Frequently Asked Questions (FAQ) on Good Manufacturing Practice (GMP) Evidence for Drug Substance Manufacturers

1. **Q:** Does the GMP compliance evidence requirement extend to DS intermediate manufacturing sites, where the DS intermediate is manufactured at a different site from the final DS manufacturing facility?

   A: Yes, the requirement for GMP compliance evidence applies to manufacturers of late-stage DS intermediates or critical DS intermediates.

   Late-stage DS intermediates are those where the core pharmacologically active structure is complete and only minor chemical modifications remain (such as salt formation, crystallisation, or purification steps) to produce the final DS. Critical DS intermediates are those that significantly impact the quality, safety, or efficacy of the final DS, such as the cytotoxic drug substance and monoclonal antibodies for antibody drug conjugates.

2. **Q:** Can an NDA-1 application under the full evaluation route be submitted to HSA concurrently with other PIC/S regulatory authorities when the GMP inspection of the DS site has not taken place yet and the required GMP compliance evidence covering the DS of interest is not available at the point of submission?

   A: Yes, an NDA-1 application under the full evaluation route may be submitted provided that the DS site inspection by a PIC/S authority has been scheduled. A commitment letter to furnish the required GMP compliance evidence covering the DS of interest by a specified date before the approval of the application must be provided.

3. **Q:** Can DS manufacturers submit GMP inspection reports directly to HSA?

   A: Yes, DS manufacturers may submit GMP inspection reports directly to HSA. The scope of the inspection should cover the DS of interest, and any close-out reports for inspection findings should be included. The relevant PRISM application number should be included in the submission.

   The submission can be made via either (a) or (b):

   (a) CD-ROM addressed to:
   Therapeutic Products Branch, Health Sciences Authority,
   11 Biopolis Way, Level 11, Helios. Singapore 138667.

(b) Cloud-based file exchange software (EasiShare). Please refer to the following for step-by-step guidance:
   i. Key Points to Note when Preparing Documents for Submission via EasiShare
   ii. EasiShare FAQ
   iii. Request for access (click here) to EasiShare for dossier submissions

4. **Q:** 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 inspection by a PIC/S authority?

   A: No, declarations from DS manufacturers, product owners, or drug product manufacturers are not acceptable. Only Written Confirmation from the PIC/S authority that issued the GMP certificate are accepted to confirm that the DS of interest was within the scope of the GMP inspection.

5. **Q:** Can GMP certificates issued by third party certification schemes for excipient manufacturers, such as EXCiPACT (International Pharmaceutical Excipients Certification), be used when the 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.

6. **Q**: If micronisation and / or sterilisation of the DS are conducted at separate sites from the main DS manufacturing facility, is additional GMP evidence required for these sites?

   A: Yes, GMP evidence is required for the DS micronisation and / or sterilisation sites if these operations are not performed at the same DS manufacturing site. The evidence should state the specific operations (i.e. micronisation or sterilisation). However, as these are general operations, the DS of interest need not be stated on the GMP certificate.

7. **Q:** Can the EOI to request HSA to conduct a GMP inspection for the overseas DS manufacturing site and product registration application be submitted concurrently?

   A: No, the product registration application may only be submitted after receiving the EOI outcome.

8. **Q**: If the DS and drug product (DP) are manufactured at the same site that requires HSA on-site GMP inspection, is EOI submission still required for the DS site inspection?

   A: Yes, an EOI is required for any request for HSA to conduct a GMP inspection of the DS site, even if the DS and DP manufacturing occur at the same location.

9. **Q**: If the product registration application involves 2 different DS manufactured at the same site, and the site requires an HSA on-site GMP inspection, are separate EOIs required?

   A: Yes, separate EOIs are required. Each GMP inspection is specific to only one DS and one manufacturing site. Hence, 2 EOIs will be required in this instance.