PHARMACY AND POISONS BOARD
OF HONG KONG

Supplementary Notes for Application for Registration of Biological Products Involving Alternative / Back Up Manufacturer(s) for Manufacturing Steps

This document serves to supplement the "Guidance Notes on Registration of Pharmaceutical Products / Substances" and specify the conditions and requirements for including alternative/ back up manufacturers for individual manufacturing steps of biological products, such as monoclonal antibodies, vaccines, etc.

Background

2. Under Regulation 36 of the Pharmacy and Poisons Regulations, Cap. 138A, the name and address of the manufacturer is a registrable particular of a pharmaceutical product. For pharmaceutical products involving multiple manufacturing steps, there should only be one manufacturer for each manufacturing step. The certificate holder would need to apply for another product registration if it is considered necessary to have an alternative/ back up manufacturer for a specific manufacturing step of the product.

3. Due to the complexity of manufacturing of biological products, there may be strong justifications to have alternative/back up manufacturer(s) for certain manufacturing step(s) in order to ensure the stable, continuous and timely supply of such pharmaceutical products.

4. To facilitate the registration of biological products, as well as subsequent application for change of manufacturer(s) for such products, the applicant may take reference to the following guidance.

Application for Registration

5. For new registration of pharmaceutical products, the applicant should provide a declaration and/or updated flow chart to illustrate the whole manufacturing process, and specify the name, address and role of the manufacturer involved in each manufacturing step. **(Appendix A)**

6. For biological products which involve alternative/back up manufacturer(s)* for particular manufacturing step(s), i.e. alternative manufacturing pathway(s), other than that specified in paragraph 5, the applicant should provide the following information:

a) Justification for introducing the alternative/back up manufacturer(s);

b) A combined manufacturing flow chart (CMFC) **(Appendix B)** which:

   i. illustrates all alternative manufacturing pathways; and
   ii. lists all the manufacturers involved in each manufacturing pathway and individual manufacturing step.

The registered and labelled manufacturer of the biological product should be the same among all the proposed alternative manufacturing pathways. Otherwise, the certificate holder would need to apply for another product registration for the product. All the listed manufacturers should be recorded in the PRS 2.0 system.

c) Evidence of PIC/S GMP compliance of all manufacturer(s) listed in the CMFC.

d) Corresponding quality documents for the alternative manufacturing pathway(s) in the CMFC, if applicable. For example, certificate of analysis and/or stability report with the alternative manufacturer(s) involved in batch release and manufacturing of dosage forms.

e) The registration certificate holder should demonstrate to the satisfaction of the Drug Office that it has a product tracing mechanism in place to identify products manufactured by a particular pathway, which should also be specified in its transaction record made readily available for inspection.

**Remark: The application for alternative/back up manufacturer(s) is only applicable for manufacturers other than the registered and labelled manufacturer.*

7. Prior to the approval of drug registration, the applicant shall provide a declaration letter of the current manufacturing pathway for the registered pharmaceutical product to be supplied in Hong Kong **(Appendix C)**.

Application for post-approval changes of manufacturer involving alternative/back up site

8. Application for the change of manufacturer of a registered pharmaceutical product should be applied under PRS 2.0. The applicant should provide a declaration and/or flow chart (or CMFC) to illustrate the proposed manufacturing process, and specify the name, address and role of the manufacturer involved in each manufacturing step **(Appendix A or B).**

9. If the proposed change involves the addition of an alternative/back up manufacturer for a biological product, the applicant should provide the updated CMFC (**Appendix B)**, together with relevant supporting documents (e.g. justification for the change, PIC/S GMP evidence, quality documents, product tracing mechanisms, etc.).

10. If the registration certificate holders of biological products with endorsed alternative/ back up manufacturer(s) wish to switch the manufacturing pathway, they should provide a declaration letter accordingly (**Appendix C**). Such applications may be expedited upon request with justification.[#]

11. As long as the proposed manufacturing pathway has already been included in the CMFC in record, the registration certificate holder will not be required to recall the old stocks from market at the time the approved change of manufacturing pathway is effective. However, The Drug Office should be informed when the first imported batch of the product manufactured under the alternative pathway is distributed, and the manufacturing pathway of the batches distributed to market should be specified in the transaction record.

12. For deletion of alternative/back up manufacturer, the applicant should submit a declaration letter and the updated CMFC or manufacturing flow chart.

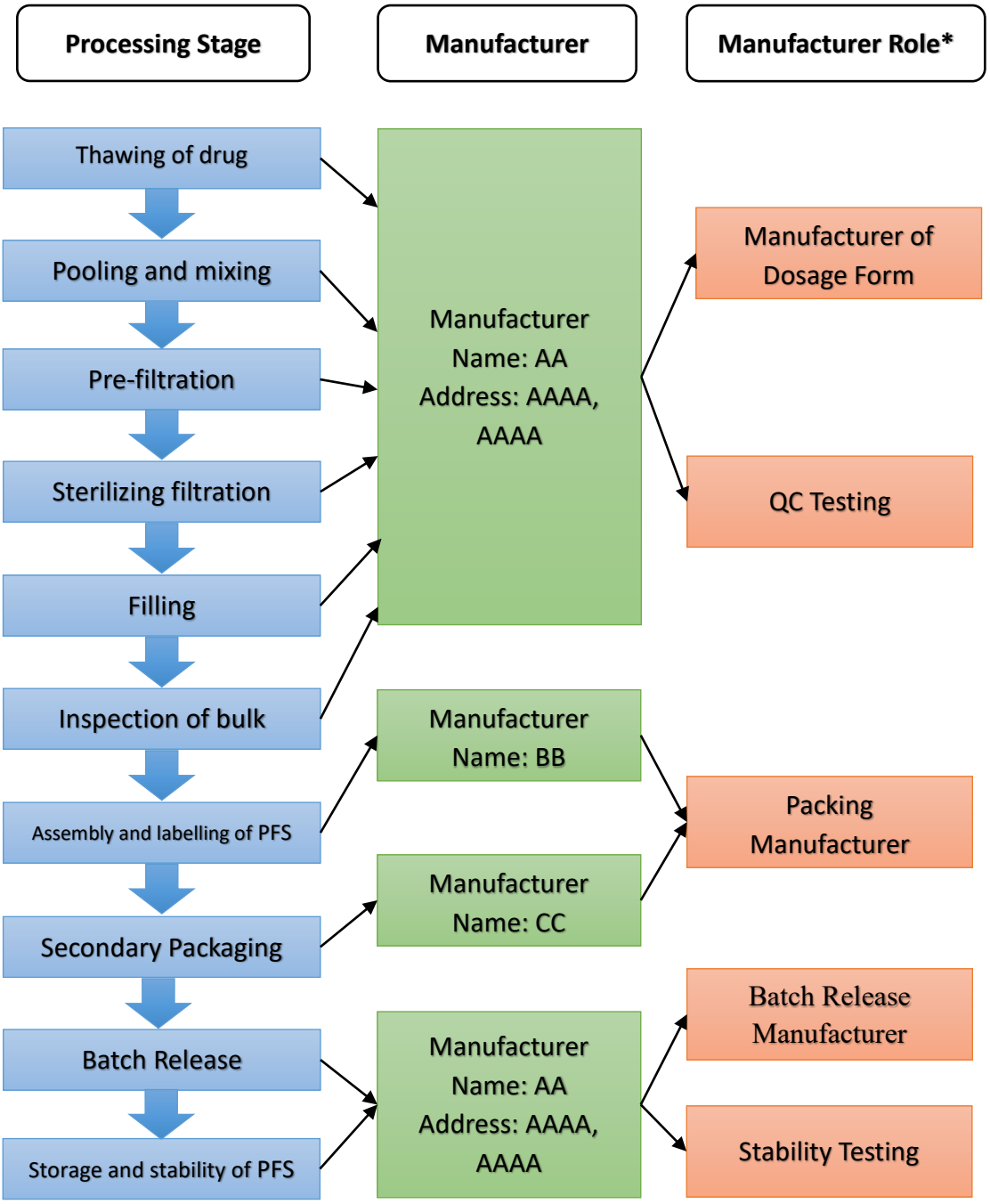
[#]Remark: If the proposed alternative manufacturing pathway(s) or manufacturer(s) has not been recorded in the CMFC on file, or if there is no up-to-date PIC/S GMP evidence, the CORP application cannot be expedited.

Appendix A: Sample Manufacturing Flow Chart

XXX Solution for Injection in PFS XXmg (proposed product name)

Registered and Labelled manufacturer[δ]: Mft AA, at Address AAAA, AAAA

Flow Chart of Manufacturing Process



This flow chat is applicable to ALL pharmaceutical products. Only one manufacturer is registered for each manufacturing step. For biological products which involve alternative/back up manufacturer(s) for the same manufacturing step (i.e. alternative manufacturing pathways), the applicant should refer to the Supplementary Notes and provide information in Appendix B & C.

δ The registered and labelled manufacturer should be the one responsible for key manufacturing role (e.g. manufacturer of dosage form, batch release manufacturer).

* The Manufacturer Role is as per PRS 2.0 system

Appendix B[#]: Sample Combined Manufacturing Flow Chart (CMFC)

XXX Solution for Injection in PFS XXmg (proposed product name)

Registered and Labelled manufacturer[δ]: Mft BB, at Address BBBB, BBBB

Flow Chart of Combined Manufacturing Process

Manufacturing Step	Name of Manufacturer*			
	Pathway 1	**Pathway 2**	**Pathway 3**	**Pathway 4**
Thawing of drug substance	Mft: AA (Address)	Mft: AA (Address)	Mft: DD (Address)	Mft: DD (Address)
Pooling and mixing				
Pre-filtration				
Sterilizing filtration				
Filling				
Inspection of bulk				
Storage and stability of bulk		Mft: DD (Address)		
Assembly and labelling of PFS	Mft: BB (Address)	Mft: CC (Address)	Mft: CC (Address)	Mft: BB (Address)
Inspection of PFS		Mft: BB (Address)	Mft: BB (Address)	
Secondary packaging	Mft: EE (Address)	Mft: EE (Address)	Mft: EE (Address)	
Batch Release[δ]	Mft: BB (Address)			
Storage and stability of PFS^	Mft: BB (Address)	Mft: DD (Address)	Mft: BB (Address)	Mft: BB (Address)

Summary of Manufacturer Role[$] by Pathway

Manufacturer Name		Manufacture Role
Pathway 1	Mft AA	Manufacturer of Dosage Form, Stability testing
	Mft BB	Packing Manufacturer, QC Testing, Batch Release Manufacturer, Stability testing
	Mft EE	Packing Manufacturer
Pathway 2	Mft AA	Manufacturer of Dosage Form
	Mft BB	QC Testing, Batch Release Manufacturer
	Mft CC	Packing Manufacturer
	Mft DD	Stability testing
	Mft EE	Packing Manufacturer
Pathway 3	Mft BB	QC Testing, Batch Release Manufacturer, Stability testing
	Mft CC	Packing Manufacturer
	Mft DD	Manufacturer of Dosage Form, Stability testing
	Mft EE	Packing Manufacturer
Pathway 4	Mft BB	Packing Manufacturer, QC Testing, Batch Release Manufacturer, Stability testing
	Mft DD	Manufacturer of Dosage Form, Stability testing

Notes:

Appendix B is only applicable for biological product applications which involve alternative / back up manufacturer(s) for specific manufacturing step. The CMFC should (i) illustrate all alternative manufacturing pathways, (ii) list all the manufacturers involved in each manufacturing pathway and individual manufacturing step; and (iii) only manufacturing pathways or manufacturers already specified in the CMFC previously submitted to the Drug Office are eligible for expedited evaluation of CORP application for change of manufacturing pathway with justification upon request.

δ The registered and labelled manufacturer should be the same among all proposed alternative manufacturing pathways and which should be the one responsible for key manufacturing role (e.g. manufacturer of dosage form, batch release manufacturer).

* All the listed manufacturers should be recorded in the PRS 2.0 system with evidence of PIC/S GMP compliance. The approved manufacturing operations shown in the PIC/S GMP certificate should match with the applied manufacturing steps.

^ Quality documents for the alternative manufacturing pathway(s) in the CMFC are required. For the above example, the certificate of analysis issued by Mft BB and DD and stability report covering manufacturing site BB and DD is required.

$^{\$}$ The Manufacturer Role is as per PRS 2.0 system.

Appendix C[#]: Sample Declaration Letter

Company Letter Head

Date: DD-MM-YYYY

Manufacturing Sites of

XXX Solution for Injection in PFS XXmg (proposed product name)

We, *Company Name of the Applicant*, hereby declare that manufacturing *pathway 2* as described in the Combined Manufacturing Flow Chart (CMFC) will be adopted in the manufacturing *XXX Solution for Injection in PFS XXmg* in Hong Kong *upon registration / with effect from DD-MM-YYYY*. Please refer to table 1 and table 2 for details.

We also confirm that a product tracing mechanism is in place and that the batches manufactured through pathway 2 which have been imported and distributed in Hong Kong will be specified in the record of transaction maintained in accordance with Regulation 28 of the Pharmacy and Poisons Regulations and readily available for inspection .The detail of the product tracing mechanism can be found in Annex 1[*].

**Remark: Please describe the system, the identification tools and illustrate the trace back procedure during recall.*

Table 1: Manufacturers involved in *Pathway 2.*

Manufacturing Step	Name of Manufacturer
	Pathway 2
Thawing of drug substance	Mft AA
Pooling and mixing	
Pre-filtration	
Sterilizing filtration	
Filling	
Inspection of bulk	
Storage and stability of bulk	Mft DD
Assembly and labelling of PFS	Mft CC
Inspection of PFS	Mft BB
Secondary packaging	Mft EE
Batch Release	Mft AA
Storage and stability of PFS	Mft DD

Table 2: Manufacturers details involved in *Pathway 2*

Manufacturer Name	Manufacturer Address	Manufacturing Role*	PIS/GMP issuing Authority	GMP Certificate Expiry Date
Mft AA	AAAA, AAAA	▪ Manufacturing of dosage form ▪ Batch Release	MHRA, United Kingdom	DD-MM-YYYY
Mft BB	BBBB, BBBB	▪ QC Testing	TGA, Australia	DD-MM-YYYY
Mft CC	CCCC, CCCC	▪ Packaging Mft	HSA, Singapore	DD-MM-YYYY
Mft DD	DDDD, DDDD	▪ Stability Testing	FDA, USA	DD-MM-YYYY
Mft EE	EEEE, EEEE	▪ Packaging Mft	HPRA, Ireland	DD-MM-YYYY

Signature and Chop

Name and title of Company representative

Notes:

Appendix C is only applicable for biological product applications which involve alternative/back up manufacturer(s) for specific manufacturing step. The proposed manufacturing pathway(s) must be specified in the CMFC previously submitted to the Drug Office (Appendix B), with detailed information of the name, address and role of the corresponding manufacturers involved in the selected pathway. Only ONE pathway should be selected and effective upon registration.

* The Manufacturer Role is as per PRS 2.0 system