

## Appendix 12:

### Documents for the Application of Registration Change of API Technical Document

Major changes
<p>Documents to be submitted:</p> <ol style="list-style-type: none"><li>1. Form for applying post-approval changes, stating the changes between old and new contents.</li><li>2. Scientific justification for the changes.</li><li>3. If it is the addition or change of manufacturing site, the documentation of GMP-compliance certificate for the API production shall be provided.</li><li>4. For the addition or change of the API manufacturing site, the submission is proceeded for that manufacturing is operated under the same Quality Assurance system, with in changes on the manufacturing process, in process control, and specification (including method and data of analysis). The submission dossiers should include <del>of</del> starting materials (including manufacturer, specification, and analysis data), reaction steps and detailed route of synthesis (including yields and the amount of all materials), materials in the manufacturing process (including solvents, reagents and catalysts etc.), specification of active substances and intermediates (including method and data of analysis), and stability study results, as well the changes should be compared and stated. *</li><li>5. If it is the changes of manufacturer, manufacturing process, control of intermediates and active ingredients, batch analysis data for two consecutive batches (at least one industrial scale batch) that are manufactured in compliance with currently approved and proposed process shall be submitted.</li><li>6. For the changes of manufacturer, synthetic route, reagents and solvents used in the manufacturing process and reaction conditions which may have a significant impact on the quality, the results of stability studies shall be provided. Alternatively, scientific evaluation and justification can be submitted for assessing if the quality of active substance has not been changed significantly. For active substances known to be stable*, the submission of stability study results should include one batch of three months data on at least pilot scale before and after changes. For active substances known to be unstable: at least three batches of six months data on at least pilot scale before and after changes should be submitted.</li><li>7. For the change of immediate packaging, at least 2 batches of six-months accelerated testing results for at least pilot scale sample shall be submitted.</li><li>8. If the comparative data before and after change cannot be provided (i.e. Lack of the original dossier), a full dossier (presented in the CTD format) of technical</li></ol>

documents shall be submitted.

9. For imported API, the submitted documentation shall include the notification letter stating the post-approval changes from the original manufacturer.

\*If it is lack of consistence between current and proposed dossiers, it is requested to submit the whole technical documents of active substance for review, or for a new registration of active substance as specified in Article 42.

\*\*If the results of two years' long-term test (25°C /60% RH or 30°C /65% RH) and six months' acceleration test (40°C /75% RH) are consistent with that at the time of product release, the active substance could be regarded as "known to be stable".

#### Changed items

1. Manufacturer	Change in the manufacturer of an intermediate used in the manufacturing process of the active substance or change in the manufacturer of the active substance.
2. Manufacturing process	1. Change in the synthetic route of active ingredients.
	2. Changes of reagents and solvents used in the manufacturing process.
	3. Changes of reaction conditions in the manufacturing process which may have a significant impact on the quality.
	4. Widening of the approved in-process test limits.
	5. Deletion of an in-process test.
3. Control of starting materials, reagents, intermediates and API	1. Deletion of an approved test limit item in the specifications.
	2. Widening of the approved specification limits.
4. Container closure system	1. Change in immediate packaging of the active substance, and the proposed packaging material is different with the approved material.
	2. Changes of the immediate packaging materials of sterile and liquid active ingredients.

#### Minor changes

Documents to be submitted:

1. The application form for post-approval changes, explaining the difference between the old and new contents.
2. Scientific basis of changes.
3. Change in the manufacturer of the active substance, the GMP-compliance certificate shall be proved.

4. Batch analysis data of one batch manufactured according to the currently approved and proposed process.
5. For the changes of manufacturer, batch size and storage conditions of active ingredients, the results of 3-month accelerated stability studies (at least one batch) or a long-term stability study that covers the claimed expiration date shall be provided.
6. Change in the specification parameters and/or limits of the immediate packaging of the active substance, stability test results are not required.
7. For imported active ingredient, the notification letter of the post approval changes of issued by the original manufacturer shall be submitted.

#### Changed items

1. Manufacturer	Changes of the manufacturer of the active substance (e.g. Changes of the manufacturer's addresses, same factory but different manufacturing area or relocation of the factory; manufacturing process does not involve changes of synthetic pathways and specifications, and in process control and analytical methods remain the same as approved) and quality control testing sites.
2. Manufacturing process	1. Up to 10-fold increase compared to the originally approved batch size.
	2. Addition or replacement of an in-process test as a result of a quality issue.
3. Control of starting materials, reagents, intermediates and drug substance	Addition or replacement of a specification parameter with its corresponding test method.
4. Container closure system	1. Addition or replacement of a specification parameter as a result of a safety or quality issue.
	2. Deletion or change of a specification parameter.
5. Stability	Change of storage conditions of active ingredients.