Checklist for Application Form for MF Registration “2b”
(Chemically Synthesized Drugs)

No.		Please check the following items for the descriptions of the MF you have prepared. This checklist does not cover all of the requirements for preparing the approval application form. For the descriptions on manufacturing methods, please refer to Attachment 1 “Guideline for Descriptions on Approval Application Forms for the Manufacturing Method of Chemical Drug Substances,” PFSB/ELD Notification No. 0210001 issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated February 10, 2005.
	Checkbox	Check Items
		[Manufacturing method]
		○ General
1	□	Documents that correspond to Module 3 of CTD Guideline (hereinafter referred to as CTDmodule3) are prepared on the basis of up-to-date information and manufacturing parameters necessary for quality assurance and other information are described in the application form for MF registration.
2	□	Descriptions in CTDmodule3 are checked against the product standard codes, standard operating procedures, manufacturing records.
3	□	When there are two or more manufacturing sites, the following information are included for each site: [Serial Number], [Name of Manufacturing Site], [Manufacturing Method], and [Serial Number of Next Manufacturing Method].
4	□	All processes from-the starting material to packaging of the drug substance are presented in the production flow. When an external manufacturing site (e.g., storage warehouse, outsourcing site for milling process) or a external testing laboratory is involved, necessary information are appropriately provided.
5	□	The names of reagents and test solutions used in the manufacturing process are described according to the latest Japanese Pharmacopoeia.
		○ Manufacturing scale
6	□	The manufacturing scale included in the application form for MF registration and CTDmodule3 is verified to be consistent with the production scale at the time of submission of the application form.
7	□	When there are two or more manufacturing methods (manufacturing scale), they are described in a distinguishable manner, e.g., numbers are provided for each content of the manufacturing methods.
8	□	The starting material,etc. are closely studied to be expressed as an absolute amount in principle based on the standard charging quantities.
		○ Control of raw materials
9	□	The justified reasons for selection of the starting material and the scientific validity can be explained.

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	Checkbox	Check Items
10	□	The name and molecular formula of the starting material are provided. The control items and control values are proposed and the rationale for selection is justified.
11	□	Of the raw materials used for critical steps, those that could significantly impact on quality or those used after the production of the final intermediate are provided with the control items and values necessary for assuring the consistency of quality being appropriately selected.
12	□	The critical intermediates and final intermediate are provided with the control items and values necessary for assuring the consistency of quality being appropriately selected.
		○ Process control
13	□	When organic solvents are used for manufacturing, there is a justified explanation that the control parameters and values for persistency of the solvents are determined based on the specifications and test methods of the drug substance and process control. If they are not required, the rationale is described in CTDmodule3.
14	□	Of the manufacturing parameters or standard charging quantities that are set as a target/set value, items for minor change notification are included in 『 』and those for partial change approval application in << >>. Items for minor change notification other than the target/set value are described in “ ”.
15	□	There is a justified explanation on whether the amounts of solvents, catalysts, reagents, operating conditions (time, temperature, etc.), process parameters, and other information are required in the application form for MF registration.
16	□	Units of mass and other parameters are verified to be consistent between the product standard codes, standard operating procedures, manufacturing records, and the application form for MF registration and CTDmodule3.
17	□	In the section of manufacturing methods, notations of control values, such as “significant figure” (e.g., difference between 98%.and 98.0%) and “or less vs. less than” (e.g., difference between 1.0% or less and less than 1.0%), are confirmed to be consistent between the product standard codes, standard operating procedures, manufacturing records, and the application form for MF registration, and CTDmodule3.

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	Checkbox	Check Items
18	□	The end point of reactions in each manufacturing process is confirmed to be required as a control item.
19	□	When a manufacturing process considered critical for assuring product quality is positioned as the critical process, the presence or absence of the need for in-process control values or critical parameters can be explained.
		○ Manufacturing site of drug substance
20	□	Information on manufacturing sites are checked against the certificate of accreditation. If updated, the information is verified to be up to date prior to the submission of the application form, e.g., the latest date of certificate of accreditation is provided.
21	□	The presence or absence of an external manufacturing site (e.g., storage warehouse, outsourcing site for milling process) or a testing laboratory is confirmed.
		○ Coordination among in-country caretaker, drug substance manufacturer(master file holder/applicant), and drug manufacturer (marketing authorization holder/applicant--MAH/MAA)
22	□	Collaboration system is established with MAH/MAA and in-country caretaker to periodically check whether the content of MF registration is consistent with the actual production conditions.
23	□	Whether the descriptions in the application form for MF registration reflect the up-to-date information on manufacturing sites can be verified in collaboration with the in-country caretaker.
24	□	When an external manufacturing site (e.g., storage warehouse, outsourcing site for milling process) or a testing laboratory is involved, updated information can be periodically verified in collaboration with the in-country caretaker even after marketing.
25	□	Up-to-date information in the Open Part of CTDmodule3 can be shared between MAH/MAA and in-country caretaker (Date of confirmation: *MM DD, YYYY*).
26	□	Necessary information such as change control can be notified MAH/MAA-in advance according to the GQP agreements and other arrangements.

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	Checkbox	Check Items
		○ Final check
27	□	At the time of document preparation and immediately before document submission, the manufacturing methods are double-checked jointly with the in-country caretaker on the basis of supporting documents such as the drug product standard codes and CTDmodule3.
28	□	At the time of document preparation and immediately before document submission, it is double-checked that the manufacturing methods are based on the procedures for change control for MAH/MAA (e.g., manufacturing site, manufacturing scale, equipment, specifications for starting material, manufacturing process) jointly with the in-country caretaker.
		[Specifications and test methods]
29	□	When the specifications and test methods of the drug substance are cited in the application form for marketing approval, the reference information on specifications and test methods as listed in the Japanese Pharmacopoeia, e.g., “as per the Japanese Pharmacopoeia ○○○” or “as per the Japanese Pharmacopoeia ○○○ and as follows,” are shared between MAH/MAA and the foreign manufacturer (MF holder/applicant) and in-country caretaker
30	□	When cited in the application form for marketing approval, the specifications and test methods of the drug substance are described in accordance with the formats, terms, and reagents and test solutions of the Japanese Pharmacopoeia. The specifications and test methods are also checked to be prepared in reference to the latest “Guideline for drafting the Japanese Pharmacopoeia.”
31	□	Test data in the manufacturing site are verified to meet the specifications in [Specifications and Test Methods]. The analytical methods used are also confirmed to be validated.
32	□	When the specifications and test methods of the drug substance are cited in the application form for marketing approval, there is a justified explanation that items for the specifications and test methods are selected in a necessary and sufficient manner (e.g., “content specifications,” “description,” “identification,” “purity test,” “ assay,” “water,” “loss on drying,” and “residual solvents”).

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	Checkbox	Check Items
33	□	When the specifications and test methods of the drug substance are cited in the application form for marketing approval and when reagents/test solutions that are not included in the Japanese Pharmacopoeia are used, the section of “Reagents and Test Solutions” is established to specify the quality.
34	□	In the section of specifications and test methods, notations of specification values, such as “significant figure” (e.g., difference between 98% and. 98.0%) and “or less vs. less than” (e.g., difference between 1.0% or less vs. less than 1.0%), are confirmed to be consistent between the manufacturing records and CTDmodule3.
35	□	At the time of document preparation and immediately before document submission, the specifications and test methods are double-checked jointly with the in-country caretaker on the basis of supporting documents such as the product standard codes and CTDmodule3.
		[Major notifications/administrative notices useful for the description of manufacturing methods]
		• “Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law” (PFSB/ELD Notification No. 0210001 issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated February 10, 2005)
		• “Q&A on the Description of Manufacturing Methods in Application Forms for Marketing Approval of Drugs” (Administrative Notice issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated May 20, 2008)
		• “Guidelines on Utilization of Master File for Drug Substances, etc.” (PFSB/ELD Notification No. 1117-3/Notification No. 1117-1 of PFSB/Medical Device and Regenerative Medicine Product Evaluation Division, issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated November 17, 2014)

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	Checkbox	Check Items
		• “Q&A on the Master File (MF) System, Part I” (Administrative Notice issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated July 28, 2005)
		• “Q&A on the Master File (MF) System, Part II” (Administrative Notice issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated December 20, 2005)
		• “Q&A on the Master File (MF) System, Part III” (Administrative Notice issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated December 28, 2012) • “Q&A on the Master File (MF) System, Part IV” (Administrative Notice issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated October 29, 2013)