3-3 Ensuring the Quality and Safety of Drugs

Management Approach of Drug Quality and Safety

Materiality Topic

Throughout PEC's value chain, from R&D, clinical trials, commercial mass production, to patients' use, we use standardized operating procedures, comprehensive quality management and complete product traceability systems, ensuring the safety, effectiveness, and quality of the drugs used by patients.

GRI | 103-2~3 SASB | HC-BP-250a.1~a.5

Policies

Internal Policy

- In terms of quality management, the "Quality Handbook" has been formulated internally along with approximately 20+ relevant policies that comply with international standards, such as the "Quality Management Policy," "Raw Material Management Policy," "Production and In-Process Control Policy," "Quality Assurance Policy", and the "Complaint and Recall Policy" etc.
- Pharmacovigilance Policy
- Standard operating procedures for drug safety, functions, and training
- Standard operating procedures for post-listing safety data collection

External Guidelines

- We comply with regulations formulated by local competent authorities, including the European Pharmacopoeia, United States Pharmacopeia, Guidance from the U.S. FDA, international standards related to GxP, and various laws including the Medical Care Act, Pharmaceutical Affairs Act, Detailed Implementations of the Pharmacist Act, Regulations for Drug Safety Monitoring, and Regulations for Reporting Serious Adverse Reactions of Medicaments.

Commitments

- As we obtain more and more regulatory marketing approvals from various countries, we commit to comply with the relevant regulations from local competent authorities to meet the local standards of sales of medicaments.
- The concept of "quality first and patient safety" is deeply rooted in the day-to-day operations and the lives of all PEC employees, allowing us to prioritize quality and safety to implement drug risk management and to ensure the safety of patients' drug use.

Responsibilities

- Doctors and pharmacovigilance personnel, and pharmacovigilance QA personnel from Taiwan headquarters, and subsidiaries in U.S., China, Japan, Korea, Hong Kong, and Singapore.
- QA department and QC department in headquarters are responsible for the quality of commercially available drugs and clinical drugs, while clinical trial QA and pharmacovigilance functional group are also involved in this process.
- Execution Center for Corporate Sustainability - Product Quality and Patient Safety Taskforce

Resources

Personnel/operational resources

- A pharmacovigilance functional group (3 persons from Medical Research department) has been set up at the Taiwan headquarters to be in charge of pharmacovigilance and management tasks.
- To meet the relevant laws and regulations on pharmacovigilance and reporting from marketed countries or regions, PEC has set up dedicated physicians or pharmacovigilance personnel to be in charge of relevant tasks at our Taiwan headquarters and subsidiaries in the U.S., China, Japan, Korea, Hong Kong, and Singapore.
- Presently, PEC has already commissioned a pharmacovigilance CRO to form a project team to manage and maintain the safety information database of PEC's BESREMi®, the collection and exchange of drug safety information, and reporting to legal competent authorities.

Expense invested

- In 2021, we invested over NT$10 million for pharmacovigilance related tasks around the world.

Goals & Targets

2022 Short-term Goals

- Amend PEC's standard operating procedures related to pharmacovigilance in line with regulatory updates and actual operating needs.
- Draw up a drug safety monitoring plan.
- Reach 100% completion rate of pharmacovigilance training for new employees.
- Update and maintain drug safety database (Argus) and provide accelerated and periodic reports on pharmacovigilance.
- Reach 100% execution rate on timely drug safety information reporting from the headquarters. Reach 100% execution rate on timely drug safety information reporting across all subsidiaries.
- Continue to collect drug safety information from academic publications and continue to identify and analyze drugs and adverse reactions, as well as to complete safety signal monitoring reports on a regular basis.
- Set up QA personnel at the headquarters to be in charge of quality assurance and auditing activities of procedures and documents related to pharmacovigilance.
- Obtain regulatory marketing approval from Japan by passing the PMDA inspection; also aim to pass inspection from competent authority in Turkey.
- Complete deployment of all processes from the quality management system (QMS).
- Evaluate the deployment of electronic equipment management system.

2023~2025 Mid-term Goals

- Continue to update or amend PEC's standard operating procedures related to pharmacovigilance. Standard operating procedures related to localized pharmacovigilance will be formulated by respective subsidiary.
- Continue to amend the drug safety monitoring plan.
- Continue to optimize the drug safety database (Argus), and to update the database based on actual practices.
- Continue to require submission of pharmacovigilance reports in line with requirements from the competent authority. Reach 100% execution rate on timely drug safety information reporting at the headquarters and across all subsidiaries.
- Continue to collect safety information from post-marketing safety reports or academic literature, and to reach 100% implementation rate on identifying and analyzing drugs and adverse reactions.
- Introduce 1 to 2 additional staff to the pharmacovigilance personnel at the headquarters, and continue to organize pharmacovigilance training for all new employees and all members of PEC.
- Pass the regular drug good practice inspections for every 2~3 years performed by the EMA, TFDA and FDA. The estimated inspection will be carried out in the following schedule:
  - 2022: EMA
  - 2023: TFDA and FDA

Goals & Targets

2026 Long-term Goals

- Continuously review the drug safety monitoring management standards and drug safety monitoring standard operating procedures and update or revise the content according to the actual situation.
- Coordinate IT and relevant personnel to develop a drug safety database autonomously managed by PEC.
- Continue to develop the pharmacovigilance team and to train new pharmacovigilance staff at the headquarters, as well as to acquire in-house execution and management over global safety data collection, analysis, and reporting.
- Pass the regular inspection by the competent authority of the country where PEC has obtained the drug certificate.

Evaluation of Management Approach

Mechanism of Evaluation

- Post-marketing pharmacovigilance will be conducted by Contract Research Organization (CRO) and physicians designated by PEC.
- Physicians or dedicated pharmacovigilance personnel at the headquarters and subsidiaries will be in charge of their local pharmacovigilance tasks.
- Internal audits: audits by QA department or commissioned by a third party.
- External audits: Drug safety inspection from both local and foreign competent authorities
- Evaluate the operations of immediate reporting mechanisms:
  - PEC Taiwan headquarters' adverse reaction reporting mailbox:
    Safety@pharmaessentia.com
  - CRO adverse reaction reporting mailbox:
    PharmaEssentia.drugsafety@labcorp.com
- Evaluate the operations of the drug safety reporting hotline (in Taiwan, the U.S., Korea, and Japan).
- Regularly monitor the status of submitting Periodic Safety Update Reports (PSUR) or post-marketing product safety reports to the U.S. FDA, the EU EMA, TFDA in Taiwan, PMDA in Japan, and MFDS in Korea.

Evaluation of Management Approach

2021 Evaluation Result

- Post-marketing safety monitoring: announce immediate reports and maintain the normal operations of our immediate reporting mechanism in line with regulations from competent authorities.
- Periodic Safety Update Report (PSUR) We regularly submit the Development Safety Update Report (DSUR) and the Periodic Safety Update Report (PSUR) to the competent authorities of respective country.
- No competent authority on drug safety has conducted inspections related to pharmacovigilance in 2021.
- All plants passed TFDA's routine Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) inspections.
- All plants passed MFDS's GMP audit certification in 2021, and regulatory marketing approval has been obtained.
- Our API manufacturing plant passed the U.S. FDA's pre-license GMP plant inspection in 2021, and regulatory marketing approval has been obtained.
- No critical violation of relevant GxP laws and regulations have been found in external official inspections.
- Results of internal quality audit: A total of 12 internal audits were carried out in 2021, and 43 minor deficiencies were found. No critical or major deficiency was found, and improvement and preventive plans have been drawn up for all 43 minor deficiencies within the deadline.
- No product-quality incident that required reporting to the competent authority has occurred.

Comprehensive Quality and Safety Operation Management and Operation Process Guidelines

PEC's Taichung Plant has a detailed organization and operation chart. It is equipped with sufficient and experienced qualified personnel, and the QA and QC departments of the quality system are responsible for the management and supervision of the manufacturing process. The Company has the internal "Quality Handbook" and over 4,000 related standard operating procedure specifications, and plans and reports, to ensure the quality and safety of products.

4000+

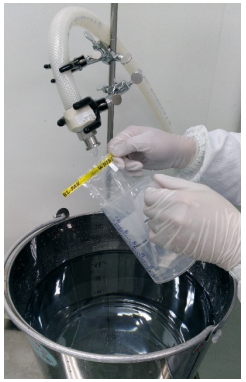
Comprehensive quality related standard operating procedures and various plans and reports

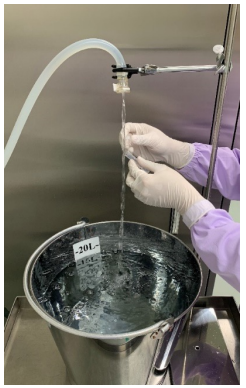
Maintenance of Manufacturing Quality

To ensure that the quality inspection of the environment, raw materials, intermediate products, APIs and finished products of the PharmaEssentia's Taichung Plant are in compliance with Good Manufacturing Practice (GMP) requirements, PEC has established the "Manufacturing and Process Control Procedures" to standardize process control, monitor labeling, inspect and control basic operation procedures. The QA department has implemented layers of controls prior to manufacturing, as well as formulated the "Cross-Contamination Prevention Management Procedures" to oversee the basic operation procedures at the manufacturing areas to reduce the risk of cross-contamination.

Monitoring Environmental Quality

The QC department is in charge of environmental quality monitoring, as well as the quality inspection of the cleanliness of raw materials, intermediate products, active pharmaceutical ingredients (APIs), products, and production equipment. PEC has formulated the "Environmental Monitoring Program Standards," " Water System Monitoring Standards" and "Microbiological Identification and Statistics Standards," etc., to ensure effective monitoring of environmental microorganisms, and timely response measures to greatly reduce the risk of microbial contamination of products. We also conduct trend analysis based on the results from environmental quality monitoring and meet annually to discuss the analysis report. Results of the 2021 monitoring trend report on the production environment (air conditioning), water system, compressed air and biosafety operation cabinet show that all systems meet their respective design requirement and comply with laws and regulations.



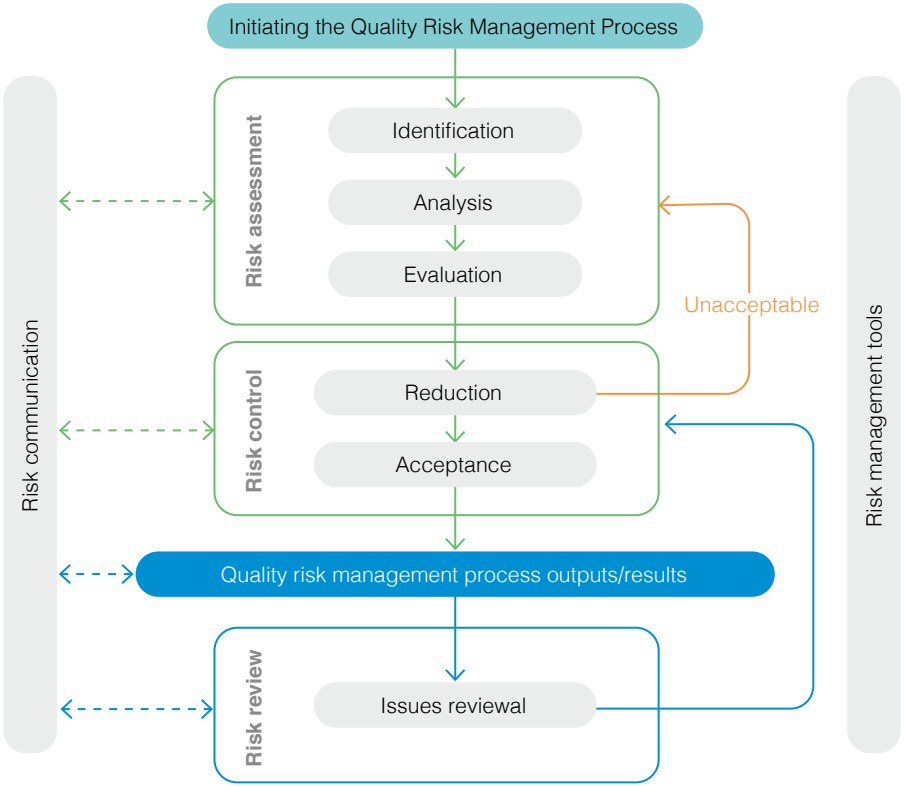


Monitoring personnel perform water system monitoring and sampling, using different fittings according to different water quality sampling points.

Management and Assessment of Quality, Safety and Risk GRI 102-15

Quality risk management is implemented throughout the product's life cycle. PEC's Taichung Plant has formulated the "Quality Risk Management Procedures" in line with ICH Q9. Protect patients' health and effectively control and reduce the risk of patients' drug use through practicing good manufacturing quality risk management.

Flow chart for quality risk management



Risk Assessment and Maintenance of Clinical Trial Quality

The risk assessment of clinical trials is performed by contract research organizations (CROs). In line with regulations from our internal operating procedures, internal and external training regarding trial product safety is held before and during the clinical trial, as well as implementing quality assurance and quality management in clinical trials. Going forward, PEC plans to formulate reasonable drug safety risk assessment SOP that complies with relevant laws and regulations, and to have internal dedicated clinical trial QA staff conduct inspections based on the SOP.

Before clinical trial:
Assessing the degree of risk that may be encountered during the trial process according to the characteristics of the trial drug and the difference in the trial design.

Key points in evaluation

Specific "Monitoring Plan" and "Audit Plan" are developed to perform QA and QC activities based on the levels of risk. Ensure that the rights and welfare of the subjects are protected and that the clinical trial is conducted and the data generated, recorded and reported in compliance with the trial plan, GCP and related regulatory requirements.

Implementation Process

Quality Assurance (QA) activities

Include an independent audit system where problems identified are properly evaluated and tracked, and CAPA is developed.

Quality Control (QC) activities

Include monitoring and assisting in monitoring tasks

Risk Management of Manufacturing Quality

PEC's Taichung Plant has formulated the "Quality Risk Management Procedures" in line with ICH Q9. To reduce the risk of quality hazards when operating equipment, the "Equipment Risk Evaluation Procedures" has also been formulated in line with the regulations on instruments and equipment from the U.S. Pharmacopeia (USP), and conducts categorized risk management accordingly. And the Company has introduced risk management to control the production process, environmental control, material supply and other matters to minimize quality hazards. Besides inspecting the risk issues within the plant via inter-departmental risk assessment team meetings, PEC also meets with global subsidiaries via video conference to coordinate information on quality risk in order to manage and follow-up.

6 sessions

Risk assessment team meetings in 2021

57 attendees

Attendees of the risk assessment team meetings in 2021

8 departments

Inter-departmental participation from Procurement, Supply Chain, QA, QC, Injection plant, Factory Affairs, Manufacturing, and R&D, etc.

5 subsidiaries

Participated by Taiwan headquarters and subsidiaries including the U.S., Japan, Korean, Beijing, and Panco Healthcare

Product Quality Assessment and Continuous Improvement

PEC inspects the validity of the quality management system and GMP compliance through routine internal audits and external audits. PEC has formulated the "Product Quality Review Procedures" and regularly performs product quality evaluation to ensure that the existing manufacturing process and the materials used can consistently produce products that meet our quality requirements. We convene quarterly product quality review meetings to improve quality incidents. Based on the severity of the incident, corrective and preventive actions (CAPA) will also be implemented to ensure the stability and consistency of product manufacturing process and product quality, which will be used as the basis for process improvement and optimization. Moreover, to provide sufficient drug supply to meet the demand in the U.S. Market, control points have also been added to the process and certain specifications of microorganisms have been tightened accordingly.

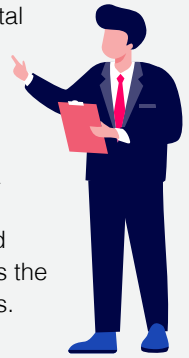
All departments within the Taichung plant will receive at least 1 internal quality audit each year. A total of 12 internal audits were carried out in 2021, and 43 minor deficiencies were found. No critical or major deficiency was found, and improvement and preventive plans have been drawn up for all 43 minor deficiencies within the deadline. In addition, the logistics center of subsidiary Panco Healthcare is also compliant with Taiwan's Good Distribution Practice (GDP) standard and its quality operations have been included in the Group's quality management system. A total of 11 minor quality system deviations were found during the internal quality audit in 2021, and all deficiencies have been properly handled.

Internal audits

- Conducting internal audits at least once every month
- Each department undergo internal audits at least once a year
- For non-conformities in the audit, a CAPA plan must be proposed and related tasks completed within the corresponding prescribed date according to the level of deficiencies.

External audits

- Undergoing governmental GMP inspection every 2-3 years.
- The first protein biopharmaceutical factory in Taiwan to obtain EMA certification.
- The short-, medium- and long-term goal is to pass the regular GMP inspections.



2021 Quality Audit / Factory Inspection / Relevant Verification Records

Audit/Inspection/ Verification Date	Audit/Inspection/ Verification Department	Audit/Inspection/Verification Process, Key Observation Items	Audit/Inspection/ Verification Results
2021/04/07~ 2021/04/09	TFDA	Routine GMP/GDP Inspection for active pharmaceutical ingredients (APIs) and Biological medical product (injection fluids)	Extended GMP certification
2021/09/20~ 2021/09/28	U.S. FDA	Pre-License Inspection for active pharmaceutical ingredients (APIs)	Obtained GMP certification
2021/1~ 2021/12	Internal audits	A total of 12 internal audits were carried out in 2021	Completed all

GMP/GDP Quality Training at the Production Plant

Through providing annual training courses, we instill the philosophy of quality management into the day-to-day operations of all relevant personnel. In addition to internal training, PharmaEssentia also appoints colleagues to participate in external trainings sponsored by related domestic and foreign academics/associations, and hires senior foreign consultants to visit the factory every year to update the knowledge of GMP or laws and regulations.

Statistics on Good Manufacturing Practice for Medicinal Products (GMP) Training in 2021

Training topic	Sessions	Participants	Training hours
GMP training in 2021	10	789	7,890
Regulation, manufacturing or new employee quality-related GMP training	28	503	14,084
Prevention and correction training	68	928	31,552
External training	13	14	1,092
Total	119	2,234	54,618

3-4 Excellent Manufacturing and Production

Advanced and High Standard Plant Equipment

The three main facilities of PharmaEssentia Taichung Plant: Polyethylene Glycol (PEG) production factory, Drug Substance (DS) manufacturing plant, and sterile agent filling plant. Our Taichung Plant is the first biopharmaceutical plant in Taiwan to pass the EU's EMA inspection and obtain Good Manufacturing Practice (GMP) certification. The sterile agent filling plant also obtained GMP and GDP certification from TFDA in April 2020, and passed MFDS GMP audit in January 2021 and U.S. FDA plant audit in September 2021. In addition to external inspections, PharmaEssentia's Taichung Plant also completed 12 internal audits in 2021, with investment of approximately NT$20 million toward repair and maintenance as well as acquisition of new equipment to ensure the high quality of drug manufacturing process.

The U.S. FDA conducted on-site audit at Taichung Plant in 2021