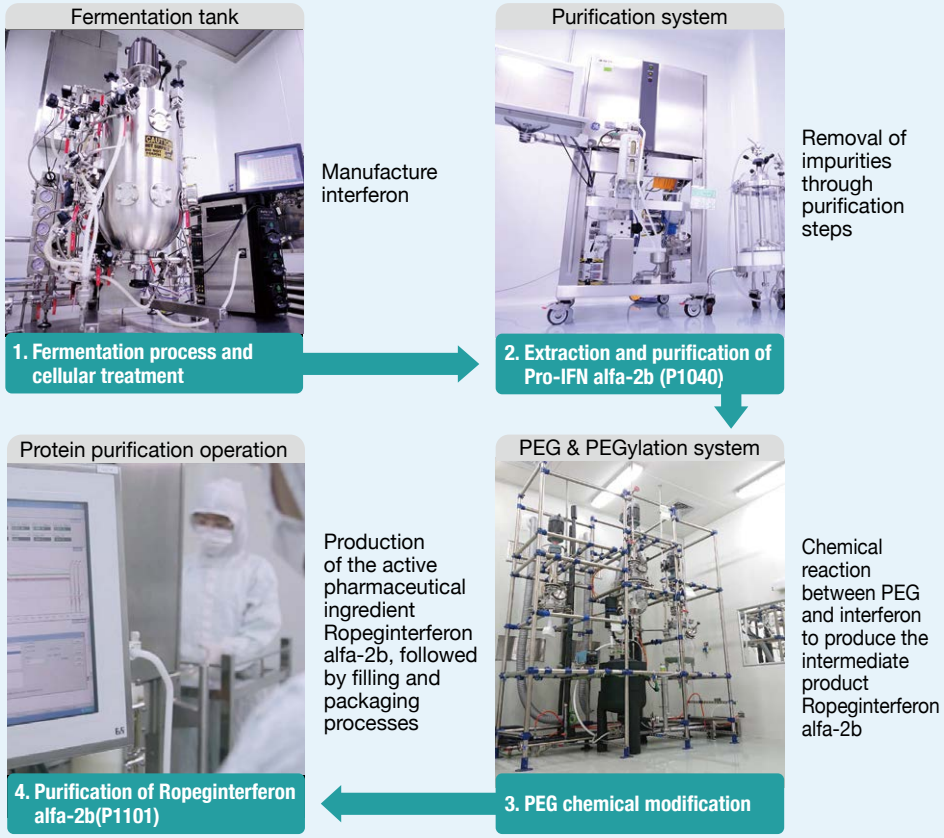
- Receive official GMP inspections every 2 to 3 years
- The first protein Biopharmaceutical factory in Taiwan to obtain GMP certification from the European Medicines Agency (EMA)
- Short, medium, and long-term goals include passing official GMP inspections on a regular basis.

Quality audit/Factory inspection/Verification record passing in 2022

Execution Date	Executing Unit	Process and Key Observation Items	Conclusion
2022/09/19-2022/09/23	European Medicines Agency (EMA)	Routine GMP Inspection for API	GMP certification successfully extended
2022/12/19-2022/12/23	Pharmaceuticals and Medical Devices Agency of Japan (PMDA)	Pre-Approval Inspection for API and Biological medical product (Injection)	No material deficiencies were found
2022/01-2022/12	Internal Audit	12 internal audits were conducted	All audits were completed without any major deficiencies

International Standard Manufacturing Process

Our company's product, Ropeginterferon alfa-2b (P1101), undergoes four main processes in its production. The first step involves the manufacturing of raw materials, followed by the filling and packaging process. Each stage strictly adheres to the Good Manufacturing Practice (GMP) for pharmaceutical products, ensuring quality management and standard operating procedures that meet international standards.



Sterile Filling and Packaging of the Highest Quality

Ropeginterferon alfa-2b (P1101) undergoes four primary processes before it goes through the filling and packaging stage based on market demands. The filling and packaging operations involve compounding, sterile filtration, aseptic filling, labeling, and packaging. Each step is performed with strict standards using aseptic techniques to ensure the highest level of medication safety for patients.

Dispensing and Aseptic Filtration

Dilution and adjustment of high-concentration raw material Ropeginterferon alfa-2b (P1101) and aseptic filtration before filling.

Aseptic Filling

Fully automatic pre-filled syringe filling method. After 100% visual inspection for foreign particles, the filled product will be stored in a high-quality environment throughout the process.

Labeling and Packaging

Labeling of pre-filled syringes according to the label, and placing relevant inserts, plunger rods, push rods, safety needles into the packaging box.

Next Generation Process Optimization

In addition to having high-quality equipment, professional staff, and internal and external audit mechanisms to maintain process and product quality, we also continuously optimize each stage of the process every year. In recent years, we have also enhanced our overall production capacity to meet commercial production demands, reduce production supply chain risks, and ensure stability in supply.

Process Stage

Improving overall production capacity

Improvement Objective

Increase overall production capacity by introducing second and third sources of raw materials to reduce supply chain risks and ensure stability in supply

Results and Benefits

In 2022, five new secondary sources for materials were added, and 3 more are still in testing. Due to the significant changes in the global supply chain caused by the COVID-19 pandemic, implementing this plan can significantly reduce production risks and ensure drug supply

Outsourcing Manufacturing Management

In addition to carrying out filling and packaging operations at our sterile pharmaceutical filling plant in Taichung, our company also outsources filling and packaging operations to internationally-certified contract manufacturers in the United States and Germany. This allows us to supply products to local patients in a timely manner. Our current partners, a US syringe filling contract manufacturer and a German syringe filling contract manufacturer, are both quality partners who have official GMP certification.

Stable and Safe Marketing in the US Market

User manual and packaging printing → Release after completing drug filling, packaging, serialization, quality assurance, and other operating procedures → Transporting products to third-party logistics → Transporting products to specialty pharmacies/ distributors

Process Quality and Safety

135,179 training hours

Conducted a total of 265 GMP/GDP-related training sessions

Our Taichung Manufacturing Plant has a Quality Manual, standard operating procedures for quality-related processes, and over 4,000 plans and reports that detail the organization's operational processes. Our quality assurance and quality control departments are responsible for managing and supervising the processes to maintain product quality, monitor environmental quality, and provide comprehensive personnel training to ensure product safety. We have also established an Emergency Response Management Standard for Plant Facilities to implement emergency response mechanisms. In the event of a natural disaster or equipment malfunction, we can ensure that equipment continues to operate normally and that all personnel perform process operations in a safe environment. In 2022, we conducted a total of 265 GMP/GDP-related training sessions, with a total training time of up to 135,000 hours.

Production Quality Maintenance

We have established the Production and Process Control Procedures and the Prevention of Cross Contamination Management Procedures to regulate process control, monitoring, labeling, and inspection procedures, reducing the risk of cross-contamination.

Environmental Quality Monitoring

We have established standards such as the Environmental Monitoring Plan Standards, the Water System Monitoring Standards, and the Microbial Identification and Statistics Standards to ensure effective monitoring of environmental microorganisms and reduce the risk of product contamination. According to the 2022 report on monitoring of production environment (air conditioning), water systems, compressed air and biological safety cabinets, all systems complied with design requirements and regulatory standards.

Good Manufacturing Practice (GMP) / Good Distribution Practice (GDP) Quality Education and Training

Through continuous annual education and training, we instill the spirit of quality management into daily operations, including training and updating knowledge of GMP regulations for employees. Panco Healthcare also prioritize GDP training for all employees involved in production, distribution and sales, ensuring quality management throughout the supply chain.

2022 GMP/GDP Training Statistics

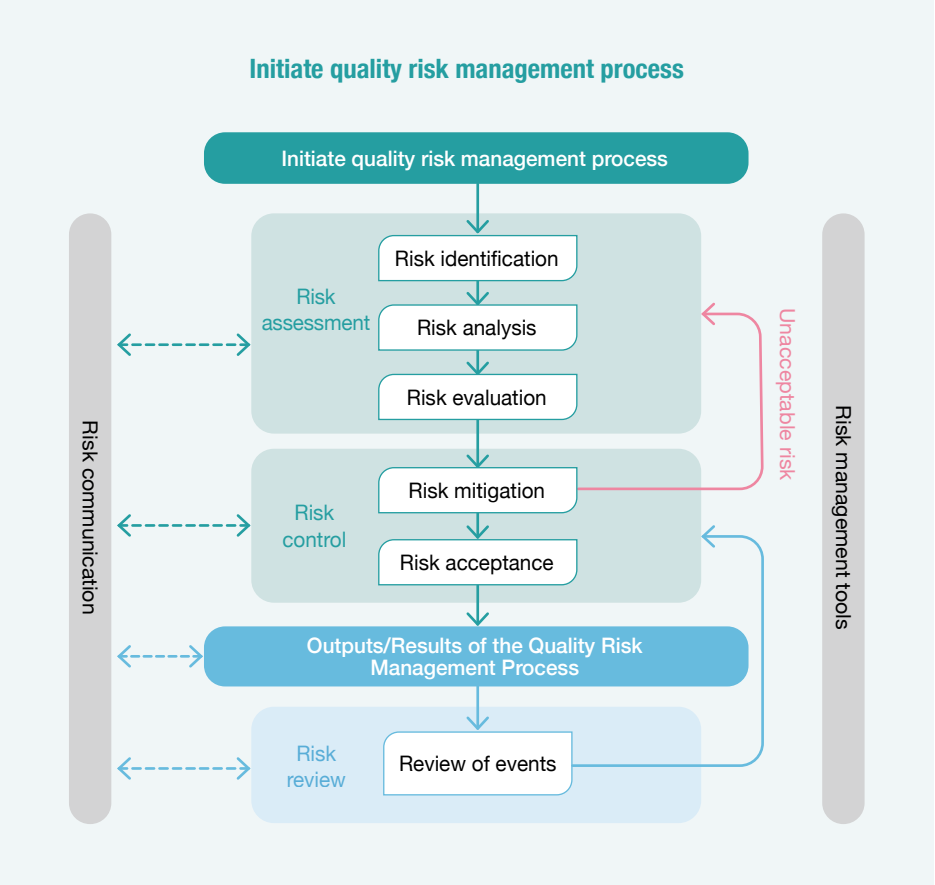
Training Units	Training Topics	Number of Sessions	Total Training (Hours)
PharmaEssentia Taichung Plant	Good Manufacturing Practice (GMP) training	13	12,350.0
	Regulatory, process, or quality-related GMP training for new employees	37	23,828.0
	Corrective and preventive action (CAPA) related training	107	97,851.5
	External training	12	1,008.0
Panco Healthcare Logistics Center	External Training on GMP/GDP Regulations and Processes	6	52.0
	Pre-job Training on GMP/GDP Quality Management System and Related Regulations for New Employees	90	90.0
Total		265	135,179.5

Risk Management for Production Quality

11 meetings

Involving participants from Headquarters and 7 subsidiary companies, with a total of 271 attendees

The Taichung Plant implements risk management to control production processes, environmental control, material supply, and annual quality review. Strict adherence to the Quality Risk Management Procedure Manual, Equipment Risk Assessment Procedure Manual, Change Control Procedure Manual and other regulations reduces hazards to quality to a minimum. In 2022, a total of 11 global cross-departmental risk assessment task force meetings were held with 271 participants to jointly review risk issues within the facilities.



Product Quality Evaluation and Continuous Improvement

Based on the Product Quality Review Procedures, regular internal and external audits are conducted to evaluate product quality and ensure stable production processes and use of materials. Product quality review meetings are held every quarter to address quality issues and implement corrective and preventive actions so as to ensure the stability and uniformity of production processes and product quality.