Guidance on the Implementation of Good Manufacturing Practice (GMP) Evidence for Drug Substance (DS) Manufacturers

Background

1. As part of continual regulatory enhancement to assure the quality standard of therapeutic products supplied in Singapore, the Health Sciences Authority (HSA) will roll out a transition plan for companies to fully comply with the requirement for Evidence of Good Manufacturing Practice (GMP) Compliance of Chemical Drug Substance (DS) manufacturers. This will align the GMP requirements for both chemical and biologic DS manufacturers. The full implementation of the GMP requirements for all DS manufacturers will enable companies to better assure the quality of therapeutic products supplied in Singapore for use in our patients.

Details of Implementation

2. The implementation will apply prospectively to New or Generic Drug Applications (NDA/GDA) and Minor Variation Applications (MIV-1) for addition of a new DS manufacturer.

3. **The types of GMP Compliance Evidence** are as follows. Companies may submit either (a), (b) or (c) to support the applications:

   a) A valid GMP certificate issued by any PIC/S* authority. For PIC/S authorities which do not issue GMP certificates, either the GMP inspection report together with the close-out letter where applicable, or other evidence from the authority such as the manufacturing licence to demonstrate that the site complies with PIC/S GMP requirements can be submitted.

      The GMP evidence must cover the DS of interest. Examples of such evidence include:

      - A GMP certificate with the DS of interest stated; or
      - A GMP inspection report or manufacturing licence with the DS of interest included in the scope; or
      - A Written Confirmation** for the DS of interest from the PIC/S authority which issued the GMP certificate

   b) A valid Active Pharmaceutical Ingredient (API) Registration Certificate covering the DS of interest listed on EUDRAGMP.

   c) A valid Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) for the DS of interest issued by EDQM.

**Pharmaceutical Inspection Co-operation Scheme (PIC/S)*

*** Written Confirmation using the European Union (EU) template or any other official document from the PIC/S authority is acceptable*

Date of Implementation

4. **Effective 1 October 2024**, NDAs, GDAs, and MIV-1 applications (Addition of new DS manufacturer) are to be supported by the required GMP Compliance Evidence for DS manufacturers. Applications submitted on or after 1 October 2024 without the required GMP evidence will not be accepted.

5. **From now until 30 September 2024**, companies are strongly encouraged to provide the GMP Compliance Evidence if it is available. This will help to ensure a smooth transition when the requirement takes effect.

6. Please refer to the **FAQ** in the next page for more information.

Frequently Asked Questions (FAQ)

1. **Q**: I am planning to submit a GDA-2 after 01 October 2024. The DS manufacturer is the same as the registered GDA-1. Do I have to support the GDA-2 with the required GMP evidence at submission?

   A: Yes, all **new** applications (NDA/GDA) submitted on or after 01 October 2024 are to be supported by the **GMP Compliance Evidence for Drug Substance (DS) Manufacturers.**

2. **Q:** Does this new requirement apply to existing registered products?

   A: No. It is not retrospectively applied to existing registered products. The requirement for **GMP Compliance Evidence for DS manufacturers** is only applicable to **new** applications for NDAs and GDAs. For existing registered products, the requirement for GMP evidence will only apply when an MIV-1 application is submitted for B1 Addition or Replacement of Manufacturer/ Site of Drug Substance (where CEP is not available).

3. **Q:** Does this requirement apply to DS intermediate manufacturers?

   A: No. The requirement for **GMP Compliance Evidence for DS Manufacturers** is only applicable to manufacturers for the final DS. It does not apply to DS intermediate manufacturers.

4. **Q:** Would applications with DS manufacturers that are located outside of a PIC/S authority jurisdiction (non – PIC/S member country) be accepted?

   A: Yes, as long as the application is supported by GMP evidence issued by a PIC/S authority. The acceptability of the required evidence is regardless of the country in which the manufacturer is located. In this regard, a DS manufacturer located in a non-PIC/S member country can apply for and obtain **GMP Compliance Evidence** issued by a PIC/S authority.

5. **Q:** Can I submit an NDA-1 application under the full evaluation route if the required GMP certificate covering the DS of interest is not yet available at the point of submission as the GMP inspection has not been completed?

   A: Yes, you can still submit the application with any valid DS GMP certificate issued by a PIC/S authority at the point of submission. However, you should also provide a commitment letter to furnish the required GMP certificate covering the DS of interest by a specified date before the approval of the product.

6. **Q:** Can the DS manufacturer provide the GMP inspection report directly to HSA if there are confidentiality concerns?

   A: Yes, the DS manufacturer can submit the GMP inspection report directly to HSA. The scope of the inspection should cover the DS of interest, and the close out report should also be provided if applicable. Please include the relevant PRISM application number in the submission.

   The submission can be made via a CD-ROM addressed to:
   Therapeutic Products Branch, Health Sciences Authority,
   11 Biopolis Way, Level 11, Helios. Singapore 138667.

7. **Q:** Does the Written Confirmation have to be provided using the *European Union (EU) template*? Does it have to be from the same PIC/S authority that issued the GMP certificate? Can a declaration from the DS manufacturer be provided instead of the written confirmation to indicate that the DS of interest was within the scope of the inspection?

   A: The Written Confirmation does not have to be submitted using the *European Union (EU) template*. We accept any official document from the PIC/S authority that has issued the GMP certificate to confirm that the DS of interest was within the scope of the GMP inspection. However, we do not accept self-declarations from the DS manufacturer or product owner.

8. **Q:** Can GMP certificates issued by third party certification schemes for excipient manufacturers, such as EXCiPACT (International Pharmaceutical Excipients Certification), be used if my DS is also commonly used as an excipient?

   A: No, GMP certificates issued by third party certification schemes are not acceptable. Only GMP evidence issued by a PIC/S authority is accepted.

9. **Q**: Are the GMP evidence requirements for chemical DS and biologic DS the same?

   A: The GMP evidence requirements are similar for chemical and biologic DS manufacturers. In addition, considering the nature of the manufacturing process of biologic DS, GMP evidence specifying the category of DS (e.g., recombinant DNA derived protein) or describing the manufacturing operations specific to the category of DS (e.g., fractionation and purification of plasma-derived products, virus inactivation of vaccines) is also acceptable.