Appendix 12-1

Matters that Should be Applied for Changes of Manufacturing Process and Batch Size of Drug Product

Manufacturing process	1. Change in the manufacturing process of bio-pharmaceuticals and the change requires an assessment of comparability in accordance with "Comparability of Biotechnological/Biological Products" guideline.
	2. Change in the sterilization process/method of drug product.
	3. Changes in the critical steps.
	4. Change in equipment to a different design and different operating principles.
	5. Deletion of an in-process test which may have a significant impact on the quality of drug product.
	6. Widening of the approved in-process control limits which may have a significant impact on the quality of drug product.
Batch size	1. Change in the batch size of bio-pharmaceuticals and the change requires an assessment of comparability in accordance with "Comparability of Biotechnological/Biological Products" guideline.
	2. Any change in the registered batch size (Note2) for dosage forms manufactured by complex manufacturing processes (Note1).
	3. Change in batch size for solid oral dosage forms which the registered batch size (Note2) is less than 100,000 dosage units (Note3).
	4. Changes in batch size beyond a factor of 10-fold of the registered batch size (Note2).

Note：

1 Complex manufacturing processes are included:

(1)The link between quality characteristics of the drug product and in-vivo performance is not fully understood, ex Nano drugs.

(2)The change in the manufacturing process may impact on the quality of drug product. The dosage forms manufactured by complex manufacturing processes may include, but not limit to liposomal product, transdermal delivery product, and inhaled product.

2 If the product had conducted the BE studies (for registration), the registered batch size refers to the size of biobatch. Otherwise, the registered batch size refers to the size of the representative drug product batch. If the product had not

conducted the BE studies, and unable to confirm the registered batch size, refer to the size of validation batch.

3 This case applies to the product for which the size of the biobatch in BE study compiled with the Article 9 of Regulation of Bioavailability and Bioequivalence Studies on 2016 January 1st.