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

Background

1. As part of HSA's continuous effort to ensure the quality standards of therapeutic products supplied in Singapore, HSA had rolled out a one-year transition plan for companies to comply with the requirement for Evidence of Good Manufacturing Practice (GMP) Compliance for manufacturers of chemical drug substance (DS) in September 2023. The requirement is mandatory as of **1 October 2024**. This will enable companies to better assure the quality of therapeutic products supplied in Singapore and safeguard the health and safety of our patients.

Evidence of GMP Compliance for DS Manufacturing Sites

2. The GMP Compliance Evidence must be specific to the DS to which the application relates. The types of acceptable GMP Compliance Evidence are as follows and companies may submit either (a), (b), (c), (d) or (e) to support the applications:

    (a) A valid GMP certificate issued by any PIC/S* authority with the DS of interest stated. If the DS of interest is not specified on the GMP certificate, a Written Confirmation** for the DS of interest from the PIC/S authority which issued the GMP certificate is to be supplemented.

    (b) The GMP inspection report, with the DS of interest included in the scope, together with the close-out letter (where applicable) for PIC/S authorities which do not issue GMP certificates.

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

    (d) Certificate of Pharmaceutical Product (CPP) – Active Pharmaceutical Ingredient (API) issued by US FDA for the DS of interest.

    (e) Other evidence such as a manufacturing licence issued by a PIC/S authority covering the DS of interest and demonstrating that the site complies with GMP requirements.

3. For applications supported by a valid Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) for the DS of interest, HSA adopts a reliance approach to leverage the GMP compliance assessment under the EDQM Inspection Program for the sites specified in the CEP. For such applications, the requirement in para 2 is optional***.

Date of Implementation

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

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

**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*

**** The EDQM inspection program is an integral component of the certification procedure for issuing CEPs which includes GMP compliance checks for the sites covered by CEP. Any GMP non-compliance statements published on the EudraGMDP database will prompt a review of the relevant CEP's validity by EDQM.*

HSA will continue to assess the applicability of the reliance approach and review the requirements as appropriate.

Frequently Asked Questions (FAQ)

1. **Q**: I am planning to submit a GDA-2 after 1 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 1 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 addition or replacement of manufacturer/ site of drug substance.

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 of the final DS. However, for critical DS intermediates (e.g. cytotoxic DS for antibody drug conjugates), the requirement for DS GMP evidence would apply.

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.

10. **Q**: The micronisation and sterilisation of the DS are not performed by the DS manufacturing site. Do I need to provide separate GMP evidence for these sites?

    A: Yes, GMP evidence is required for the DS micronisation and sterilisation sites if these operations are not performed at the same DS manufacturing site. However, as these are

general operations, the DS of interest does not need to be stated on the GMP certificate. Only the specific operation (i.e. micronisation or sterilisation) needs to be stated.