Key-points of Post approval variation in Korea

Eunkyung Kim, Ph.D.
Drug Evaluation Department, NIFDS, MFDS

식품의약품안전처

Disclaimer

The information in this presentation is based on my experience.

The following slides represent the presenter’s views and not necessarily the views of the Korea MFDS.

Summary of GMP Compliance Qualification Process in "Korea"

Question1: ***Among the following proposed change cases "1-4", which case requires "a-c" for GMP qualification of the related manufacturing sites (Yes or No)?***

Assumption: ***For small molecule API or DP (including recombinant protein products)*** *change, proposed change would not create new impurity*

(*) Additional document includes Process validation report, copies of analytical raw data, batch record, and submission of GMP certificate at the time of change submission

Change cases and requirements	1) Change of Manufacturing process	2) Change of Test Methods	3) Change of Manufacturing sites	4) Change of Packaging
a) Requirement of on-site inspection	For API: No For DP: No	For API: No For DP: No	For API: Yes[1)] For DP: Yes [1)]	For API: No For DP: No
b) Additional documents(*) (if needed)	For API: Yes For DP: Yes	For API: Yes For DP: Yes	For API: Yes For DP: Yes	For API: Yes For DP: Yes
c) Review period is longer than 6 months[2)]	For API: No For DP: No	For API: No For DP: No	For API: No For DP: No	For API: No For DP: No

1) On-site inspection or document review

2) It depends on degree of changes(major, moderate, minor), submitted data quality and on-site inspection schedule. The official review period is not longer than 6 months. (API; 60days, DP; 90days)

(*) For change of manufacturing sites, additional documents are required for GMP qualification while they are required for CMC review in case of the other changes.

Summary of Stability study documents required for the variations in "Korea"
Question2-1: ***For the following proposed change cases "1 – 4", does your agency requires to submit stability data at the time of change proposal (Yes or No) ?***

Assumption: ***For small molecule API change(chemical),*** *proposed change would not create new impurity.*
For small molecule DP change, API process/site remains the same as original submission.

Change cases and requirements	1) Change of Manuf. process	2) Change of Test Methods	3) Change of Manuf. sites	4) Change of Primary Packaging
a) Real time stability data is required.	For API: Depends* For DP: Depends*	For API: No For DP: No	For API: Yes For DP: Depends*	For API: Yes For DP: Depends**
b) NLT 6 months data is required for long term stability.	For API: Yes (if applicable) For DP: Yes (if applicable)	For API: No For DP: No	For API: Yes For DP: Yes	For API: Yes For DP: Yes (if applicable)
c) Stability Commitment can be applied.(commitment only)	For API: Depends** For DP: No	For API: No For DP: No	For API: No For DP: No	For API: No For DP: Depends**
d) Bracketing / Matrixing approach is acceptable.	For API: Yes For DP: Yes	For API: Yes For DP: Yes	For API: Yes For DP: Yes	For API: Yes For DP: Yes

- **API(Drug master file)** ; ***Major changes** which are defined in the **'Regulation on Safety of Medicinal Products, etc'** (Ordinance of the Prime Minister) **require stability data**.
  **For change of Manuf. Process, real time stability data could be replaced with stability commitment if it is demonstrated that the quality is equivalent.
- **DP**; ***The changes demanding bioequivalence study require real time stability data**. The level of changes and required documents are defined in the **'Standard on Pharmaceutical Equivalence Study'** (MFDS Notification). **It is considered if packaging has been already marketed or not.

Summary of Stability study documents required for the variations in "Korea"

Question2-2: ***For the following proposed change cases "1 – 4", does your agency requires to submit stability data at the time of change proposal (Yes or No) ?***

Assumption: ***For recombinant protein products****, proposed change would not create new impurity.*
For small molecule DP change, API process/site remains the same as original submission.

Change cases and requirements	1) Change of Manuf. process	2) Change of Test Methods	3) Change of Manuf. sites	4) Change of Primary Packaging
a) Real time stability data is required.	For API: Yes For DP: Yes	For API: No For DP: No	For API: Yes For DP: Yes	For API: Yes For DP: Yes
b) NLT 6 months data is required for long term stability.	For API: Yes For DP: Yes	For API: No For DP: No	For API: Yes For DP: Yes	For API: Yes For DP: Yes
c) Stability Commitment can be applied.[1)]	For API: Yes For DP: Yes	For API: No For DP: No	For API: Yes For DP: Yes	For API: Yes For DP: Yes
d) Bracketing / Matrixing approach is acceptable.	For API: Yes For DP: Yes	For API: No For DP: No	For API: Yes For DP: Yes	For API: Yes For DP: Yes

1) NLT 6 months long term stability data + commitment

Question 3: Please describe required documents in the following variations.

Change of manufacturing process		
Classification	**Required documents**	**Detailed Requirements**
Chemical Drug Products ** The level of changes is defined in 'Standard on Pharmaceutical Equivalence Study' (MFDS Notification); level A ~ D.*	Manufacturing methods	• Detailed manufacturing process • Process validation report or validation protocol (for changes demanding bioequivalence study ; level D) • Production documents (batch record)
	Spec and test method	• Spec. and test method, batch analysis • Justification of Spec., method validation report (if changed)
	Stability studies	• Accelerated and long-term stability data ; NLT 6M, 3 batches (for changes demanding bioequivalence study ; level D)
	Bioequivalence studies	• Necessary for changes with significant effect on quality; level D
	Others	• More CMC data in CTD format (for changes demanding bioequivalence study; level D) (if applicable)
Biological Drug Products (in case of recombinant protein products) ** Major manufacturing process change*	Manufacturing methods	• IPC test results • Process validation report in production scale
	Spec and test method (if changed)	• Justification of Spec., Method validation • Test results by modified test method • Comparison of before and after modified test method results
	Stability studies	• NLT 6M long-term (commitment) • NLT 3M accelerated and/or stress condition
	Bioequivalence studies	• Comparison of IPC, batch release test, stability results • Characterization studies (if needed)
	Others	• Batch release test results(CoA) • Extractable and leachable studies (if needed)

Question 4: Please describe required documents in the following variations.

Change (Addition) of manufacturing site (by the same manufacturing process)		
Classification	Required documents	Detailed Requirements
Chemical Drug Products ** Change of manufacturing site with different manufacturer*	Manufacturing methods	• Detailed manufacturing process • Process validation report or validation protocol • Production documents (batch record)
	Spec and test method	• Spec. and test method, batch analysis • Justification of Spec., method validation report (if changed)
	Stability studies	• Accelerated and long-term stability data ; NLT 6M, 3 batches
	Bioequivalence studies	• Necessary
	Others	• More CMC data in CTD format (if applicable)
Biological Drug Products (in case of recombinant protein products)	Manufacturing methods	• IPC test results • Process validation report in production scale
	Spec and test method (if changed)	• Justification of spec., Method validation • Test results by modified test method • Comparison of before and after modified test method results
	Stability studies	• NLT 6M long-term(commitment) • NLT 3M accelerated and/or stress condition
	Bioequivalence studies	• Comparison of IPC, batch release test, stability results • Characterization studies (if needed)
	Others	• Batch release test result (CoA) • Extractable and leachable studies (if needed)

Question 5: Please describe required documents in the following variations.

Formulation Change or Addition of Primary Packaging		
Classification	**Required documents**	**Detailed Requirements**
Chemical Drug Products ** Different formulation*	Manufacturing methods	• Changed manufacturing process (if applicable)
	Spec and test method (if changed)	• Spec. and test method, batch analysis • Justification of spec., method validation report
	Stability studies	• Accelerated and long-term stability data; NLT 6M, 3 batches (if the primary packaging is not marketed before)
	Bioequivalence studies	• Unnecessary
	Others	• Suitability, compatibility data (if applicable)
Biological Drug Products (in case of recombinant protein products) ** Same formulation and different fill volume*	Manufacturing methods	• IPC test results, Process validation report in production scale
	Spec and test method (if changed)	• Justification of spec., method validation • Test results by modified test method • Comparison of before and after modified test method results
	Stability studies	• NLT 6M long-term(commitment) • NLT 3M accelerated and/or stress condition
	Bioequivalence studies	• Comparison of IPC, batch release, stability results • Characterization studies (if needed)
	Others (Information of Drug Product in CTD)	• Batch release test results (CoA) • Information of batch formula, manufacturing process, process controls, critical steps, intermediates • Supporting clinical data or justification for why such data are not needed • Extractable and leachable studies (if needed)