| Amendments to Pharmaceutical GMP Ministerial Ordinance and Changes to Global Standards for Pharmaceutical Excipients

Regarding pharmaceutical GMP, following Japan's accession to PIC/S[i], additional matters that had been operated as notifications were added, and international consistency such as pharmaceutical quality system (ICHQ10) and quality risk management (ICHQ9) was added. The revision of the GMP Ministerial Ordinance was made on April 28, 2021.
Table 1 shows the main additional points of the ministerial ordinance revision. It requires creating a mechanism to ensure the integrity of data and incorporating the elements for data integrity into the procedure manual.

Table 1
[Points of revision of GMP ministerial ordinance for pharmaceuticals]

Article 4 Responsibilities of Senior Management
Article 5 Quality Risk Management
Article 6 Arrangements with marketing authorization holders
Article 15 Review of Product Quality
Article 16 Stability monitoring
Article 17 Supplier management of raw materials, etc.
Article 18 Management of Outsourcing Contractors

In particular, the revision of the GMP Ministerial Ordinance for Pharmaceuticals, which is relevant to companies that manufacture pharmaceutical excipients, is Article 17, the provision of supplier management of raw materials, etc., which was previously concerned with supplier management of active pharmaceutical ingredients. However, the scope has expanded to include supplier management including excipients.
That meant, it has become essential for pharmaceutical manufacturers to conclude supply contracts and quality contracts with suppliers of pharmaceutical excipients, and to maintain and manage them. The content required by pharmaceutical GMP in quality contracts is based on global standards.

GAB's investigation of the status of implementation of GMP for pharmaceutical excipients so far has been considered under the Health Labour and Welfare Scientific Research Subsidy Pharmaceuticals and Medical Devices Regulatory Science Policy Research Project. We have been conducting our activities in accordance with the "GMP Standard for Pharmaceutical Excipients 2016" issued an administrative notice. The GMP Standards for Pharmaceutical Excipients 2016 was partially revised, and a revised draft was formulated as “GMP Standard for Pharmaceutical Excipients 2022”.

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Specifically, in addition to the basic elements of the Standards 2016, we have added important points for quality assurance, such as data integrity, risk assessment, and elemental impurities, which are currently required for pharmaceutical excipients, is an important factor in supplying high-quality pharmaceutical excipients and aiming to continuously improve the level of quality assurance.

"GMP Standard for Pharmaceutical Excipients 2022"
Major changes/additions

- ❑ **Risk assessment and management**
- ❑ **Maintain data integrity**
- ❑ **Assessment of elemental impurities**

These are also used in pharmaceutical GMP, but since pharmaceutical excipients and pharmaceuticals may differ in terms of production methods, manufacturing methods, raw materials, process control methods, and required quality, they are not considered practical requirements. Different points may occur.

From the standpoint of manufacturing pharmaceutical excipients, it is necessary to ensure that these key points are addressed, and IPEC has issued guidelines for each of the major items.

IPEC Guide

- ❑ Certificate of Analysis Guide for Pharmaceutical Excipients[ii]
- ❑ Good Distribution Practices Guide for Pharmaceutical Excipients[iii]
- ❑ The IPEC Risk Assessment Guide for Pharmaceutical Excipients[iv]
  Part 1-Risk Assessment for Excipient Manufacturers
- ❑ The IPEC Significant Change Guide for Pharmaceutical Excipients[v]
- ❑ The IPEC Excipients Stability Program Guide[vi]
- ❑ Technically Unavoidable Particle Profile Guide[vii]
- ❑ IPEC Position Paper: Data Integrity for Pharmaceutical Grade Excipient[viii]

| MAIN REVISED & POINTS

POINT 1

3. Quality management system

3.1 General requirements

"The manufacturer must have a clear quality management process necessary to ensure the quality of the pharmaceutical excipients ".

"The elements of the quality control process should be addressed appropriately at each stage of the product life cycle. Considering the legal, technical, cultural, and social environment, it is

desirable to clarify and implement the quality control process necessary to guarantee the quality of the product." was added.

'Each stage of the product life cycle' What and how are required in the quality control elements and processes required at each stage from product development to market introduction, growth, maturity, and termination? It is necessary to respond in the same way as possible, or to take a more specific response. For example, from development to introduction, during the growth period, changes in production methods due to an increase in production volume, enlargement of facilities, outsourcing to other companies, etc. may occur. It is wide-ranging. Also, during the decline period, other products may be prioritized in various management, and it is possible that dealing with aging equipment will become an important management item. These matters are required to be comprehensively managed as a quality management system.

In this way, it is stipulated that " If you outsource manufacturing, testing, or other work that may affect the quality of your product, you need to inform your customers."

POINT 2

3.2 Documentation requirements

3.2.2 Quality Manual

The quality manual should "include the scope of the quality management system, reference information to supplement the procedures of the quality management system, and a description of the interrelationships between the processes of the quality management system".
In addition, the quality manual requires that the processes subject to GMP be described along with the reasons, stating that "The manufacturer should clarify the process for which GMP control is considered necessary based on the grounds." increase.

POINT 3

3.2.3 Document managements

Document management requirements as follows: "Manufacturers shall establish and maintain procedures for identifying, collecting, classifying, storing, maintaining and disposing of control documents, including external documents that are part of the quality management system."
In addition to this, if there are documents to be submitted to the regulatory authorities, there may be documents to the regulatory authorities, such as a drug master file (DMF) for excipients or the certificate of suitability to the European Pharmacopoeia (CEP). Establish procedures for appropriate periodic review and update of submitted documents, where they exist. It is a content that requires a review of the content.

POINT 4

3.2.4 Records managements

"The manufacturers shall establish and maintain procedures for identification, collection,

classification, storage, maintenance and disposal of records."

The specific content of this requirement is as follows.
"Take steps to always maintain data integrity. For example, the analysis results and calculation methods should always ensure traceability with the original data and measured values. Data integrity requirements apply equally to manual (paper) and electronic data.
Electronic recording should follow the same management procedures required for other recordings. It is desirable to utilize the audit trails that are stored electronically. If you use electronic signatures, they must be certified, secure electronic signatures and comply with applicable regulatory requirements." was added.

Proper documentation is an integral part of the quality management system and the cornerstone of meeting GMP requirements.
It is necessary to specify how to use and manage various forms of documents and media. Documents and records exist in various forms such as paper-based, electronic media, and photographic media. The main purpose of using the document system is to define, control, monitor and record all work methods and procedures that directly or indirectly affect the quality of the product.

At this time, data integrity is required, but to put it simply, data integrity is "complete," "consistent," and "accurate" data, it means to store the “real thing'' of the document written” when it is done'' in such a way that it is “readable” for the “necessary period''.
Maintaining the integrity of data and documents is also a basic requirement for demonstrating that the quality management system was functioning reliably. This section seeks the importance of document management by setting data integrity as a requirement.
Data integrity is an essential requirement for both paper records and computerized records.

POINT 5

3.3 Change Managements

“The manufacturer shall establish and maintain procedures for assessing changes that may affect product quality, and for approving the implementation of changes.'' is provided, but “Outsourcing of manufacturing, testing, or other work, supply chains, and computerized systems” was added. Currently, with the increase in the number of outsourcing opportunities for various operations, the issues of complicating the supply chain and optimizing distribution are becoming more important. As computerized systems are used, it is necessary to properly implement change management, so it is added to the management target. Change control is one of the most important control items in GMP, and IPEC Guidelines have been published as The IPEC Significant Change Guide for Pharmaceutical Excipients.[V]

POINT 6

4.5 Responsibilities, Authority and Communication

4.5.1 Responsibilities and Authority

"Senior management should clearly define responsibilities and authorities and make them known throughout the organization. The following matters should be the responsibility of the quality department, which is independent of the manufacturing department."

To confirm that there are no abnormalities or deviations, review manufacturing records, test records, complaints, etc. (including quality-related information). If there are any deviations, thoroughly investigate them. Confirmation and approval of evaluation results and measures for the impact of abnormalities and deviations on product quality. Departments are expanding their functions as quality assurance.

POINT 7

4.6 Management review

4.6.2 Review Input

By adding "new, revised or proposed regulatory requirements" to the items to be input, we clarify compliance with legal and regulatory requirements as management control items.

POINT 8

5. Resource management

5.2 Human resources

5.2.1 General

Regarding personnel engaged in production, in addition “the person who performs the work should be specified in the procedure manual (4.5.1 Responsibilities and authority).” We require that the procedure manual stipulate what kind of education and training a person can take on the task. It should be noted that this requirement also applies mutatis mutandis when the relevant work is outsourced. When outsourcing, it is necessary to confirm that the outsourcing company has workers with equivalent skills, and if not, to implement prior education and training on the shortcomings.

POINT 9

5.3 Infrastructure

5.3.2 Equipment

Regarding structural equipment, etc., it is required to identify and document areas where pharmaceutical excipients are at risk of contamination due to defects in buildings and facilities, based on the purpose of use of the structural equipment. If a risk area is identified and if there is an area where corrective action is possible, it must be addressed. In addition, it is necessary to create a record of use, cleaning, and maintenance and to identify the condition of the equipment that is expected to affect the risk of breakage and quality. All these items should be recorded through the creation of a logbook.

POINT 10

5.4 Work environment

If there is a possibility of product contamination due to the working environment or cross-contamination with other items, it is required to perform a risk assessment and take necessary control measures. The main risk items include air treatment systems, special product-specific environments (temperature and humidity, etc.), Cleanliness and hygiene conditions (sterility, etc.), insect control management, waste separation and disposal, etc. A wide range of environmental management is required, such as dealing with raw materials.

Some wastes have different disposal/treatment methods, such as sorting by type (chemical substances, biological substances, hazardous substances), so it is required to display and properly identify and store them.

Work environment and hygiene management

Hygiene Controls: To protect excipients from contamination, a documented risk assessment should be conducted to identify areas at risk of contamination by personnel or their work.

The table below is taken from IPEC's risk assessment for the manufacturing environment.

Risk	Assessment	Counter measures
Employee clothing, including personnel and personal protective equipment		
Items that are easy to drop, including items in pockets (risk of dropping parts)		
Entry of unauthorized personnel into designated areas		
Potential impact from personnel with obvious illness or inflammation wounds or swelling		
Storage and use of food, beverages, personal medicines, tobacco products or the like.		

Buildings/Equipment: Document and perform risk assessments to identify where excipients are at risk of contamination

Risk	Assessment	Counter measures
Work area, location (e.g. internal, external)		
Repair and maintenance status of buildings and facilities		
Appropriate size, structure, and location *If equipment is installed outdoors, proper controls are required to minimize risks to excipient quality from the environment, including seasonal variations.		
Ability to maintain a reasonably clean building and facility environment		
Manipulations that can affect the quality of excipients		
Presence of airborne contaminants, especially sensitive or toxic substances		

Insect repellent and rat repellent

Risk	Assessment	Counter measures
Implementation status of insect and rat control measures		

The IPEC Risk Assessment Guide for Pharmaceutical Excipients [IV] (risk assessment)
Part 1-Risk Assessment for Excipient Manufacturers

Point 11

5.4.3 Cleaning and hygiene management

To maintain clean and hygienic conditions in buildings used for the manufacture, processing, packaging, or storage of pharmaceutical excipients, the detergents and disinfectants required for cleaning are risk-assessed and their suitability determined. It is recommended to use from.

5.4.4 Insect control management

When pest control management is outsourced to an external specialist, it is required to conclude a contract, create an insect control program as a pharmaceutical excipient manufacturer, and implement pest control management in a planned manner. Also, the use of pesticides and rodenticides should be documented.

Point 12

5.4.8 Waste

Contents related to waste treatment are summarized, " Waste should be sorted according to its type (chemicals, biological substances, harmful substances), labeled as necessary, and disposed of at the appropriate time and in the appropriate manner. If the waste is not disposed of promptly, properly identify and store it."

Point 13

6.2 Customer-related processes

6.2.1 Clarification of requirements related to products

Clarification of customer requirements related to product quality, labeling, and delivery, and agreement with customers based on compliance with laws and regulations are the most important points in supplying products. Specific examples are given of what will occur as additional requirements.

Examples include general compendial requirements, TSE/BSE, residual solvents, elemental impurities, impurities from naturally occurring raw materials, mycotoxins, and pesticide residues.

For pharmaceuticals, TSE/BSE is a matter related to approval details, and residual pesticides derived from naturally derived raw materials always require attention.
In addition, elemental impurities are items that are required to be controlled as impurities based on the results of ICHQ3 below.

Regarding elemental impurities, it is necessary to conduct a risk assessment and document whether testing for elemental impurities should be included in the specifications of pharmaceutical excipients when using metal catalysts in the manufacturing process. In the 18th revision of the Japanese Pharmacopoeia (notified on June 7, 2021), "control of elemental impurities in pharmaceuticals" was listed as a general rule. Evaluation and control of elemental

impurities according to the Japanese Pharmacopoeia have begun.

If it is determined that control of elemental impurities is necessary to ensure the quality of excipients, it is necessary to take measures to ensure quality by referring to ICH Q3D.

ICH Q3D Elemental Impurities

Class Rating: 1 Toxic to humans All routes of administration require evaluation
Arsenic (As), Cadmium (Cd), Mercury (Hg), Lead (Pb)

Class Rating: 2A Naturally occurring; all routes of administration require evaluation
Cobalt (Co), Nickel (Ni), Vanadium (V)

Class Rating: 2B Needs evaluation if intentionally added
Silver (Ag), Gold (Au), Iridium (Ir), Osmium (Os), Palladium (Pd), Platinum (Pt), Rhodium (Rh), Ruthenium (Ru), Selenium (Se), Thallium (Tl)

Class Rating: 3 Relatively low toxicity Oral: No evaluation required unless intentionally added Injection, Inhalation: Evaluation required
Barium (Ba), Chromium (Cr), Copper (Cu), Lithium (Li), Molybdenum (Mo), Antimony (Sb), Tin(Sn)

No. 0626 No. 1 June 26, 2020 Ministry of Health Labour and Welfare Notification[ix]
Amendments to Guidelines for Elemental Impurities in Pharmaceuticals

6.2.3 Customer Communication

Accurate and appropriate communication with customers is essential for supplying products that meet customer requirements. To better clarify customer needs, in addition to important changes, the items to be notified to customers include “the origin of the drug excipient、problems detected after delivery” of the products to be supplied.

POINT 14

6.4 Purchasing

6.4.1 Purchasing process, 6.4.3 Verification of Purchased product

In manufacturing pharmaceutical excipients, the selection of raw materials that are important in terms of quality and outsourcing to external testing institutions have important quality elements, and it is required to conduct a risk assessment at the time of selection as part of the purchasing process. Added to the matter. In addition, management of the receipt of purchased raw materials has been added as a verification item for purchased products.

POINT 15

6.5. Production and service provision (including manufacturing support systems)

The provision of services here has the meaning of indirectly supporting manufacturing, and the explanation that it includes manufacturing support systems has been added. Manufacturing support systems refer to manufacturing water manufacturing systems and air-conditioning systems in pharmaceutical GMP, so we hope you will take the same meaning here as various systems that support manufacturing.

6.5.1.2 Cleaning the device

For equipment cleaning, it is added that “cleaning procedures should be defined based on a risk assessment and their effectiveness should be demonstrated. Their effectiveness should be evaluated based on pre-determined criteria.” increase. In other words, it is required that a series of procedures be established based on the results of the risk assessment, and that the series of operations for judging the results of cleaning implementation be procedural and reproducible.

It also contains a sentence "disinfect if necessary" to ensure cleanliness. It is a natural act, but here is the meaning of stipulating it as a document.
In addition, " Document the rationale for the validity period of cleaning / disinfection and the conformity assessment of cleaning / disinfecting agents. In addition, display and record the cleaning status of the equipment so that it can be easily identified." It requires effective period, appropriate cleaning and disinfection methods, assurance that materials are being used, and easy identification of whether cleaning has been performed or not, and measures to reliably prevent misuse.

POINT 16

6.5.1.4 In-process Blending or mixing

This item is stipulated independently because mixing in the process is the difference between mixing performed to assure homogeneity within a lot and mixing performed for other purposes. Content added to clearly define the difference between prohibited and unacceptable mixtures. This means that the practice of acceptable in-process mixing is only acceptable for the purposes listed below.
Acceptable mixing operations for the final product include, but are not limited to:

- Mix small lots to increase the lot size.
- Mix fractions of lots of the same excipients to form a single lot.

The mixing process needs to be documented, allowing traceability to the individual batches that make up the mixing. Properly control the mixing process to ensure the uniformity of the mixed lots. Test that the mixed lot meets established standards.
These actions must be documented about their implementation details and procedures and must be approved by the person in charge (Quality Assurance Department, etc.).

POINT 17

6.5.2 Validation of Production and Service Provision (including Manufacturing support system)

Here, it is defined as “To be able to operate the manufacturing process constantly based on knowledge of process parameters, product characteristics and their interrelationships. Knowledge of the process may be based, for example, on process capability surveys, development and scale-up reports, and regular product reviews. Assess and document the impact on process capacity after making significant changes." has been added.

This addition states in the preamble that " Manufacturers do not necessarily have to perform full content validation, which is primarily done in the pharmaceutical industry, but do process validation by qualifying equipment or equipment according to risk. ", indicating the points necessary for process validation for excipient manufacturing.

POINT 18

6.5.3 Identification and traceability

To state the importance of identification and traceability, “Confirmation and traceability are regulatory requirements for raw materials, intermediates, and products. Providing documents that facilitate traceability, such as test reports, on a per-shipment basis in a manner agreed with the customer.”, followed by 6.5.3.1 Traceability, 6.5.3.2 Inspection and testing status, and 6.5.3.3 Labeling from what each package is labeled to meet quality and handling requirements. is required to be able to identify or trace manufacturing and quality.

POINT 19

6.5.5. Preservation of Product

6.5.5.1 Handling, Storage and Preservation

Regarding product storage, until now to have required temperature and humidity conditions, handling conditions, storage conditions for special raw materials, and product name labeling. "It is necessary to clearly label the contents of pharmaceutical excipients." A more explicit request for action has been added.

POINT 20

6.5.5.2 Packaging system 6.5.5.3 Delivery and Distribution

Additional requirements for packaging systems for excipients. Additional requirements have been added to avoid the risk of packaging containers affecting product quality, and to ensure product quality during the distribution process. It is especially important to avoid risks when recycling containers, and documentation and records are important.

- Documented standards based on the properties and stability of pharmaceutical excipients
- Incoming inspection and / or test method
- Anti-tampering seal (if possible)

- When reusing the container, follow a verified cleaning procedure and keep a record of cleaning / disinfection.

Regarding transporters, it is necessary to take measures to protect the transportation conditions (e.g. temperature conditions) of products (additives). It is a requirement to keep a record of cleaning according to the cleaning procedure.

7 MEASUREMENT, ANALYSIS AND IMPROVEMENT
In 7.1 General, “Manufacturers plan necessary monitoring, evaluation, and remedial measures to demonstrate that pharmaceutical excipients meet customer requirements and to ensure that they meet the quality management system of this standard. To carry out.
Manufacturers identify opportunities for improvement through research and analysis of product and process trends.” An important addition has been added for each to make this point even more thorough.

POINT 21

7.2.4.1 Laboratory Controls

The following content has been added as an important item for laboratory management as data integrity.
“Take steps to always maintain data integrity. The manufacturer shall establish procedures to ensure the integrity of the data. Maintain data traceability and make it readily available.”

In addition to the preservation of records of test results performed in the laboratory, this time, "records of test equipment and their qualification/calibration traceability" have been added. It is necessary to manage it together with the logbook of the test equipment.
As part of the management of the reagents and test solutions used, it was stipulated that the expiry date should be indicated on the container after opening.
Data Integrity requires adherence to the following principles:

Principles of ALCOA+

Attributable:	A person's record of who did what and when.
Legible:	All records must be legible at any time, indelible, and indelible. In the case of electronic records, it should be readable even if the software changes.
Contemporaneous:	Recording at the time (even when recording of time is required), including actions, events, judgments, and dates.
Original:	Whether it is on paper or electronically, the information that is first captured is the original, and in the case of a note taken and transcribed, the note is the original.
Accurate:	Equipment used must be calibrated. Records must be reviewed for accuracy and maintained for accuracy.

Complete:	Reproducibility of implementation using information.
Consistent:	Recording should be consistent according to written procedures. Change management and education are essential if changes are to be made.
Enduring:	Preservation in accordance with laws and company regulations. Create a mechanism to prevent accidental disposal.
Available:	Must be able to be quickly retrieved and presented if required.

Data integrity is as demanding of computerized systems as it is of paper records. In the case of a computerized system, who entered the system is managed by a password that belongs to everyone, and password management is a very important point. In addition, the "Audit Trail" proves that there are no discrepancies in the content recorded by the computer system and that there are no problems with the reliability of the data. It is the foundation for demonstrating completeness.

Excerpt from GAB GMP Audit Handbook[x]

POINT 22

7.2.4.3 Out-of-Specification Test Results

Previously, the statement was "Out-of-specification test results should be investigated and documented according to written procedures. The original test results should be retested only if the original test results were proven to be erroneous by investigation." It can be replaced with the result of the specimen.", It was written.

Out-of-specification test results are also called OOS (Our of Specification), and generally refer to cases in which laboratory test results are outside the specified test standards. A non-standard test result means that the sample is unsuitable, and the product is unsuitable, but the product should have been manufactured according to the prescribed procedure, and it should be verified that the test results were correct. is needed. The test method and its implementation procedure are also strictly regulated, and it is necessary to investigate the possibility that there was an error in any of the results and to make a correct judgment.

The following points were added to the procedure. The important point is to establish a procedure manual, conduct the survey according to the procedure, and document the progress and results.

The results of non-standard tests should be investigated and documented according to the procedure manual.

Only if the results of the original test are proven to be erroneous by investigation, the results of the retested specimen may be substituted for the results of the original test.

If the cause is unknown, follow the procedure below to deal with non-standard test results.

- Criteria for retesting and using the results of retested samples
- Criteria for resampling

POINT 23

7.2.4.6 Impurities

Previously, this section read, " If possible, the manufacturer should identify impurities and set appropriate tolerance limits. The permissible limits shall be based on the permissible limits and appropriate GMP considerations set forth in appropriate safety data, official statements, or other requirements. Appropriately manage the manufacturing process so that impurities do not exceed the set tolerance." "Manufacturers should perform risk assessments to determine if their pharmaceutical excipients specifications need to include testing and limitations of elemental impurities such as metal catalysts."

Many pharmaceutical excipients are extracted and purified using organic solvents, and these residual solvents are usually removed by drying. to include tests and acceptance limits for

Also, note the following points

- Types of microorganisms that may be present,
- Naturally derived raw material impurities. Mycotoxins, residual pesticides

Moreover, some manufacturing processes cannot completely exclude insoluble and visible particles. The manufacturer should keep the generation of such particles below acceptable levels based on risk assessment. is added

Elemental impurities are items that are required to be controlled as impurities based on the results of ICH Q3D. (Refer to 6.2 ICH Q3D Elemental Impurities)

Regarding elemental impurities, it is necessary to conduct a risk assessment and document whether testing for elemental impurities should be included in the specifications of pharmaceutical excipients when using metal catalysts in the manufacturing process. In the 18th revision of the Japanese Pharmacopoeia (notified on June 7, 2021), "control of elemental impurities in pharmaceuticals" was listed as a general rule. Evaluation and control of elemental impurities according to the Japanese Pharmacopoeia have begun.

If it is determined that control of elemental impurities is necessary to ensure the quality of excipients, it is necessary to take measures to ensure quality by referring to ICH Q3D. PMDA's ICH Q3 impurities[xi] are helpful.

REFERENCE

[i] PIC/S：Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme(医薬品査察協定及び医薬品査察共同スキーム)
[ii] https://www.ipec-europe.org/uploads/publications/coa-guide-2013-1536242359.pdf
[iii] https://www.ipec-europe.org/uploads/publications/20170515-gdp-guide-2017-final-1553012432.pdf
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