Distinctions between Partial Change Approval Application and Minor Change Notification

Partial Change Approval Application	Minor Partial Change Notification
Change in the principle of unit operation of critical process	Process parameter to control the quality endpoint criteria
Change in process control criteria as quality endpoint criteria	

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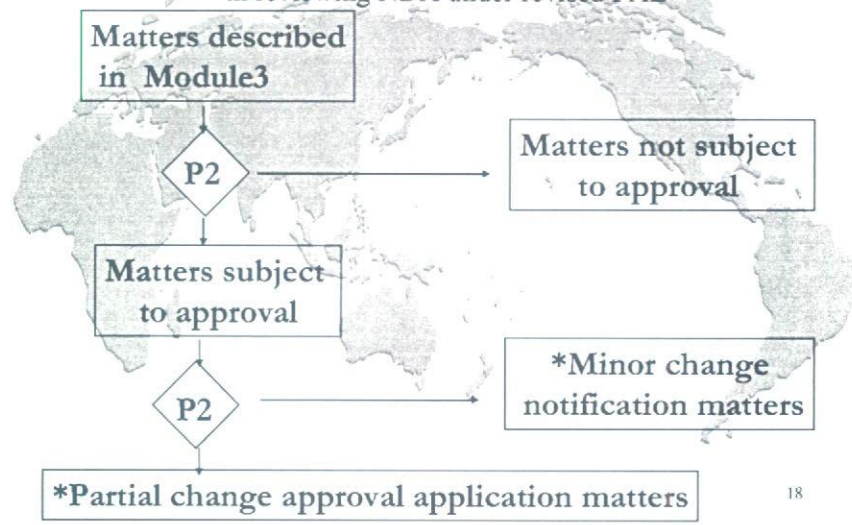
The Role of Pharmaceutical Development(P2) section -Science and Risk based- in reviewing NDA under revised PAL



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Challenges when implementing rPAL regulations with ICH Q8(-Q10)

- Baseline expectations for P.2 need to be clarified

"At minimum(identify risks and risks controlled)" expectations do not seem to be traditionally submitted in Japanese NDA. With "traditionally" submitted contents, it is difficult to sort out pre-approval matters, minor change matters.← Q8(R) reached step2

- Range for excipients as a design space: scientific basis, description in approval letter←under consideration with "approval matters" study group
- Design spaces with interacting multi-variables and with interacting unit operations:description in approval letter←see industry's creativity. Q8R helps.
- Real time release:process and facility dependence ←Need final scale data to justify. A good Quality system(Q10?) expected. Specification with test method would not go away because of need for later evaluations including generics

Role of Module 2(QoS)

- Module 2 bridges NDA Application Form (approval matters) and Module 3
- Module 2 is one of the key review documents
  - Reviewers evaluate Module 2 and then narrow down into Module 3, 4, or 5 when they need more detailed information.
  - Module 1 and 2 together with reports written by reviewers are evaluated in Pharmaceutical Affairs and Food Sanitation Council.

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Revision Mockup of Japanese QoS

- Old Version was published by Pharmaceutical Manufacturers Association of Tokyo, Osaka Pharmaceutical Manufacturers Association and Japan Health Sciences Foundation in July 2002
- Merely shows an example of description for each module 2 section and just a reference for an applicant to prepare QoS.
- Not covers all information required for each NDA, nor shows acceptance criteria for each categories.
- **NEED more description on pharmaceutical development and on justification of manufacturing process according to ICH Q8, Q9 and the revised PAL.←2006-2008 MHLW "Approval matters" study group**

Thank you for your kind attention.

Welfare and Labour Science Research in Fiscal 2005
Comprehensive Research Projects for Regulatory Science of Pharmaceutical Products and Medical Devices
Study Related to Quality Management Systems for Pharmaceutical Products and Medical Devices based on Science and Risk Management

Yukio Hiyama, Ph. D., Section Chief
Division of Drugs, National Institute of Health Sciences

GMP Guideline for Drugs and Quasi-drugs (Drug Products)

● **Study Group Members for Preparation of "GMP Guideline for Drugs and Quasi-drugs, Drug Products"** ●

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Contents page

The regulatory requirements for the manufacturing control and quality control at manufacturing sites, i.e., the minimum standards to be followed, which may accompany enforcement measures including improvement orders when a nonconformity occurs, include the following: "Ministerial Ordinance for Good Manufacturing Practice for Drugs and Quasi-drugs" (MHLW Ministerial Ordinance No. 176, 2004) (hereinafter referred to as "GMP Ministerial Ordinance for Drugs and Quasi-drugs") that was revised and issued in accordance with the revised Pharmaceutical Affairs Law that is to come into effect from April 2005, "Regulations for Buildings and Facilities for Pharmacies, etc." (MHW Ministerial Ordinance No. 2, 1961) (hereinafter referred to as "Regulations for Buildings and Facilities), and the notification "Concerning Establishment and Amendment/Abolition of Ministerial Ordinance and Notifications Related to Manufacturing Control and Quality Control (GMP/QMS) for Pharmaceuticals and Medical Devices in association with the enforcement of the laws related to partial revisions of the Pharmaceutical Affairs Law and Regulations for Agencies of Blood Collection and Donation" (MHLW-PFSB-CND Notification No. 0330001, dated March 30, 2005) (hereinafter referred to as "Enforcement Notification"), in which the interpretations, etc. of the aforementioned regulations are shown, and other related notifications. However, beyond such compliance with the regulatory requirements, further efforts for continuous improvements are required for actual implementation of manufacturing control and quality control of drugs and quasi-drugs (limited to those to which the GMP Ministerial Ordinance for Drugs and Quasi-drugs is applied; the same is applied in the following) by incorporating voluntarily and positively the ICH Q7 Guideline (hereinafter referred to as "Q7") and requirements shown in the standards and guidance adopted in Western countries, as well as other control methods on which a global consensus has been reached with the progress of knowledge and technology.

1. Introduction

1.1 Objective

In regard to general matters on manufacturing control and quality control of drug products (except for matters related to production of specified drug products such as sterile drugs and biological-origin drugs, etc.), this guideline has been prepared with the

intention of providing, as specifically as possible, control methods that are not clearly specified as requirements in the GMP Ministerial Ordinance for Drugs and Quasi-drugs and other related laws, and that need to be voluntarily addressed according to current knowledge, etc. In this guideline, the word "should" indicates recommendations for applying the relevant matters unless there are alternative control methods that can provide equivalent levels of manufacturing control and quality control. This guideline is not intended to cover safety and health for personnel or environmental protection.

2. Quality Management System

2.1 Principles

2.10 Each manufacturer should establish, document, and implement an effective system for supervising quality control. To establish and maintain a quality management system, control supervisors and personnel engaging in manufacturing operations should be actively involved.

2.11 The components of the quality management system should encompass the activities necessary for manufacturing control and quality control of drugs or quasi-drugs, as well as organizations and other required resources to implement the activities. In establishing the quality management system, all quality-related activities should be defined and documented.

2.12 The quality unit defined under the provision of Article 4, Paragraph 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs (including cases to which Article 32 is applied; the same hereinafter) can take the form of multiple divisions or be a single individual, depending upon the size and structure of the organization.

2.13 All quality-related activities should be documented at the time they are performed, and the documents should be archived.

2.14　Any deviation from established procedures should be documented and explained, and the documents should be archived. Critical deviations for which impacts on product quality cannot be completely ruled out should be handled as defined under the provision of Article 15, Paragraph 1-c of the GMP Ministerial Ordinance for Drugs and Quasi-drugs.

2.15　Neither the decision for release from manufacturing sites defined under the provision of Article 12, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs (hereinafter referred to as "release decision"), nor the use of products, etc., and packaging/labeling materials in subsequent processes should be implemented before completion of evaluation by the quality unit, unless there are appropriate systems in place to allow for such use (e.g., release from manufacturing sites under quarantine or the use of products or packaging/labeling materials pending completion of evaluation).

2.2 Responsibilities of Quality Unit

2.20　The quality unit should be involved in all quality-related matters.

2.21　The quality unit should appropriately review, confirm and approve all quality-related documents.

2.22　The main responsibilities of the quality unit should not be delegated in order to preserve the independence of the unit. These responsibilities should be documented, and should include but are not necessarily limited to:

1)　Establishing and maintaining a system for deciding release or rejection for receipt or use of products and packaging/labeling materials in subsequent processes;

2)　Reviewing all manufacturing instructions, completed batch records and laboratory control records of critical processes for the lots concerned when the

release from manufacturing sites is decided[1];

3) Approving the manufacturing control standard code, hygienic control standard code, and master manufacturing instructions;

4) Approving all procedures influencing product quality;

5) Confirming the results of self-inspections;

6) Approving contract matters related to quality aspects concluded with suppliers of raw materials (except for the contracted matters concluded between Licensed Marketing Approval Holders and suppliers);

7) Confirming the plans and results of validation reported as defined under the provision of Article 13, Paragraph 1, Item 2 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs[2];

8) Confirming whether an efficient system is used for periodic inspections and maintenance of important buildings and facilities, in addition to those related to laboratory testing/inspection;

9) Confirming whether stability data, from which the date of retest or expiry for use and storage conditions of products can be identified, are available, when necessary.

10) Reviewing product quality (refer to Chapter 2.5); and

11) Confirming the status of implementation of education and training.

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1 With respect to the provision of Article 10, Paragraph 9 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, this guideline stipulates that the quality unit should review whether manufacturing control is appropriately implemented from the standpoint of a third party.

2 In this guideline, this is stipulated considering that approval of a validation plan and validation results is originally the responsibility of the quality unit, and that it is necessary for the quality unit to be actively involved in validation.

2.3 Responsibilities of Production Unit

The responsibilities of the production unit should be documented, and should include but are not necessarily limited to:

1) The manufacturing instructions defined under the provision of Article 10, Item 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should be prepared in accordance with the product master formula, manufacturing control standard code and hygiene control standard code, as well as the review, approval and distribution of the completed manufacturing instructions;

2) Reviewing batch records of all production lots to ascertain whether the instructions made for the relevant lots are completed, and ensuring that the batch records are appropriately prepared, signed and sealed[3] ;

3) Making sure that all deviations noted at production are reported to the person predesignated under the provision of Article 15, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, and that the results of the deviation assessments made by the designee are confirmed by the quality unit;

4) Confirming hygiene of buildings and facilities defined under the provision of Article 10, Item 6 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs; while making sure that the relevant buildings and facilities are sanitized and sterilized when necessary;

5) Making sure that validation plans and reports that have been prepared by persons predesignated under the provision of Article 13, Paragraph 1 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs are reported to and reviewed and approved by the quality unit;

6) Involving persons predesignated under the provision of Article 14 of the GMP

[3] A seal that has been registered for the manufacturer should be used, and it is necessary to establish a control system for use of the relevant seal (locking control by the user, or always carrying the seal, etc).

Ministerial Ordinance for Drugs and Quasi-drugs in assessing impacts of changes in manufacturing procedures on product quality where appropriate; and

7) Making sure that new and, when appropriate, modified facilities and equipment are qualified, in addition to the validation-related operations defined under the provision of Article 13 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs.

2.4 Self-inspection

2.40 In addition to the self-inspection for manufacturing sites defined under the provision of Article 18 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs, self-inspection across the entire operation of the manufacturer should be performed periodically in accordance with the approved schedule.[4]

2.41 Self-inspection results and the required measures to be taken should be brought to the attention of control supervisors. The relevant measures should be completed in a timely and effective manner.

2.5 Product Quality Review

2.50 Regular quality reviews of the products should be conducted by the quality unit with the objective of verifying the consistency of the manufacturing process (hereinafter referred to as "product quality review"). The product quality review should be conducted at least annually, and documented and archived. In addition to the periodic reviews of process control, reviews of at least the following matters should be included in the product quality review:

1) A review of results of critical matters related to acceptance testing/inspection of

[4] In addition to the self-inspection defined under the GMP Ministerial Ordinance for Drugs and Quasi-drugs, quality assurance at manufacturing sites may be implemented as part of the overall quality assurance at the manufacturer. For example, handling of quality information, recall handling, contracts between outsourcers and trustees, and confirmation whether self-inspection has been performed appropriately are included in the operations of self-inspection.

raw materials and packaging/labeling materials, and testing/ inspection related to in-process control, and testing/inspection of products;

2) A review of all batches or control units that failed to meet established specification(s);

3) A review of all critical deviations or non-conformances and related investigations;

4) A review of any changes carried out related to the processes or analytical methods;

5) A review of results of the stability monitoring program[5];

6) A review of quality-related returns, complaints and recalls; and

7) A review of adequacy of corrective actions.

2.51 The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. When corrective actions are required, the reason should be documented, and the documents should be archived. Agreed corrective actions should be completed in a timely and effective manner.

2.6 Technology Transfer[6]

2.60 There are two types of technical transfer including that from the R&D to

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5 This stability monitoring program includes both time-associated stability evaluation by stability monitoring tests and periodic confirmation of product quality (post-marketing stability evaluation).

6 The consistency in product quality between the pivotal manufacturing batch in the development stages and the actual manufacturing batch (validated batch) is important for technical transfer from R&D to production. The same has been described in the Q7 12.52. The pivotal manufacturing batch refers to that related to investigational drugs used for phase III clinical studies or biological equivalence studies, and that related to the samples to be used for stability tests for approval application. The aim and importance of assurance of product quality consistency before and after technical transfer should be the same also in the post-marketing technical transfer for contract manufacturing.

production and that after commercialization. In each case, technical information (including quality-related information) subject to the transfer should be documented, and the necessary information should be shared between the parties involved in the transfer.

2.61 The information (documents) to be shared includes the following as examples:

1) Product Development Report: The document that summarizes the manufacturing technique-related information obtained by research and development, which includes the quality design of drug products, specifications of raw materials and packaging/labeling materials and laboratory testing methods, as well as the justification for establishing these matters.

2) Technical transfer documents: A series of documents including product specifications that describe the manufacturing method and test methods of the drug product subject to the transfer, as well as the technical transfer plan prepared on the basis of product specifications.

2.62 The responsibilities of the organization and the management system related to the technical transfer should be clarified for both the transferring party and the receiving party.

2.63 All the matters related to technical transfer should be approved or confirmed by the quality unit.

2.64 The consistency of manufacturing quality before and after the relevant technical transfer should be confirmed at the final step of the technical transfer by the process validation, etc.

3. Personnel

3.1 Personnel Qualifications

3.10 All the employees involved in the manufacturing control and quality control of drugs or quasi-drugs should understand GMP.

3.2 Education and Training

3.20 An education and training program should be prepared for each task of the personnel who are to receive the education and training. The education and training program should be prepared by the production unit, quality unit and other related divisions, and it should be approved by the person who has been predesignated under the provision of Article 19 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs (hereinafter referred to as "Education and Training Manager"). In addition, the education and training program should be regularly reviewed.

3.21 The Education and Training Manager should report the implementation status of the education and training program to the quality unit and this should be confirmed by the quality unit.

3.22 Special education and training should be given to the employees who work in the areas where contamination would cause problems; for example, the clean area, aseptic area, and working rooms for the operations related to products that are easily scattered or spilt and could cause anaphylactic reactions if present even in trace amounts, or those having major impacts on other products through cross-contamination.

3.23 Visitors or employees who have not received any education or participated in a training program should not be allowed to enter the working areas and the areas for testing operations (hereinafter referred to as "testing areas"). In unavoidable

circumstances, these persons should be appropriately instructed, such as by notifying them of precautions in advance.

3.3 Personnel Hygiene Control

3.30 Personnel should wear clean work clothing suitable for the operations in which they are involved, and the clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand and arm coverings, should be worn when necessary, to protect products from contamination.

3.31 Personnel should avoid direct contact with objects that may affect product quality wherever possible.

3.32 Smoking, eating, and the storage of food should be restricted to certain predesignated spaces separate from the working areas.

3.33 Personnel having health conditions that may have impacts on product quality (for example, having an infectious disease or wounds, etc.) should not be engaged in manufacturing operations. Any person shown by medical examination or supervisory observation to have an apparent illness or open lesions should be excluded from operations where the health condition could adversely affect product quality until the condition is rectified or qualified medical personnel determine that the person's inclusion would not jeopardize product quality.

4. Buildings and Facilities

4.1 Design, etc. of Buildings and Facilities

4.10 Buildings and facilities should be designed so that mix-ups, contamination or cross-contamination of the flow lines of products and packaging/labeling materials, as well as of personnel, in manufacturing sites can be avoided.

4.11 There should be defined areas in manufacturing sites for the following operations, and a control system should be established for these operations[7]:

- Receipt, identification, sampling, quarantine and pending release of raw materials and packaging/labeling materials;
- Storage of rejected products and packaging/labeling materials that have been separated from accepted ones, for example, in locked containers;
- Quarantine of recovered or returned products;
- Aseptic operation (only in the case of manufacturing of aseptic preparations)
- Storage of products pending release or rejection
- Storage of products where it has been decided to release them from manufacturing sites;
- Storage of products that are not allowed to be released from manufacturing sites;
- Testing and inspection; and
- In-process control testing and inspection (when appropriate)

4.12 Washing facilities defined under the provision of Article 6, Item 3 of the Regulations for Buildings and Facilities should be provided with a hot water supply as appropriate. In addition, soap or detergent, air driers or single service towels should be provided. The hand washing and toilet facilities should be separated, but easily accessible, from manufacturing working spaces. When necessary, an appropriate facility for taking showers should be installed.

4.13 In principle, testing and inspection laboratory areas should be separated from manufacturing working spaces. However, testing and inspection laboratory areas are allowed in the manufacturing working spaces provided that the manufacturing operations and products are not adversely affected, and those related to in-process control are allowed in the manufacturing working spaces provided that the precision of the relevant laboratory testing/inspection is not adversely affected. In addition, testing and inspection laboratory areas can be

[7] When decision on release to the market or rejection is made at manufacturing sites, it is necessary to specify the place of storage of the relevant products. Moreover, an isolation area, etc., separate from the specified area, should be considered as a measure for prevention of cross-contamination and chemical hazards, as appropriate.

located in the manufacturing working spaces provided that manufacturing operations and products are not adversely affected.

4.14 The testing and inspection laboratory rooms should be appropriately designed for the operations to be conducted there. Appropriate management should be made such as providing a sufficient space to prevent mix-ups, contamination and cross-contamination. A sufficient and appropriate space for storage of collected samples and records should be provided.

4.2 Buildings and Facilities for Utilities

4.20 Appropriate monitoring should be performed to check whether all the utilities (e.g., steam, gases, compressed air, etc.) that may affect product quality conform to the predefined specifications. Necessary measures should be taken when data have exceeded the allowable limits.[8]

4.21 Buildings and facilities necessary for adequate ventilation, air filtration and exhaust should be provided. These building and facilities should be designed and constructed to minimize the risks of contamination and cross-contamination.

4.22 If there are no impediments to air recirculation in the manufacturing working spaces and in the testing and inspection laboratory areas, appropriate measures should be taken for the buildings and facilities to minimize the risks of contamination and cross-contamination.

[8] The control specifications for steam are related to contamination by foreign matter, particulate matter, and pipe cleaning agents, etc. In addition, control specifications for gases and compressed air include oil content, foreign matter, particulate matter, and those related to dew points. In any case, control items and control specifications (limits) are set in consideration of product quality.

4.23　Permanently installed piping should be identified in an appropriate manner (for example, labeling of individual lines, etc.). Piping should be located to avoid the risks of product contamination.[9]

4.24　Drainpipes should be of an adequate size and should be provided with an air break device[10] and other suitable devices to prevent backward flow, when appropriate.

4.3 Buildings and Facilities for Process Water

4.30　It should be demonstrated that process water is suitable for its intended use. When any water outside the specifications listed in the compendium, such as the Japanese Pharmacopoeia, is used, internal specifications with valid grounds should be established and documented.[11]

4.31　Unless otherwise justified, process water should at least meet the water quality standards based on the Japanese Pharmacopoeia, or the Tap Water Law or the World Health Organization (WHO) guidelines for drinking water quality.

4.32　If the purity level of process water is insufficient to assure product quality, and more strict biological and physicochemical control limits are required, appropriate specifications should be established for necessary items among physicochemical characteristics, total microbial count[12], count of specified microorganisms and endotoxin level.

9　Piping is identified, normally, by direct labeling or by attaching a tag, etc. to it. With regard to insulated piping, when removal of the identification labels, etc. is unavoidable for the operations of replacement of the insulating materials, identification by labeling should be made immediately after completion of the relevant operations.

10　"Air break device" is denoted as a device that is aimed at prevention of backflow from drains; for example, it corresponds to an air break, etc. equipped with a funnel for pressure reduction to atmospheric level.

11　It is desirable to identify process water for which internal specifications have been established by use of such terms as "ultrafiltration water" or "ion-exchange water," to avoid mix-ups with the water to be used for drug manufacturing (purified water, water for injection, etc.) listed in the compendium, such as the Japanese Pharmacopoeia.

12　(Reference) According to the USP and EP specifications, total microbial count is specified as 10 cfu/100 mL for water for injection (excluding water that is sealed in an air-tight container and is specified as sterile), while it is specified as 100 cfu/mL for purified water.

4.33 When water is purified to achieve a defined quality for use in a manufacturing process, the purification process should be verified and monitored by establishing appropriate control limits; for this purpose, suitable buildings and facilities should be provided.

4.4 Sewage and Waste Materials

4.40 Sewage and waste materials from manufacturing sites (including the sewage or waste materials formed as by-products in the manufacturing process) should be disposed in a sanitary, safe and timely manner. Containers and/or pipes for waste materials should be clearly distinguished from those for products and packaging/labeling materials by identification labeling.

4.5 Sanitation and Maintenance

4.50 The items defined under the provision of Article 6, Paragraph 4 of the GMP Ministerial Ordinance for Drugs and Quasi-drugs should include the responsibilities and the control system related to hygiene control. Plans related to the cleaning of buildings and facilities, and matters related to the use of buildings and facilities, and chemicals, etc., should be included in the hygiene control standard code defined under the provision of Article 8, Paragraph 1 of GMP Ministerial Ordinance for Drugs and Quasi-drugs.

4.51 Matters related to the use of the chemicals, such as rodenticides, insecticides, fungicides, disinfectants, and cleaning agents, etc. should be included in the hygiene control standard code.