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Administrative Notice
January 16, 2025

To: Appended Parties

Center for Product Evaluation
Pharmaceuticals and Medical Devices Agency

Checklist for Common Inquiry Cases to Be Noted When Submitting Approval Applications for New Active Ingredient Containing Pharmaceuticals (Chemical Products) (Early Consideration)

We would like to express our sincere gratitude for your understanding and cooperation with the review and other operations of the Pharmaceuticals and Medical Devices Agency (PMDA).

The Quality Group for the Chemical Products, Center for Product Evaluation at PMDA has prepared the attached checklist. This checklist is based on frequently raised inquiries during the quality assessment process for new drug applications by the Office of New Drug I -V. We hereby inform you of its availability.

Please note that "Early Consideration" is a reference for promoting the practical application of new technologies and the development of innovative pharmaceuticals, even though scientific knowledge and information have not necessarily been sufficiently accumulated at this stage, and that it may change in the future due to newly obtained knowledge and scientific progress.

(Appended Parties)

The Federation of Pharmaceutical Manufacturers' Association of Japan

Japan Pharmaceutical Manufacturers Association

Pharmaceutical Research and Manufacturers of America

European Federation of Pharmaceutical Industries and Associations

Checklist for Common Inquiry Cases to Be Noted When Submitting Approval Applications for New Active Ingredient Containing Pharmaceuticals (Chemical Products) (Early Consideration)

January 16, 2025

Center for Product Evaluation
Pharmaceuticals and Medical Devices Agency

This checklist has been developed based on frequently raised inquiries during the quality assessment process for new drug applications conducted by the Office of New Drug I -V. It serves as a reference for applicants to voluntarily verify the contents of their application forms by summarizing key points to note, along with their reasons and supplementary explanations.

Please note that it is not necessary to fulfill all items listed in this checklist. Applicants may refer to it as appropriate, considering the characteristics and circumstances of each product. The use of this checklist is expected to facilitate more efficient submission and assessment processes for approval applications.

If you have any questions or concerns regarding the points mentioned in this checklist, please consult with the relevant office responsible for the product you plan to submit. Additionally, please be aware that this checklist has been prepared based on scientific knowledge and findings as of January 2025, and that it may change in the future due to newly obtained knowledge and scientific progress.

	Key Points to note	Reasons and Supplementary Explanations	✓
Application Form			
	Is the description of the manufacturing site's licensing/accredited classification and code appropriate?	If an error in classification is identified during the review period and an additional manufacturing site classification is required, the approval timeline may be delayed. If there is any uncertainty regarding the manufacturing site classification, consult with the relevant office as early as possible.	
	Is the Master File (MF) incorrectly referenced in the specifications and test methods section?	The specifications for the drug substance are generally considered open-part information, and it is appropriate to include such open-part information in the application form. If, for any special reason, the MF holder does not disclose the information, consult with the PMDA as early as possible.	
	Are the parameters designated as target value/set value and the standard batch size appropriately enclosed in 《》 or 『』? Are terms such as "not less than" or "not more than" placed outside the brackets indicating the target value/set value? Additionally, are process control values being incorrectly designated as target value/set value?	It is necessary to establish target value/set value based on the concept outlined in the "Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law (PFSB/ELD Notification No. 0210001 dated February 10, 2005, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)".	
	When controlling impurities based on the manufacturing process capability, are the critical elements necessary to ensure process capability appropriately described in the application form under the correct change category (partial change approval application/minor change notification)?	For example, critical manufacturing process elements that affect the residual levels of impurities must be described in the application form.	
	Are the change categories (partial change approval application/minor change notification) of process parameters and their appropriateness, as	For process parameters that impact product quality, the rationale for their settings, including supporting data, must be described in CTD	

	described in the manufacturing method section of the application form, fully documented in CTD Module 2?	Module 2. Additionally, in the following cases, the appropriateness of the description in the application form may be subject to discussion. Therefore, the justification data or the rationale for considering the description unnecessary should also be explained in CTD Module 2: ✓ When the upper or lower limits of the proven acceptable range (PAR) are described as minor change notification. ✓ When the details of endpoint control (e.g., reaction, concentration, drying) are not included in the application form. ✓ The amount of seed crystal added.	
	Are the testing procedures for confirming compliance with the specifications of the drug substance and drug product described in the manufacturing process of the manufacturing site where release testing is conducted?	Ensure that the location where the release testing is conducted is clearly specified.	
	Is it clearly stated in the manufacturing process of the manufacturing site conducting the final release decision, in accordance with the MRA/MOU, that the final release decision is being performed?	When the final release decision in Japan is based on test results obtained overseas, ensure that it is clearly specified where the final release testing is conducted and where the final release decision is made.	
	Is the list of target value/set value, etc., in the manufacturing method section of the application form included in CTD Module 1.13? Additionally, does the list comprehensively include the parameters classified as minor change notification (excluding charge quantities) and the manufacturing process parameters that affect product quality in ways not described in the application form? (Including submissions from the MF holder in cases where the MF is utilized.)	In accordance with the "Format for Preparing the Common Technical Document for Submission of New Drug Applications to Reduce Total Review Time (Administrative Notice dated January 17, 2011, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)", prepare a list of target value/set value, etc. Additionally, for drug substances utilizing the MF, ensure that the list is submitted along with the CTD Module 2 document.	
	Is the name of the column used in the specifications and test methods	In examples described in the "Notification on the Handling of Changes	

	described in the application form?	to Marketing Approval Items Related to the Quality of Pharmaceuticals (PSEHB/PSD Notification No. 0309-1 and PSEHB/CND Notification No. 0309-1 dated March 9, 2018, by the Pharmaceutical Evaluation Division and the Compliance and Narcotics Division , Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)", column names are not specified because they are based on individual monographs of the Japanese Pharmacopoeia. However, this does not imply that column names are unnecessary. Generally, column names should be specified.	
	Are the container specifications (e.g., "tight container") described in the storage conditions and shelf-life sections for the drug substance and drug product in the application form?	The storage conditions and shelf-life sections of the application form must include descriptions related to the container.	
	When tests are conducted using pharmacopoeial methods from overseas, except for tests deemed interchangeable in the ICH Q4B guideline and its annexes, is the complete test method fully described in the application form?	For test methods not deemed interchangeable in the "Guideline on the Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions (ICH Q4B Guideline)" (PFSB/ELD Notification No. 0526001 dated May 26, 2009, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) and its annexes, the full test method must be described in the application form.	
	When phrases such as "if necessary" are used in the application form, is a concrete explanation provided regarding the specific situations being anticipated?	Provide an explanation of the specific cases being anticipated about “if needed” and then consider describing them specifically in the application form.	
	Are the tables and figures in the appendices of the application form referenced within the main text of the application form?	The content of the appendices must be referenced in the main text of the application form as part of the approval items.	
CTD Module 2			
General Matters	Is an abbreviation list attached?	When abbreviations are used, providing them in a list of abbreviations	

		facilitates effective communication with assessors.	
S.2 Manufacture	Has the starting material been appropriately selected in accordance with the ICH Q11 guideline, and have control elements and acceptance criteria been adequately established?	It is necessary to explain that the selection of starting materials has been appropriately justified based on the considerations described in the ICH Q11 guideline. Additionally, it should be demonstrated that appropriate control elements and acceptance criteria have been established.	
	Do the CQAs include, at a minimum, all items specified in the specifications and test methods?	The items to be included in the specifications and test methods typically correspond to CQAs. In addition to those identified through quality risk management, CQAs also include quality attributes that are required to be controlled due to regulatory authority requirements, such as pharmacopoeial standards. Therefore, the determination of CQAs is not solely based on the results of quality risk management.	
	Do the batches used in the evaluation of the design space (DS)/proven acceptable ranges (PARs) appropriately reflect commercial production?	It is necessary to demonstrate that the proposed DS/PAR is applicable to commercial production scale.	
	If solvents are recovered and reused, is this adequately explained? When using recovered solvents, are the control specifications, the steps for recovering solvents, the steps for using the recovered solvents, and whether distillation purification is performed clearly described?	It is necessary to clearly specify whether recovered solvents are being used. Additionally, since the reuse of solvents may the impact impurity profile, appropriate measures must be taken based on the level of risk.	
	Is the fate of impurities, including those purged during the process leading to the drug substance, adequately explained?	Provide, if necessary, a fate map of impurities and the results of purge studies.	
	If reprocessing steps are defined, are the rationale and background for establishing the reprocessing steps (e.g., measures taken to improve the robustness of the manufacturing process), as well as the reprocessing history and validation results, adequately explained?	Submit and explain documentation that allows for the assessment of the appropriateness of the reprocessing steps.	
S.3 Characterisation	Regarding mutagenic (DNA-reactive) impurities, are potential impurities comprehensively listed? Are the results of two types of QSAR analyses presented? Is the rationale for the calculation of the estimated	It is necessary to explain that classification and management based on the ICH M7 Guideline are being conducted.	

	purge factor clearly stated?		
S.4 Control of Drug Substance	Based on batch data and stability data, are acceptance criteria appropriately set?	The establishment of acceptance criteria that are excessively broader than batch data is not appropriate. If batch data used for setting acceptance criteria include data obtained in the early stages of development, provide an explanation for the rationale behind considering such batch data as a basis for establishing the acceptance criteria.	
	Is the correlation clearly specified between the batch number of the drug product, manufacturing site, manufacturing date, classification (pilot scale/production), intended use, and the batch number of the drug substance used?	Provide the basic batch information.	
	Are the established acceptance criteria less stringent compared to the approved specifications in the US and Europe?	Setting broader specifications for drug substances intended solely for the Japanese market is generally considered inappropriate. If such an approach is necessary, provide the rationale in detail.	
	Does the analytical procedure validation comply with the requirements of the ICH Q2 Guideline (selection of performance characteristics and methodology of validation tests)?	Settings should comply with the ICH Q2 Guideline.	
	Have the acceptance criteria for system suitability tests (SST) been established based on the results of analytical procedure validation? Are the validation data and supporting information that justify the acceptable criteria of SST clearly provided? Are the settings consistent with the Japanese Pharmacopoeia?	The purpose of the SST is to confirm that the measurement system, which was verified to be appropriate during analytical procedure validation, remains in an appropriate state during the time period of analysis. Therefore, SST settings that differ from the analytical procedure validation results cannot be considered appropriate. Furthermore, SST settings should comply with the general tests outlined in the Japanese Pharmacopoeia.	
	If the number of replicate injections for system reproducibility in liquid	If the number of replicate injections for system reproducibility in liquid	

	chromatography is reduced to fewer than six, have appropriate acceptance criteria been established in accordance with the Japanese Pharmacopoeia's General information "System Suitability," specifically Section 2.1.2, " Method for decreasing the number of replicate injections without losing the quality of system repeatability testing "?	chromatography is fewer than six, stricter acceptance criteria should be established in accordance with the requirements of the Japanese Pharmacopoeia.	
	When adopting a rationalized description, are the specific operational procedures clearly described in the CTD?	Even when adopting a rationalized description in the application form, the specific operational procedures must be detailed in the CTD.	
	For test methods other than those listed in official compendia in Japan or internationally harmonized test methods, have appropriate validation results been provided?	When using test methods other than those listed in official compendia in Japan or internationally harmonized test methods, validation results for the test methods are required.	
	Are the format, units, symbols, names, and order of specification items described in accordance with the Japanese Pharmacopoeia and the "Guideline for Drafting Monographs for the Japanese Pharmacopoeia, Nineteenth Edition (Partial Revision)" [in Japanese] (Administrative Notification No. 11 dated April 18, 2023, by the Office of Review Management, Pharmaceuticals and Medical Devices Agency)?	The format of the description should comply with the Japanese Pharmacopoeia.	
	For identification tests, are two or more tests based on different principles established?	If a single test is not considered specific, multiple methods must be combined for identification tests. Additionally, in the case of salts, tests for counterions are required.	
S.5 Reference Standards or Materials	Has "equivalence to foreign pharmacopoeial reference standards" been claimed without clarifying the specifications of the foreign pharmacopoeial reference standards?	Reference standard specifications should not rely on foreign pharmacopoeias but, in principle, should establish acceptance criteria and test methods. If it is challenging to establish such specifications, consult with PMDA in advance.	
	For the identification tests of reference materials, have the specifications been appropriately established?	If the specification states "shows the same spectrum as the reference material," it becomes a self-referential comparison, which is inappropriate. Additionally, "supports the chemical structure" alone is	

		insufficient. It is necessary to specify that the spectrum matches the reference spectrum (attached as an annex to the application form) or define specific peaks (e.g., wavenumbers or coupling/peak area ratios in the case of NMR).	
S.7 Stability	If photostability testing is conducted with wrapping coverage, has sufficient UV transmission been verified?	If wrapping is used, provide an explanation to confirm that it does not obstruct light exposure.	
	Does the batch meet the definition of a primary batch as described in the ICH Q1A Guideline?	The batches used for formal stability studies must meet the definition of primary batches as described in the guidelines.	
	If the test methods used in the specifications differ from those used in stability studies (including cases where test methods were changed during stability testing), are the differences and their potential impacts adequately discussed?	Discuss the impact of differences in test methods on measurement results and provide a rationale for the validity before and after the test method change.	
	Has the possibility of crystalline form changes during storage been addressed?	Even if polymorphism is not observed or crystalline form is not included in the specifications and test methods, provide an explanation regarding the potential for changes in crystalline form during storage.	
	Is the packaging configuration used during the stability studies the same as the one specified in the application form?	The packaging configuration should be identical. If different packaging is used, provide a scientific explanation for the rationale behind considering stability data from the different packaging configuration as acceptable.	
	When establishing a retest period or shelf-life based on the ICH Q1E Guideline, has it been clearly stated, and has the appropriateness of extrapolation using the ICH Q1E Guideline been explained in accordance with the guideline?	An explanation in accordance with the guideline is required.	
P.1 Description and Composition of	Is there any inappropriate description suggesting that the formulation changes on a batch-by-batch basis?	Ensure that one formulation corresponds to one prescription.	

the Drug Product			
P.2 Pharmaceutical Development	Do the batches used in the evaluation of the design space (DS)/proven acceptable ranges (PAR) appropriately reflect commercial production?	It is necessary to demonstrate that the proposed DS/PAR is applicable to commercial production scale.	
	If the clinical trial formulation differs from the intended commercial formulation, has the bioequivalence (BE) between the two formulations been appropriately confirmed?	The commercial formulation should be the formulation for which efficacy and safety were confirmed in clinical trials or a formulation that has been demonstrated to be bioequivalent to that formulation.	
	For drug products requiring preparation at the time of use, has the compatibility with the intended containers, devices, and other equipment been appropriately evaluated?	It is necessary to evaluate issues such as adsorption and stability under conditions simulating actual use (this should be explained in this section or in CTD P.2.6).	
	Based on the ICH Q8 to Q11 Guidelines, has the necessary information regarding the development history of the manufacturing process been provided?	Include the following points in the explanation: ✓ Rationale for establishing critical quality attributes (CQAs), including their relationship with the target product quality profile (QTPP). ✓ Details of risk assessments, design of experiments (DoE), and other activities conducted during development. ✓ Control strategy for CQAs, such as management through process parameters or specifications and test methods. Provide a summary table showing how each CQA is managed. ✓ Selection process for critical processes, critical process parameters (CPPs), and critical intermediates, including the rationale and development history.	
	Do the CQAs include, at a minimum, all items specified in the specifications and test methods?	The items to be included in the specifications and test methods typically correspond to CQAs. In addition to those identified through quality risk management, CQAs also include quality attributes that are required to be controlled due to regulatory authority requirements, such as	

		pharmacopoeial standards. Therefore, the determination of CQAs is not solely based on the results of quality risk management.	
	Has the necessity of the scored tablet been explained? Additionally, have data related to the quality of the split tablets, such as content uniformity, dissolution, and stability, been obtained?	Adding unnecessary score lines is generally not acceptable. If a score line is necessary, data should be provided to ensure the quality of the tablet when split, including aspects such as content uniformity, dissolution, and stability.	
P.3 Manufacture	Are the process parameters related to sterility assurance defined as partial change approval applications?	Sterility assurance is ensured through the control of the manufacturing process. Even if the management of sterility-related process parameters is relatively straightforward, they must be defined as partial change approval applications.	
	Do the batches used in the evaluation of the design space (DS)/proven acceptable ranges (PAR) appropriately reflect commercial production?	It is necessary to demonstrate that the proposed DS/PAR is applicable to commercial production scale.	
	If solvents are recovered and reused, is this adequately explained? Additionally, when using recovered solvents, are the control specifications, recovery and reuse steps, and whether distillation purification is performed clearly described?	It is necessary to clearly specify whether recovered solvents are being used. Additionally, since the reuse of solvents may impact the impurity profile, appropriate measures must be taken based on the level of risk.	
	Have partial change approval applications and minor change notifications been appropriately selected based on their impact on quality, and has their rationale been explained? Additionally, for process parameters not included in the application form, has the reasoning for this determination been provided?	A scientific explanation is required for the change categories (partial change approval application/ minor change notification), as well as for the exclusion of process parameters from the application form.	

	Is the fate of impurities, including those purged during the process leading to the drug substance, adequately explained?	Provide, if necessary, a fate map of impurities and the results of purge studies.	
	If reprocessing steps are defined, are the rationale and background for establishing the reprocessing steps (e.g., measures taken to improve the robustness of the manufacturing process), as well as the reprocessing history and validation results, adequately explained?	Submit and explain documentation that allows for the assessment of the appropriateness of the reprocessing steps.	
P.4 Control of Excipients	For premixed excipients, have the description tests established, and have the identification tests and assay methods been established for the main components?	For premixed excipients, it is necessary to establish at least the tests for description, identification, and assay methods. For cases where the blending ratio to the total amount is 0.1% or less, refer to the "Matters to be Described in the Application Form for Pharmaceuticals" [in Japanese] (PMSB/ELD Notification No. 39 dated February 8, 2000, by the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, PFSB/ELD Notification No. 0112001 dated January 12, 2007, partially revised by Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare).	
	For premixed excipients (except when identical to those used in already approved drug products), have the results of lot analysis, analytical procedure validation, and stability studies been obtained?	Data should be submitted to establish the specifications and test methods, as well as the storage conditions and shelf life, for premixed excipients.	
	For functional excipients, have specifications characterizing their functionality been established?	To achieve the quality target product profile (QTPP), the critical characteristics of important excipients should be controlled through specifications.	

	When using excipients listed in official compendia in Japan, are compendial-grade materials (meeting the compendial standards) being used?	For excipients listed in official compendia in Japan, they should, in principle, meet the compendial standards.	
	For test methods other than those listed in official compendia in Japan or internationally harmonized test methods, have appropriate validation results been provided?	When using test methods other than those listed in official compendia in Japan or internationally harmonized test methods, validation results for the test methods are required.	
P.5 Control of Drug Product	Are acceptance criteria appropriately set, taking into account the actual measured values?	The setting of acceptance criteria that deviate excessively from actual measured values is not appropriate.	
	Are the established acceptance criteria less stringent compared to the approved specifications in the US and Europe?	Setting broader specifications for drug products intended solely for the Japanese market is generally considered inappropriate. If such an approach is necessary, provide the rationale in detail.	
	Does the analytical procedure validation comply with the requirements of the ICH Q2 Guideline (selection of performance characteristics and methodology of validation tests)?	Settings should comply with the ICH Q2 Guideline.	
	Have the acceptance criteria for system suitability tests (SST) been established based on the results of analytical procedure validation? Are the validation data and supporting information that justify the acceptable criteria of SST clearly provided? Are the settings consistent with the Japanese Pharmacopoeia?	The purpose of the System Suitability Test (SST) is to confirm that the measurement system, which was verified to be appropriate during analytical procedure validation, remains in an appropriate state during the time period of analysis. Therefore, SST settings that differ from the analytical procedure validation results cannot be considered appropriate. Furthermore, SST settings should comply with the general tests outlined in the Japanese Pharmacopoeia.	
	If the number of replicate injections for system reproducibility in liquid chromatography is reduced to fewer than six, have appropriate acceptance criteria been established in accordance with the Japanese Pharmacopoeia's General information "System Suitability," specifically	If the number of replicate injections for system reproducibility in liquid chromatography is fewer than six, stricter acceptance criteria should be established in accordance with the requirements of the Japanese Pharmacopoeia.	

	Section 2.1.2, " Method for decreasing the number of replicate injections without losing the quality of system repeatability testing "?		
	When adopting a rationalized description, are the specific operational procedures clearly described in the CTD?	Even when adopting a rationalized description in the application form, the specific operational procedures must be detailed in the CTD.	
	Does the explanation appropriately follow the descriptions in the ICH Q3D and M7 guidelines regarding the control of elemental impurities and mutagenic (DNA-reactive) impurities, respectively?	An explanation in accordance with the ICH guidelines is required. If batch analysis results are available, those results should also be provided.	
	For test methods other than those listed in official compendia in Japan or internationally harmonized test methods, have appropriate validation results been provided?	When using test methods other than those listed in official compendia in Japan or internationally harmonized test methods, validation results for the test methods are required.	
	If proposing to omit release tests in Japan, are the test records to be utilized those from an appropriate importing country (e.g., a country subject to an MRA or MOU)?	Release tests must be conducted at an appropriate manufacturing site (country).	
	Has the appropriateness of the dissolution test (including specification values) been explained, including from the perspective of discriminative ability?	The dissolution test should be established to identify products that are deemed unsuitable in terms of quality or exhibit significant biological inequivalence.	
	Are the format, units, symbols, names, and order of specification items described in accordance with the Japanese Pharmacopoeia and the "Guideline for Drafting Monographs for the Japanese Pharmacopoeia, Nineteenth Edition (Partial Revision)" [in Japanese] (Administrative Notification No. 11 dated April 18, 2023, by the Office of Review Management, Pharmaceuticals and Medical Devices Agency)?	The format of the description should comply with the Japanese Pharmacopoeia.	
	For identification tests, are two or more tests based on different principles established?	If a single test is not considered specific, multiple methods must be combined for identification tests. Additionally, in the case of salts, tests for counterions are required.	
P.6 Reference	Has "equivalence to foreign pharmacopoeial reference standards" been	Reference standard specifications should not rely on foreign	

Standards or Materials	claimed without clarifying the specifications of the foreign pharmacopoeial reference standards?	pharmacopoeias but, in principle, should establish acceptance criteria and test methods. If it is challenging to establish such specifications, consult with PMDA in advance.	
	For the identification tests of reference materials, have the specifications been appropriately established?	If the specification states "shows the same spectrum as the reference material," it becomes a self-referential comparison, which is inappropriate. Additionally, "supports the chemical structure" alone is insufficient. It is necessary to specify that the spectrum matches the reference spectrum (attached as an annex to the application form) or define specific peaks (e.g., wavenumbers or coupling/peak area ratios in the case of NMR).	
P.7 Container Closure System	Does the document specify whether the rubber stopper is halogenated and whether it is coated?	As it comes into direct contact with the drug product, if applicable, the impact on quality due to coatings or other treatments should also be explained.	
	For sterile products, is the sterilization method of the primary container described? Additionally, in the case of ethylene oxide gas (EOG) sterilization, are specifications for residuals specified? For gamma irradiation, is the radiation dose (upper limit) specified?	These factors can potentially affect the quality of the drug product such as sterility, residual gas, and stability and should therefore be described.	
	If silicone oil or similar substances are used in syringes, are their specifications described in the CTD and the application form?	As it comes into direct contact with the drug product and may affect its quality, it is necessary to establish specifications for such substances.	
	Based on the results of stress testing (e.g., photostability testing, humidity testing), does the document address the need to include precautionary statements regarding post-opening handling in the package insert?	For drug products that become unstable after the opening of the primary packaging, considering the possibility of repackaging at pharmacies, it is necessary to include precautionary statements (e.g., protection from light, moisture prevention) in the package insert as needed.	
	Does the document provide the results of studies on extractables and leachables from the container to explain the appropriateness of the closure system? Additionally, does it present the results of risk	An explanation of the appropriateness of the containers and filters used is required.	

	assessments for plastic products, such as filters, used in the manufacturing process?		
	If the container includes child-resistant features, is this explained in CTD Modules 2 and 3?	If the container has special features or mechanisms, it is necessary to provide an explanation of those details.	
P.8 Stability	Does the batch meet the definition of a primary batch as described in the ICH Q1A Guideline?	The batches used for formal stability studies must meet the definition of primary batches as described in the guidelines.	
	Has stability testing under actual use conditions (e.g., drop tests, cyclic tests, tests evaluating the impact of short-term temperature increases) been appropriately conducted, particularly for multi-dose drug products?	It is necessary to explain that appropriate quality is ensured under actual use conditions.	
	Have the stability test parameters been appropriately selected? For suspensions, has the impact of Ostwald ripening been evaluated? For transdermal patches, has the precipitation of the active ingredient been assessed?	In addition to the parameters established in the specifications, it is necessary to evaluate characteristics deemed important for assessing the stability of the formulation.	
	If a drug product is a solution, has stability evaluation been conducted under appropriate storage conditions, such as horizontal or inverted positions?	Since stability cannot be fully evaluated with upright storage alone, due to factors such as the impact of the container-closure system that does not come into contact with the formulation, it is necessary to assess stability under horizontal and inverted storage conditions.	
	If the test methods used in the specifications differ from those used in stability studies (including cases where test methods were changed during stability testing), are the differences and their potential impacts adequately discussed?	Discuss the impact of differences in test methods on measurement results and provide a rationale for the validity before and after the test method change.	
	Has the photostability testing been conducted in accordance with ICH Q1B, and are the results for the fully exposed drug product presented?	In accordance with ICH Q1B, it is necessary to conduct testing under direct exposure to light to evaluate the presence and extent of the impact of light.	
	Is the possibility of changes in the crystal form of the drug substance during storage explained?	An explanation is required even if no crystal polymorphism is observed or if the crystal form is not included in the specifications and test	

		methods.	
	Is the packaging configuration used during the stability studies the same as the one specified in the application form?	The packaging configuration should be identical. If different packaging is used, provide a scientific explanation for the rationale behind considering stability study data from the different packaging configuration as acceptable.	
	When establishing the shelf-life based on the ICH Q1E guideline, is it explicitly stated, and is the appropriateness of extrapolation using the ICH Q1E guideline explained in accordance with the guideline?	An explanation in accordance with the guideline is required.	
	If time-dependent changes are observed in some batches but not in others during stability testing, has the reasoning for these differences been considered and explained?	If there are batches showing different trends during stability testing, it is necessary to consider and explain the reasons for these differences.	
	If the manufacturing site for the stability test product differs from the intended commercial manufacturing site, has it been explained, based on actual measured values and stability test results, that the intended commercial manufacturing site can produce a product equivalent to the stability test product?	It is necessary to explain that the stability test results of the product manufactured at a different site from the intended commercial manufacturing site can be used to evaluate the stability of the intended commercial product.	
A.2 Adventitious Agents Safety Evaluation	If biological raw materials are used, has an explanation been provided in accordance with the Standards for Biological Raw Materials?	Rather than explaining compliance with overseas standards, an explanation must be provided in accordance with Japan's Standards for Biological Raw Materials.	
Others			
	When utilizing an MF, is the information from the disclosed section, such as specifications and test methods, appropriately included in the Marketing Authorization Holder's CTD?	As a general rule, disclosed information should also be included in the Marketing Authorization Holder's CTD.	
	In cases where a GMP inspection is omitted, has the basis for omission been explained in accordance with the "Handling of GMP Conformity Investigation Applications" [in Japanese] (PSEHB/PED Notification No.	Explanations should be provided, and the required documents submitted, in accordance with the aforementioned notification.	

	0713-1 and PSEHB/CND No. 0713-8 dated July 13, 2021, by the Pharmaceutical Evaluation Division and the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare), specifying which of the criteria (4)(a) to (e) in the notification applies, along with the submission of the required documents?		
	If the GMP inspection authority is a prefectural government, has the inspection schedule been communicated to the PMDA reviewer once it has been determined?	Since it is necessary to replace the application form before the GMP inspection, the inspection schedule should be communicated to the responsible review office.	
	Are there any transcription errors from CTD Module 3 and the Standard Operating Procedures (SOPs) to the application form and CTD Module 2? Additionally, is the content of CTD Module 3 consistent with the latest version of the SOPs?	Ensure consistency between the descriptions in the application form, CTD Module 2, and CTD Module 3 before submission. All supporting documents for the content described in the application form and Module 2 should be fully included in Module 3. Particularly for drug products already approved overseas, thoroughly verify the consistency between the latest overseas manufacturing practices and the application details in Japan prior to submission.	
	Are the critical processes and critical intermediates clearly specified in the CTD and the application form?	Ensure that the critical processes and critical intermediates are explained in the CTD section "Control of Critical Steps and Intermediates" and explicitly stated in the application form.	
	If the draft package insert mentions storage conditions different from those specified in the application form’s "Storage Conditions and Shelf Life," have supporting data been provided to explain and justify the validity of these conditions?	The storage conditions listed in the draft package insert must not conflict with those stated in the application form. All necessary supporting data should be presented and explained in the CTD to ensure consistency.	