GMP Committee for Sterile Products
February 2024
Chairperson, Yasuto Ikematsu, Osaka University
Vice-chairperson, Mitsu Mori, Kyowa Kirin Company Limited.
Vice-chairperson, Satoshi Sugimoto, Takeda Pharmaceutical Company Limited.

This committee has the largest number of participants and has been active since 2004. The research is actively conducted either bimonthly and as needed within the 7 research groups and 1 subcommittee which has 2 research groups.

1 Group: Container Closure Integrity research
For sterile products, qualification of the barrier function for microorganisms needs to be demonstrated throughout their life cycle, and control of container closure integrity is one of the critical control elements.
In recent years, a description of barrier function for gas has been added to USP<1207> and JP 18 general information. Thus, the requirement for the control of container closure integrity of parenteral products is increasingly being enhanced. However, the same test is not able to be applied to all products, and from among many test methods, an appropriate test method suitable for the product characteristics needs to be selected from the viewpoints of feasibility and reliability.
In this group, factors that impair container closure integrity and their effects on contamination risk are sorted out, and discusses the ideal way for ensuring container closure integrity.

2 Group: Injectable foreign matter visual inspection research
This group has been conducting research on insoluble foreign matter in injectable drug with the aim of standardizing the assurance method to meet the quality requirements in the Japanese market and eventually spreading it internationally. As the background, although the inspection methods for foreign matter have been harmonized among the Japanese Pharmacopoeia, the European Pharmacopoeia, and the United States Pharmacopoeia, the standard for foreign matter to be removed is still ambiguous: “Insoluble foreign matter that can be easily detected must not be accepted.”
In Japan, the quality requirements for foreign matter in injectable drug tend to be higher than those in other countries, and therefore, additional visual inspection must be performed in Japan for products manufactured at overseas manufacturing sites. We are currently considering quantifying the detection ability of visual inspectors and standardizing the assessment method. If we can establish a quality assurance procedure with standardized level of inspectors, we will be able to be explain the objective qualification of the visual detectability objectively against the ambiguous criteria of ”easily detectable insoluble foreign matter” required by the Japanese Pharmacopoeia, and it will be easier to achieve the

quality required by the Japanese market internationally even in foreign manufacturing sites.

3 Group: Rapid microbiological method research

In manufacturing facilities for pharmaceuticals, human cell therapy and gene therapy products, microbiological quality control and environmental monitoring in the manufacturing process are important. It is necessary to minimize the risk of microbiological contamination to products and to monitor the quality and environment. In recent years, the value of rapid microbiological methods (RMM) for the detection of microorganisms has been rapidly recognized, and their frequency of description in guidelines such as the Japanese Pharmacopoeia 18 General Information and PIC/S GMP Annex1 has been increasing. Therefore, there is a need to realize new optimal and effective microbial control using RMM. The purpose of this group is to contribute to the creation of new value in the microbial control of regulatory authorities, users (pharmaceutical companies), and suppliers (equipment suppliers) by researching the concept and application methods of RMM and continuously publishing the results. In addition, this group is composed of users and suppliers, and it focuses on implementation and qualification at manufacturing sites, *etc*. by approaches from both sides, and it also conducts research that can be applied flexibly.

4 Group: PIC/S GMP Annex1 Environmental Monitoring Research

With the implementation of PIC/S GMP Annex1 starting from August 2023, it has become clear that manufacturing facilities for sterile products (including regenerative medical products) will need to transition to comply with Annex1. In particular, the development and implementation of a contamination control strategy (CCS) is crucial. Therefore, in this group, we will focus on ”environmental and process monitoring” in the context of CCS development and operation, and conduct research on the establishment of practical environmental monitoring programs based on risk assessment, as well as aseptic process simulation (APS).

5 Group: Barrier Systems Research

In recent years, aseptic pharmaceutical manufacturing sites have been equipped with state-of-the-art barrier systems that enable advanced aseptic environment control, such as isolators and RABS, and the practical use of fully automated aseptic glove-less isolators without human intervention is just around the corner.

While progress has been made in the aseptic pharmaceutical manufacturing technology, the laws, regulations, and guidance related to aseptic pharmaceutical manufacturing are still based on the conventional clean room manufacturing method, and GAPs have emerged between the actual manufacturing method and the actual situation.

In this group, we are researching new sterility assurance for pharmaceutical manufacturing using advanced sterile environment control technology, and barrier systems that contribute to the contamination control strategy (CCS) of PIC/S GMP Annex 1 with a

science-based and risk-based approach.

6 Group: Containment Technologies Research

There are increasing opportunities to manufacture products with high pharmacological activity (high potent drugs) such as anticancer agents in respect of pharmaceutical manufacturing. There is also a growing demand for containment technologies to deal with chemical hazards and biohazards for production of vaccines which have been attracting attention in recent years, and for regenerative medicinal products in the manufacture of gene therapy products such as viral vectors or cell processing products with genetical modifications. It is desirable that such containment measures enable to take reasonable correspondence procedures suitably after evaluating impacts on products to be handled or workers within the facility by classifying the target hazard and the risk.
This group will organize the impact of objects requiring containment on other products and workers and discuss appropriate equipment to address hazards and risks.
The group also discusses the technical issues on achieving both hazard control and aseptic manufacturing.

7 Group: Research on PIC/S GMP Annex 1 – Facility Establishment and Management

Modern aseptic manufacturing has a wide range of expectations and demands for corporate practices, such as quality assurance for protecting the patient, active utilization of the latest technologies, QRM-based process understanding and rationale, and justification of control strategies based on design concepts and the data obtained. The interest in PIC/S GMP Annex 1 has been increasing year by year in order to establish and/or continuously improve them. This group discusses how to address the gaps between establishment, practice and management in current facilities, and their requirements in Annex 1. Our activity will provide the suggestions and recommendations to the industry on their corporate practice based on the understanding of essential points of GMP.

Subcommittee on Advanced Therapy Medicinal Products (ATMP)/Regenerative medicine

ATMPs (including regenerative medical products) are aseptic products and the requirements for their manufacturing and quality control are based on the GMP.
Compared to the manufacturing of pharmaceutical products, ATMPs are manufactured in smaller lots and require more human intervention, and more technical challenges for automation and mechanization, and thus relies on the manual skills of workers.
In addition, there are a wide variability of raw materials (Human cells) and final products, which often require case-by-case operation. Due to these circumstances, the industrialization of ATMP are still their immature, and there are many issues that differ from those of aseptic drug products, especially in the manufacturing and quality control.
Our committee believes that there is an urgent need for the development of technical know-how and regulatory science to discuss these issues and lead them to a global standard.

This subcommittee will address ATMP specific issues, and will establish two research groups (8 Group: Research on GxP in ATMP/Regenerative medicine, 9 Group: Research on aseptic procedure in ATMPs) to study the issues and the solution faced in the manufacturing and quality control of these products.
The objective is to promote the revitalization and industrialization of the industry by conducting research on the issues and the solutions and presenting the results to domestic and international audiences.

8 Group: Research on GxP in ATMP/Regenerative medicine
In this group, we will conduct research and analysis of GxP (GCTP, PIC/S GMP, cGMP, cGTP, GVP, GQP, GDP, etc.) guidelines for ATMPs or regenerative medicine-related products under the Pharmaceutical Acts in US or Japan, and achieve standardization of concepts or methodologies including regulations with the aim of harmonizing them not only domestically but also internationally. This group aims to support industries in standardization activities to meet various GxP guidelines in the manufacturing and quality control of products related to regenerative medicine, and to implement rational and effective manufacturing and quality control practices according to GxPs with global perspective.

9 Group: Research on aseptic procedure in ATMPs
Aseptic processing is an essential element in the manufacture of ATMPs (including regenerative medical products) to ensure the quality of sterile. Especially in the facilities installed open chamber system such as bio-safety cabinet, there is higher potential risks of extrinsic contamination due to human intervention, etc. It is not an exaggeration to say that aseptic processing itself is the key to product quality for safety. Since aseptic processing is not limited to the manual manipulation of operators, but is established in all aspects of manufacturing, including facilities and the environment, it is necessary to fully discuss how aseptic processing should be performed. However, unlike the manufacturing of sterile products, ATMPs have little history, so knowledge and experience are limited, and regulations regarding aseptic processing themselves are not enough. This group will consider the concept of optimized aseptic processing for the production of ATMPs by identifying the risks necessary to establish aseptic processing, evaluating and verifying those risks, and standardizing the method with a global perspective.