

Letter from PFSB/ELD

22nd October 2001

To: Public Health Bureau
Prefectural Government

From: Evaluation & Licensing Division,
Pharmaceutical & Food Safety Bureau,
The Ministry of Health, Labour and Welfare

On the Q&A to the Guideline for Common Technical Documents

The Guideline for Common Technical Document (CTD) has been notified to the Director of Public Health Bureau, Prefectural Government, in the Notification entitled as “On Organization of Application Dossier Appended to New Drug Application (NDA) for Approval” (PMSB/ELD Notification No. 899 dated June 21, 2001, hereinafter referred to as “the CTD Guideline”). This letter comprises Q&A, for your operational reference, to the CTD-Quality Guideline provided as *Annex 3* to the CTD Guideline.

This Q&A will be subject to be revised based on newly coming information.

ATTACHMENT

Q&A on the CTD-Quality Guideline

Overall

Q1: There are items clearly specified to be applied to new chemical entities (NCE) and/or biotechnological/biological products (Biotech) and those which are not specified. How should the each item be applied?

A1: Unless otherwise specified or if both NCE and Biotech are stated, the item should be applied for both NCE and Biotech. If only Biotech is stated, the content is the additional information for Biotech.

Q2: Is the CTD-Quality Guideline (hereinafter referred to as “this Guideline”) attached as Annex 3 to the Notification (PMSB/ELD Notification No. 899 dated June 21, 2001, hereinafter referred to as “CTD Guideline”) same as the ICH agreement on CTD-quality? Or, are there any additions or deletions made for Japan?

A2: There are no additions or deletions made for Japan.

Q3: No relevant guidelines are provided for some items in Module 3 of CTD. To what extent should information be provided for these items?

A3: For these items that have no relevant guidelines, the information which the applicant considers necessary should be described in reference to the explanation presented in this Guideline.

Q4: In foreign countries, confidentiality is secured in regulations by means of Drug Master Files (hereinafter referred to as “DMF”), etc. for the confidential information of the company, such as manufacturing methods of drug substances and drug products. It may be difficult to provide these information in Module 2 and/or 3 especially in the case when drug substances etc. are imported from foreign countries. How should these information be dealt with?

A4: The information on drug substances has been essentially subject to be reviewed irrespectively of type of NDA. Thus, the documents for the essential information should be submitted. Applicants may consult for each given case, just as previously, if there are any particular reasons in the case of importing drug substance from foreign countries.

- Q5: Is even the confidential information of the company, such as manufacturing methods for drug substances or drug products, subject to be disclosed after approval?
- A5: The confidential information of the company has not been and will not be made public in principle.
- Q6: It is said that the contents in Module 2 and 3 are dealt with as “matters subject to approval” in foreign countries. Is it right to understand that, in Japan, Module 2 and 3 constitute documents required for regulatory review but are not dealt with as “matters subject to approval”?
- A6: The contents provided in the NDA application form are dealt with as “matters subject to approval”, in Japan. It is not necessary to file an application for partial changes to “matters subject to approval” insofar as there is no change to them. Matters necessary for quality assurance such as manufacturing methods, that are provided in Module 3 and/or other Modules, should be reflected in the NDA application form.
- Q7: With regard to the passage: “Matters necessary for quality assurance, such as manufacturing methods, that are provided in Module 3 and/or other Modules” in the A6 above, is it possible to define these items, etc.?
- A7: It is impossible to define the necessary items uniformly since those items vary on case-by-case basis. The applicant should set those items based on scientific rationales, as have been the case, and provide their justification.
- Q8: It has been required that the contents in the attached documents to NDA should be supported by the data. However, Module 3 would contain some items that differ to some extent from those conventionally required, such as flow diagram of manufacturing methods, formulation development, etc. Is it right to understand that the supporting data are not always necessary for each content in the Module 3?
- A8: For the parts pointed out in Q8 as well, supporting data that the applicant judges to be valid to those parts are necessary in principle. However, it has conventionally been left to the judgment of the applicant what evidential documents should be attached to the NDA dossier, and supporting data are not necessarily requested if there is a proper reason.

Q9: How should the cross-reference in the NDA dossier be expressed?

A9: If the NDA dossier is composed of separate volumes, the table of contents should include the volume number (e.g., Vol....). A concise description for cross-references should be provided so that the cited contents can be precisely traced. For example: See 3.2.S. [name of drug substance] 3.2.S.4.4 Batch Analyses, Table 3.2.S. [name of drug substance] 3.2.S.4.4-1.

Scope of the Guideline

Q1: The scope of application of this Guideline comprises the drugs under the scopes of application in ICH Guidelines Q6A [NCE] and Q6B [Biotech]. On the other hand, in the Section 2 of the CTD-Guideline, it is stipulated that the CTD-Guideline shall apply to the NDA dossier for prescription drug. Is this Guideline to be also applied to drugs not subject to ICH Guideline Q6A or Q6B in Japan?

A1: This Guideline states in “Scope of the Guideline” that this format may also be appropriate for certain other categories of products (categories of product outside the scope of the ICH Guidelines Q6A and Q6B). In Japan, this Guideline shall apply in principle to these drugs as well. In other words, this Guideline shall apply to NDA dossiers of prescription drugs. However, NDA dossiers of prescription drugs corresponding to categories of (7), (7-1) and (8) addressed in the Appendix 2-1 of the Notification entitled as "On new pharmaceuticals applications"(PMSB Notification No.481 dated April 8, 1999) may also be handled as have been done to date. Consult for each case if there is any difficulty.

3.2.S DRUG SUBSTANCE

Q1: If a drug product contains two or more drug substances, how should the documents of each drug substance be compiled?

A1: If a drug product contains two or more drug substances, the documents of S sections should be compiled for each drug substance.

Examples: 3.2.S Drug Substance [Name of the substance A]

3.2.S Drug Substance [Name of the substance B]

Q2: For drug substances listed in the Japanese Pharmacopoeia (hereinafter referred to as “JP”) or other compendia and also the drug substances whose specifications have been allowed to be provided in the NDA application form in the same manner as those substances listed in JP (i.e., drug substances included in the Japan Pharmaceutical Codex, Minimum Requirements for Antibiotic Products of Japan, etc.), is it acceptable to describe information of 3.2.S.1.1 Nomenclature: the compendial name of the drug substance, name of the compendium, etc., 3.2.S.1.2 Structure, 3.2.S.2.1 Manufacturer(s), and 3.2.S.6 Container Closure System?

A2: Yes. However, if any additional testing item(s), modification of acceptance criteria, etc. are involved, the relevant information should be provided in an appropriate manner.

Q3: Regarding the NDA dossier for drugs under the categories of new combination prescription drugs, drugs with new routes of administration and drugs with new dosage forms, to what extent should information on the drug substance be provided if the drug substance have already been approved?

A3: Information on 3.2.S.2.1 Manufacturer(s) (with the license number) should be provided in principle. For any other information, as much information as GAIYO or Module 2 for the approved drug substance should be attached.

3.2.S.1 General Information

3.2.S.1.3 General Properties

Q1: What is the relationship between the description in this section and that in 3.2.S.3 Characterization?

A1: Characteristic properties should be described in tabulated summary concretely with numeral data, etc. in this section, whereas physicochemical properties should be described in detail in 3.2.S.3. If tabulated summary is difficult, a concise description

should be provided, as appropriate.

3.2.S.2 Manufacture

Q1: When information on a pilot scale manufacture is provided in Module 3 in the NDA dossier at the time of NDA application, is it acceptable that detailed information on a commercial scale manufacture at the time of licensing application is inconsistent in part (e.g., operational parameters, performance parameters, etc.) with what are described in Module 3 in the NDA dossier?

A1: A pilot scale manufacture should, in principle, reflect the commercial scale manufacture. Nevertheless, this does not necessarily apply if there exist an appropriate explanation that justifies the partial change in information of Module 3 at the time of NDA and the data to demonstrating that a product equivalent/identical in quality to the approved drug substance and drug product has been obtained.

3.2.S.2.1 Manufacturer(s)

Q1: What type of manufacturers does the phrase “each manufacturer, including contractors,” mean?

A1: It means manufacturers including contractors who manufacture the drug substance.

Q2: Should the information on manufacturers for the raw materials, other materials, and starting materials be provided?

A2: The term “manufacturer” used in this section does not include manufacturers for the raw materials, materials, and starting materials.

3.2.S.2.2 Description of Manufacturing Process and Process Controls

(1) NCE

Q1: To what extent should the manufacturing method be described? Is the definition of “starting materials” as used in this Guideline same as that of “starting material” in ICH Guideline Q7A ?

A1: The description should cover from the process affecting the quality of the drug substance with appropriate raw materials or intermediates as the starting material. There is some cases where the definition of “starting materials” used in this Guideline is not same as that of “starting materials” used in ICH Guideline Q7A.

- Q2: What does “representative batch scale for commercial scale manufacture” mean?
- A2: It means the pilot or greater scale manufacture in principle.
- Q3: Is the information provided in this section “matters subject to approval”?
- A3: This section is intended to explain how the drug substance is manufactured and how the process control is performed. “Matters subject to approval”, on the other hand, are contents provided in the NDA application form. Same as previously, if there is any change in those contents, an application for partial change should be filed.
- Q4: It is considered that process control items, control values etc. cannot be finally determined unless they are validated in commercial scale manufacture. To what extent should the description be required?
- A4: At the time of NDA application, those items and values established on a pilot or greater scale manufacture reflecting commercial scale manufacture should be provided in Module 3. What are not directly related to “matters subject to approval”, such as action limits etc., may be internally changed as appropriate in accordance with scale up, accumulation of manufacturing experiences, etc.
- Q5: For description of “equipment”, is it necessary to provide the name(s) of manufacturer(s) so that the equipment can be specified?
- A5: Information explaining what the equipment is like (e.g., production capability) is acceptable.
- Q6: What are the difference between the description to be provided in this section and that to be provided in the NDA application form?
- A6: In this section, a sequential procedure of the manufacturing process should be provided. In the NDA application form, a description should be given of the critical processes, process controls, etc. for quality assurance of the product as appropriate customarily. Therefore, some of contents in this section, for example, quantities of starting materials and intermediates, yield ranges, quantities of reagents, quantities of raw materials, solvents, catalyst and reagents, detailed operating conditions, etc. need not be included in the NDA application form.

(2) Biotech

Q1: This guideline states “Cell Culture and Harvest:should include all steps (i.e., unit operations) and intermediates”. Does the term ”all steps” mean the steps regarded as one process?

A1: As it means unit operations of varying types, it cannot be regarded as one process.

Q2: What does the term “operational parameters” in “Cell Culture and Harvest:(including in-process tests and operational parameters,)” mean concretely?

A2: It means operational parameters to be controlled in the process. The examples of operational parameters are temperature, dissolved oxygen, etc.

Q3: How should the term “intermediate” in “Cell Culture and Harvest:, intermediates” be presented?

A3: Intermediates should be explicitly indicated in a flow diagram. The acceptance criteria, etc. should be presented in 3.2.S.2.4.

Q4: What is meant by the term “holding times” in “Purification and Modification Reactions:.....holding times”?

A4: The holding time in chromatograms is one of examples.

3.2.S.2.3 *Control of Materials*

Q1: What is meant by the term “characterisation” in “For biologically-sourced materials, this can include information regarding the source, manufacture, and characterisation” and to what extent should information be provided?

A1: Information on physicochemical, biological and immunochemical characteristics, etc. that can properly indicate characteristics required as materials for manufacture should be provided. The level of detail required for the information depends on the degree of the impact on the quality of drug substance.

Q2: Regarding materials, is such a material as nitrogen gas used in the manufacture also subject to the description in this section?

A2: It is also subject to the description if it impacts on the quality of the product.

3.2.S.2.4 *Controls of Critical Steps and Intermediates*

Q1: What processes does the term “critical steps” denote?

A1: They are considered as the steps critical for the quality assurance of the product.

Q2: Does the term “intermediates” denote all the intermediates that are isolated during the manufacturing process?

A2: Yes. The quality and control method of intermediates should be established appropriately in light of considering their positioning in quality assurance of drug substance (see Q3).

Q3: Are action limits and specification that assure proper controls of critical steps and intermediates regarded as “matters subject to approval”?

A3: Action limits may be internally controlled in the manufacture and need not be described in the NDA application form. Specification should be described as “matters subject to approval” in the NDA application form, as is the case with specification for drug substances and drug products.

3.2.S.2.5 Process Validation and/or Evaluation

Q1: Is it necessary to both process validation and process evaluation for aseptic processing and sterilization?

A1: If the validation is possible, the process validation should be described. If validation is impossible, the process evaluation should be described.

3.2.S.2.6 Manufacturing Process Development

(1) NCE

Q1: What are “the significant changes made to the manufacturing process and/or manufacturing site”?

A1: A change to the manufacturing process that is considered to impact on the impurity profile is one of examples.

(2) Biotech

Q1: What does the passage: “Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies” mean?

A1: It means that explanation may be made with cross-reference to nonclinical or clinical study data as required, in evaluating the potential of the change to impact on the quality.

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification

Q1: Is it right to understand that the content in this section is the same as specification described in NDA application form?

A1: A tabulated summary of specification(i.e., testing items, analytical procedures, and acceptance criteria) should be provided here. In the NDA application form, the information provided in 3.2.S.4.1 and 3.2.S.4.2 should be described.

3.2.S.4.2 Analytical Procedures

Q1: To what extent should information be provided?

A1: The analytical procedures described under “Specification” in the NDA application form should be provided.

3.2.S.4.3 Validation of Analytical Procedures

Q1: Description of validation of analytical procedures is required. We would like to confirm that the analytical procedures to be described are only those for the drug substance. The analytical procedures described in the documents attached to NDA application form include analytical procedures for reference standards, etc. Is it right to consider that those analytical procedures are not necessary here?

A1: The validation relevant to the analytical procedures in 3.2.S.4.2 should be described for this section. Information on other analytical procedures should be provided in appropriate sections as necessary.

3.2.S.4.4 Batch Analyses

Q1: Should information on all batches be described?

A1: The analytical results on all batches used in nonclinical studies (e.g., toxicity studies), clinical studies, stability studies, establishment of specification, etc. should be summarized in this section of the document attached to NDA application form. It is more convenient that batch numbers, manufacturing scale, manufacturing methods, manufacturing site, purpose of use, testing items, test results, analytical procedures, etc. are given in the tabulated summary. Such documents as certificate of analysis covering these items may also be acceptable. In that case the format in which the results are provided should be easy to review.

3.2.S.4.5 *Justification of Specification*

Q1: Is it right to describe in this section the reason(s) why the testing items and analytical procedures are not adopted in “Specification”, where appropriate?

A1: Yes.

Q2: Is it right to describe in this section the data from studies conducted for establishing the specifications?

A2: Yes. However, establishment of the specification should be based on data of the batches used for the nonclinical studies, clinical studies, stability studies, etc. described in 3.2.S.4.4.

3.2.S.5 **Reference Standards or Materials**

Q1: Should the specification for reference standards or materials be provided?

A1: Refer to the texts and glossary in ICH Guidelines Q6A and Q6B.

Q2: What are reference materials?

A2: A clear definition is given of reference material in ICH Guideline Q6B. It means an in-house reference material. The “in house primary reference material” and “in-house working reference material” prescribed in ICH Guideline Q6B is to be used at the time of NDA for a drug containing with new active ingredient(s), because international or domestic reference standards are not usually available at that time. In case international or domestic reference standards are available, they are regarded as “reference standards”.

Q3: For related substances, internal standards, reagents, etc. which are not listed in compendia but are used in the specification, is it right to describe them in this section?

A3: They should be described at the end of 3.2.S.4.2 Analytical Procedures.

3.2.S.6 **Container Closure System**

Q1: To what extent should information be provided?

A1: A description of the shape/form, material(s), etc. should be provided where appropriate.

Q2: What compendia should be applied?

A2: Such compendia as JP are applicable to container closure systems.

Compendial methods will include, for example, Test of Glass Containers for Injections, Test of Plastic Containers for Pharmaceuticals, and Test of Rubber Closure for Aqueous Infusions in the JP.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

Q1: What does the passage: “The summary should include results from forced degradation studies and stress conditions.” mean?

A1: Not only results of long-term storage tests but also results of all relevant studies conducted for the application (long-term storage tests, accelerated tests, stress tests) should be summarized.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

Q1: What does the passage: “The post-approval stability protocol and stability commitment should be provided” mean?

A1: A description of the protocol and handling of retention of the data actually obtained should be given in accordance with ICH Guidelines Q1A(R) and Q5C. This is also applied to 3.2.P.8.2 for Drug Product.

3.2.S.7.3 Stability Data

Q1: What does the passage: “Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative” mean?

A1: Results of the stability studies conducted may be summarized in a comprehensive format. For example, tabulation of all analytical items, a graphical illustration of changes in content, etc. may be provided.

3.2.P.1 Description and Composition of the Drug Product

Q1: What does the term “if applicable” mean in the passage: “Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable, should be provided”?

A1: A description should be provided in such an instance where the type(s) might affect the quality (e.g., hygroscopicity) of the drug product.

Q2: What does the passage: “compendial monographs or manufacturer’s specifications” mean?

A2: For raw materials listed in the JP or the drug substances whose specifications have been allowed to be provided in the NDA application form in the same manner as those substances listed in JP (i.e., raw materials included in the Japan Pharmaceutical Codex, Japan Pharmaceutical Excipients, etc.), “JP”, “JPC”, etc. may be stated. For raw materials which are not listed in such compendia, “Manufacturer’s specifications” may be stated.

Q3: What should be provided in the Item “Accompanying reconstitution diluent”?

A3: The information on the components, amount, specifications, etc. of the accompanying reconstitution diluents should be provided.

3.2.P.2 Pharmaceutical Development

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

Q1: What does the passage: “Results from comparative *in vitro* studies (e.g., dissolution) or comparative *in vivo* studies (e.g., bioequivalence) should be discussed when appropriate” mean?

A1: In the event where there is any difference between the formulation used in clinical studies, etc. and that described in 3.2.P.1, it should be discussed here that these drug products are equivalent and identical. For the discussion *in vitro* studies and/or *in vivo* studies may be required. In such a case, the discussion should be carried out with reference to results of those studies.

Q2: In case the formulation has been changed in the development, where should results of *in vitro* studies (e.g., dissolution) and/or *in vivo* studies be described?

A2: The results of the dissolution study should be described in this section. The results of *in vivo* study should be provided in Module 4 or Module 5 while an explanation should be given, referred to those results in this section if applicable.

3.2.P.2.2.2 Overages

Q1: Is it right to understand that the term “overage” means a target quantity set over the labeled quantity?

A1: Yes.

3.2.P.2.4 Container Closure System

Q1: What types of container correspond to the category subject to discussion of “safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product)”?

A1: In general, there would be no problem for safety of materials of construction. It will be acceptable to describe briefly that the system has no effect upon the human body. As the containers requiring description of performance, syringe-type kit products may be included.

3.2.P.3.1 Manufacturer(s)

Q1: What should be provided in the case of NDA to import a drug?

A1: The importer should provide description of the manufacturing facilities of exporters.

Q2: What does the term “responsibility of each manufacturer” mean?

A2: Such matters as shared processes of production between a contractor and a contractee correspond to this category in the case of domestic manufacturing.

3.2.P.3.2 Batch Formula

Q1: To what extent should “reference to quality specifications/standards” be described?

A1: “JP”, “JPC”, “manufacturer’s specifications”, etc. should be described (refer to 3.2.P.1 Description and Composition of the Drug Product, Q2).

Q2: Does the “all components of the dosage form” include, for example, such component as water?

A2: Yes. All components of the dosage form to be used in the manufacturing process should be listed.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

Q1: What are “process controls”?

A1: “Process controls” are measures to control manufacturing process in order to assure the quality and consistency, complementary to the specification of the drug product. A typical example of the process control is the in-process control testing.

Q2: What does the passage: “Associated numeric values can be presented as an expected range” mean?

A2: The applicant may use a range for the target of process control in order to ensure the control of quality of products in the manufacturing processes. In the case of NDA with pilot scale data, however, provisional (estimated) values may be presented instead since it is impracticable to completely estimate the parameters on a commercial scale manufacture. What are not directly related to “matters subject to approval”, such as action limits, can be internally changed as appropriate in accordance with scale-up, accumulated experiences, etc.

3.2.P.3.5 Process Validation and/or Evaluation

Q1: What does the term “documentation” mean?

A1: A description of what format the validation methods, results etc. are recorded and how they are stored should be provided, regarding process validation and/or evaluation stated in this section.

3.2.P.4 Control of Excipients

Q1: For the excipients listed in the JP or other compendia and also excipients whose component specifications are allowed to be provided in the NDA application form in the same manner with those excipients listed in JP (i.e., excipients listed in JPC, Japan Pharmaceutical Excipients, etc.), is it acceptable to describe information of the compendial name of the excipient, name of the compendium, the manufacturer and the container closure system?

A1: Yes. However, if any additional testing item(s), modification of acceptance criteria, etc. are involved, the relevant information should be provided in appropriate items..

3.2.P.4.6 Novel Excipients

Q1: What does the passage: “full details of manufacture, characterisation, and controls, with cross-references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format” mean?

A1: For novel excipients, unlike other excipients, the same extent of the description and data as those required for drug substances such as manufacturing method should be provided. A brief description may be provided in this section, and details of data, etc. should be provided in 3.2.A.3.

Q2: What does the passage: “with cross references to supporting safety data (nonclinical and/or clinical)” mean?

A2: It is enough to describe with reference to pertinent parts of nonclinical and clinical study results, but not necessary to describe a full repetition those results. Summary should be presented if necessary.

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specification(s)

Q1: To what extent should information be provided?

A1: A tabulated summary of “Specification” (testing items, analytical procedures, and acceptance criteria) should be provided. Information in 3.2.P.5.1 and 3.2.P.5.2 should be provided in the NDA application form.

3.2.P.5.2 Analytical Procedures

Q1: To what extent should information be provided?

A1: The analytical procedures provided under “Specification” in the NDA application form should be provided.

3.2.P.5.4 Batch Analyses

Q1: To what extent should information be provided in this section?

A1: The analytical on all batches used for nonclinical studies (e.g., toxicity studies), clinical studies, stability studies, establishment of specification, etc. should be summarized in this section in the same manner as described in 3.2.S.4.4 on drug substance. It is more convenient that batch numbers, manufacturing scale, manufacturing methods, manufacturing site, purpose of use, testing items, test results, analytical procedures, etc. are given in the tabulated summary. Such documents as certificate of analysis covering these items may also be acceptable. In that case, the format in which the results are provided should be easy to review.

3.2.P.5.5 Characterisation of Impurities

Q1: Is it acceptable to discuss the impurities that newly form or increase during the manufacturing process or storage of the drug product? If any significant change occurs in the drug product, is it right to understand it necessary to be included in the

specification of drug product?

A1 Yes.

3.2.P.5.6 Justification of Specification(s)

Q1: Is it right to provide in this section the reason(s) why the testing items and analytical procedures not adopted in “Specification”, if necessary?

A1: Yes.

Q2: Is it right to provide in this section the data from studies conducted for establishing the specification?

A2: Yes. However, specification should be based on data obtained for batches, whose formulation is the same as that stated in the NDA application form, used in the nonclinical studies, clinical studies, stability tests, etc. described in 3.2.P.5.4.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

Q1: What does the passage “if applicable, in-use storage conditions” mean?

A1: It means such storage conditions as those to maintain the stability of reconstituted injections.

3.2.P.8.3 Stability Data

Q1: In the case of injections, is it right to understand that compatibility studies with other drugs should be provided in this section?

A1: Yes.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Biotech:

Q1: What is the phrase: “its use (dedicated or multi-use)” referred to?

A1: A description of whether the equipment is used exclusively for the product or, otherwise, commonly for two or more products should be provided.

Q2: What is the pertinent scope of implication of the passage: “Information should be included on procedures (e.g., cleaning and production scheduling) and design features

of the facility (e.g., area classifications) to prevent contamination or cross-contamination of area and equipment”?

A2: The scope is from the preparation of cells for manufacture (use of stored cell in cell banks) to manufacturing the finished product. As for the level of the information, use as a guide the data required for application for verification of compliance with the guideline for manufacture of drugs by application of recombinant DNA technology.

3.2.A.3 Novel Excipients

Q1: To what extent should information be provided in this section?

A1: The same extent of the description and data as those required for drug substances such as manufacturing method of novel excipients should be provided. A brief description should be provided in *3.2.P.4.6*.

3.2.R REGIONAL INFORMATION

Q1: Are there any requirements specific to Japanese NDA's?

A1: Since there are no such requirements, no additional information needs to be submitted.