STANDARD CHEM.& PHARM.CO.,LTD

4th Joint Conference of Taiwan and Japan on Medical Products Regulation

Regulatory Comparison of Post-Approval Change for Medicinal Products

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Background

1. The “Taiwan-Japan Cooperation Agreement on Pharmaceutical Regulations” (台日藥物法規合作框架協議) was signed on November 5, 2013.
2. This agreement is a response to the globalization of the industry, and aims to expand the multifarious cooperation in bilateral pharmaceutical regulations between Taiwan and Japan.
3. Since the signing of the agreement in 2013, the “Joint Conference of Taiwan and Japan on Medical Product Regulation” (台日醫藥交流會議) is held annually. Until the 4th symposium, the industry delegates are honored to be invited to attend the conference.

(Quoted from Center of Drug Evaluation, Taiwan, International Cooperation)

Scope

- Post-Approval Change
- Oral Solid Dosage Form
- The Quality Difference Caused by Post-Approval Change
- Bioequivalence Study Requirement Harmonization

Post-Approval Change Reporting Categories

Risk of Change	Taiwan (TFDA)[1]	Japan (MHLW)[2]	U.S.A (FDA)[3]
High	Major Change (Prior Approval Change)	Partial Change Approval Application (Application for approval of variation)	Major Change (Prior Approval Supplement (PAS))
Moderate	Minor Change (Prior Approval Change)	Minor Change Notification (Notification within 30 days after implementation or shipping)	Moderate Change (Supplement-Changes Being Effected in 30 days (CBE30)) (Supplement-Changes Being Effected (CBE))
Low	Non-approved matters	Non-approved matters	Minor Change Annual Report (AR)

Reference :

1 : Regulations for Registration of Medicinal Products (2016.04.06), Article 46 and TFDA notification (No. 0900018043, dated 2001/03/19)

2 : Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law, PFSB/ELD Notification No. 0210001 February 10,2005

3 : Guidance for Industry Changes to an Approved NDA or ANDA (April 2004 CMC Revision 1)

The Change Item (Taiwan)

- Components and Composition
- Batch Size
- Manufacturing Equipment
- Manufacturing Process
- Manufacturing Site
- API Source Change

The Change Degree (Taiwan)

Change Item	Change Degree	
	Minor Change	Major Change
Article 46: Definitions of major changes and minor changes are as announced by the central health competent authority		
Components and Composition Batch Size Manufacturing Equipment Manufacturing Process	For minor changes: a drug dissolution profile comparison report should be submitted.	For major changes: BE test reports should be submitted

Reference :
1 : Regulations for Registration of Medicinal Products (2016.04.06), Article 46 and Article 53 Paragraph 4
2 : TFDA notification (No. 0900018043, dated 2001/03/19)

Components and Composition (Taiwan)

Change Item			Change Degree	
			Minor Change	Major Change
Components and Composition	Filler		>5% and ≦10%	>10%
	Disintegrant	Starch	>3% and ≦6%	>6%
		Other	>1% and ≦2%	>2%
	Binder		>0.5% and ≦1%	>1%
	Lubricant	Ca or Mg Stearate	>0.25% and ≦0.5%	>0.5%
		Other	>1% and ≦2%	>2%
	Glidant	Talc	>1% and ≦2%	>2%
		Other	>0.1% and ≦0.2%	>0.2%
	Film Coat		>1% and ≦2%	>2%
	Others: Preservative、Color、 Flavor, etc.		Case by case; the following case does not belong to major or minor change: The deletion or reduction of an ingredient (color or flavor)	
	Note: (1) Percentage change (%) means the absolute value in percentage of the change weight (before and after) of an ingredient divided by the total weight of the formula. (2) If the sum of each change percentage (%) exceeds the 5% and not more than 10%, the change belongs to minor change. (3) If the sum of each change percentage (%) exceeds 10%, the change belongs to major change. (4) If the change is to add or delete one excipient (including filler, disintegrant, binder, lubricant, glidant, film coat), the change belongs to major change.			

Reference : TFDA notification (No. 0900018043, dated 2001/03/19)

Manufacturing (Taiwan)

Change Item	Change Degree	
	Minor Change	Major Change
Batch Size	>10 folds	No
Manufacturing Equipment	Change to use the different design or principle equipment	No
Manufacturing Process	1. For the validated process, the process change exceeds the validated range. 2. The other changes depend on the case.	Change on process step For example: From wet granulation to dry granulation or direct compression.

Reference : TFDA notification (No. 0900018043, dated 2001/03/19)

Manufacturing Site (Taiwan)

Change Item	The following information should be provided for changes of the manufacturing site of drugs:
Manufacturing Site	1. A comparison between formulation and the manufacturing process, including raw material sources, specifications and manufacturing equipment. 2. Drug dissolution profile comparison 3. If according to the assessment, a major change is classified or more information is needed, then the BE test report should be submitted.

Reference:
1 : Regulations for Registration of Medicinal Products (2016.04.06), Article 46
2 : TFDA notification (No. 0900018043, dated 2001/03/19)

Active Pharmaceutical Ingredient Source Change (Taiwan)

Article 53 Paragraph 4	The following documents shall be submitted:
API Source Change	1. The application form for post-approval changes; 2. Original copy of the drug license; 3. GMP compliance certificate of the newly added or changed 4. The approval of the technical documents of the active; ingredients issued by the central health competent authority; 5. Description of the differences of specification between the new and old source of active ingredient with evidential proof; 6. Comparison and evaluation data of the finished preparations according to the characteristics of the dosage forms; 7. According to the preceding paragraph, a dissolution test shall be conducted；if the comparison results of dissolution profile are dissimilar (f2<50), a drug BE test report shall be submitted.

Reference：Regulations for Registration of Medicinal Products (2016.04.06), Article 53 Paragraph 4

The Change Item (Japan)

- Components and Composition
- Ingredient Properties
- Manufacturing Scale
- Equipment
- Manufacturing Site
- Manufacturing Process
- API Source Change

Manufacturing (Japan)

Change Item (Immediate-release, enteric-coated, sustained-release)	Change Degree	
	Minor Change (Level 1)	Moderate Change (Level 2)
Ingredient Properties	Changes in bulk drug crystal form, particle size, etc., or changes to the grade of excipients, etc., that have virtually no effect on quality	Changes in bulk drug crystal form, particle size, etc., or changes to the grade of excipients, etc., that could have an effect on quality
Manufacturing Scale	Manufacturing scale changes with virtually no effect on quality (Equipment with same form and operating principles, similar SOPs) Manufacturing scale change within 10-fold scale-up or scale-down	Manufacturing scale change that could affect quality (Equipment with same form and operating principles, similar SOPs) Manufacturing scale change greater than 10-fold scale-up or scale-down

Reference：経口固形製剤の製法変更の生物学的同等性試験に係る考え方等について(厚生労働省医薬食品局審査管理課 事務連絡 平成25年4月19日)

Manufacturing (Japan)

Change Item (Immediate-release, enteric-coated, sustained-release)	Change Degree	
	Minor Change (Level 1)	Moderate Change (Level 2)
Equipment	Change to different equipment with same form and operating principles	Change to equipment with different form and operating principles
Site	Transfer to manufacturing site with same staff education and training systems (same SOPs, environment, management)	Transfer to manufacturing site with different staff education and training systems (Equipment with same form and operating principles, same SOPs, environment, management)

Reference：経口固形製剤の製法変更の生物学的同等性試験に係る考え方等について(厚生労働省医薬食品局審査管理課 事務連絡 平成25年4月19日)

Manufacturing Process (Japan)

Change Item	Change Degree		
Manufacturing Process	Minor Change (Level 1)	Moderate Change (Level 2)	Major Change (Level 3)
Details of Change / Tests Required	Changes in operating parameters, such as mixing time and operating speed, within range specified in application or validation.	Changes in operating parameters, such as mixing time and operating speed, outside range specified in application or validation.	Changes that could significantly affect formulation quality beyond the range described above. E.g. Change from wet granulation to dry tableting manufacturing processes.
Immediate-release and enteric-coated dosage forms	1) If dissolutions tests are set in accordance with 'Setting specifications and test procedures for new drugs' (PMSB Notification No. 568): Conformity with specification 2) If specification dissolution tests have high discriminatory power: Equivalence of dissolution behavior under specification test conditions 3) Other: Equivalence of dissolution behavior under all conditions in the Generics Guideline	1) If dissolutions tests are set in accordance with 'Setting specifications and test procedures for new drugs' (PMSB Notification No. 568): equivalence of dissolution behavior under specification test conditions 2) Other: Equivalence of dissolution behavior under all conditions in the Generics Guideline	1) If ≥85% dissolution occurs within 30 min in medicinal products with a wide therapeutic concentration range under all conditions of the Generics Guideline: Equivalent dissolution behavior. 2) Other: Bioequivalence tests in accordance with Generics Guideline
Sustained-release dosage forms	1) If dissolutions tests are set in accordance with 'Setting specifications and test procedures for new drugs' (PMSB Notification No. 568): Conformity with specification 2) Other: Equivalence of dissolution behavior under conditions in the Generics Guideline	1) If dissolutions tests are set in accordance with 'Setting specifications and test procedures for new drugs' (PMSB Notification No. 568): Equivalence of dissolution behavior under specification test conditions 2) Other: Equivalence of dissolution behavior under conditions in the Generics Guideline	Bioequivalence tests in accordance with Generics guideline

Reference：経口固形製剤の製法変更の生物学的同等性試験に係る考え方等について(厚生労働省医薬食品局審査管理課 事務連絡 平成25年4月19日)

Active Pharmaceutical Ingredient Source Change (Japan)

Attachment 1	Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law
API Source Change	1. Since changes in manufacturing sites require adequate change control, they shall be, in principle, addressed in partial change approval applications for matters that have been approved. 2. However, if a change falls under one of the following and its change control has been carried out properly, it shall be addressed in a minor change notification. ① A change to a manufacturing site that exists in Japan, of which the change in the manufacturing method falls within the scope of a minor change notification, is classified in the same license or accreditation category, and complies with GMP (refers to cases where the same status is expected to be maintained thereafter, such as there not being any GMP non-compliances found; the same applies hereinafter) in GMP inspections (i.e., on-site inspection only; the same applies hereinafter) conducted within the last 2 years for a product of a similar class that shares related processes. ② A change in the facilities related to testing ③ A change in the facilities related only to packaging, labeling, and storage. 3. Changes from a domestic manufacturing site to a foreign manufacturing site, and changes in manufacturing sites within foreign countries shall also be addressed in a minor change notification if they meet the above conditions.

Reference : Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law, PFSB/ELD Notification No. 0210001 February 10,2005

Industry Perspective (1/2)

- When post-approval changes of a new or generic drug are categorized as major or minor changes, it is prudent to evaluate the necessity of re-conducting comparative dissolution studies or the bioequivalence study.
- There are still significant differences between Japan and Taiwan in regards to the current regulatory requirements of post-approval changes.

Industry Perspective (2/2)

- Alignment of bilateral regulations on bioequivalence between Japan and Taiwan should be a primary focus as we seek to expedite regulatory harmonization of post-approval changes.
- This is one crucial step towards mutual recognition that could reduce development costs without foregoing quality, and accelerate the international approval timeline.


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