The 10th APAC

Revisions of Japanese BE Guidelines

Ryosuke Kuribayashi, Ph.D.
PMDA Office of Generic Drugs
13 April 2021

Disclaimer

The views and opinions expressed in this presentation are those of the individual presenter.

COI

The speaker has no conflicts of interest to declare.

Agenda

1. Revised BE Guidelines
2. Addition of Fed state BE study
3. Reconsideration Pilot Study and Add-on Study
4. Acceptance of Foreign Subjects in BE study
5. Clarification of Requirement of Reference Product
6. Conclusions

Revisions on BE in Generics

The MHLW issued the Revisions of Japanese BE Guidelines in March 2020.

- ✓ Addition of a fed-state BE Study
- ✓ Reconsideration of the pilot study and add-on study
- ✓ Acceptance of foreign subjects in a BE study
- ✓ Clarification of the requirement of a reference product

Fed-state BE study

Until now, the PMDA required a fed-state BE study for only extended release products.

After revisions of BE guidelines,
the following products are also required a fed-state BE study.

- ✓ Enteric-coated products (Delayed release products)
- ✓ Solubility enhanced products
  e.g., Solid dispersion, Microemulsion,
  Amorphous, Nano particle etc

Fed-state BE study

What is the reason ?

Solubility enhanced products

To assure the bioequivalence of product functions (i.e., enhancing solubility) of special controlled release mechanism and product design in the severe condition.

Enteric-coated products

To have a concern the possibility that the drug concentration-time profiles may differ due to the differences of gastrointestinal transit time between generic and original product.

What is the Food effect to GI functions ?

- Changing the intragastric pH
- Promotion the secretion bile acid and enzyme
- Promotion the digestion of drug products (destruction and crush)
- Solubilization of insoluble API by meal
- Delay of gastric emptying rates

Fed-state BE study

pH in the fasted and fed states

Table II. Gastric pH Species Comparison

Species	Source	Method	Number of Subjects	Fasted pH	Peak pH After Meal	Fed pH (60 min)
Cynomolgus monkey	Present study (slurry meal)	Bravo® capsule	6[a]	1.1–2.1[b]	6.1–6.2[b]	4.2–5.6[b]
	Present study (standard meal)	Bravo® capsule	5	1.2–3.0[b]	6.1–6.6[b]	3.0–5.9[b]
	(37)	pH electrode	10	1–3[c]	–	5–7[c]
	(38)	gastric fluid aspirates	16	1.2–4.3[d]	–	–
Human	(40)	Heidelberg capsule	10	0.4–4.0[d]	–	–
Human (young)	(31)	Heidelberg capsule	24	1.4–2.1[b]	6.4–7.0[b]	~2–4.5[e]
Human (elderly)	(30)	Heidelberg capsule	79	1.1–1.6[b]	3.9–5.5[b]	~2–6[f]

[a] Six monkeys were included in the Fasted (slurry meal) pH analysis and five monkeys included in the Fed (slurry meal) pH analysis as the pH transmission from one monkey, 24504, ceased upon feeding
[b] Interquartile range (IQR), fed pH represents data between 0 and 60 min post meal
[c] Median range
[d] Range
[e] IQR estimated from Fig. 4 (31)
[f] IQR estimated from Fig. 4 (30)

∗ Chen EP et al., Pharm Res. 2008 25(1): 123-34.

Intragastric pH and pH behavior were completely different between the fasted and fed states

Fed-state BE study

	Package inserts	IR				ER		EC	
		Ordinary		SE					
		Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed
Past	Not specified	○	×	○	×	○	○	○	×
	Only Fasted	○	×	○	×	○	○	○	×
	Only Fed	○	×	○	×	○	○	○	×
Present	Not specified	○	×	○	○	○	○	○	○
	Only Fasted	○	×	○	×	○	○	○	×
	Only Fed	○	×	○	○	○	○	○	○

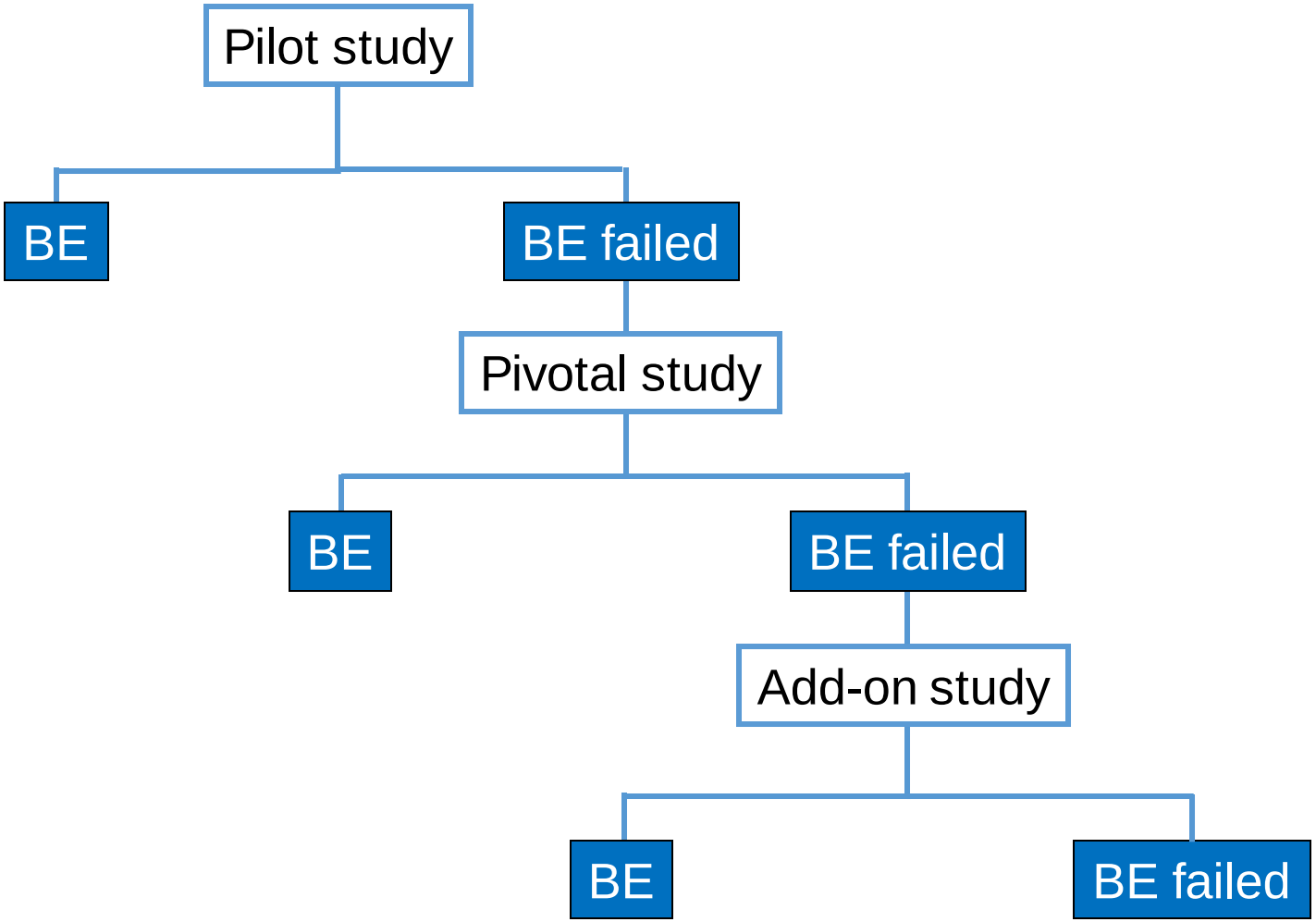
IR: Immediate release; SE: Solubility enhanced; ER Extended release; EC: Enteric-coated

○ The indicated data is required. × The indicated data is not required.

Note: If the original products are administered in only fasted state specified in the Dosage and Administration of package inserts, the sponsors are requested an only fasted BE study .

Amendments of Pilot Study and Add-on Study

Past regulation



Current regulation

Pilot study

- If the generic applicant can't explain the appropriateness of test condition of BE study, the pilot study should be conducted. (e.g., Sampling points, Subject number)
- Generally, this appropriateness is explained the public information based on the original products.
- Therefore, the generic sponsor must conduct the pivotal BE Study, even if the result of pilot study meet the BE criteria.
- Because objective of pilot study is to plan the suitable and proper BE study, not to confirm BE.

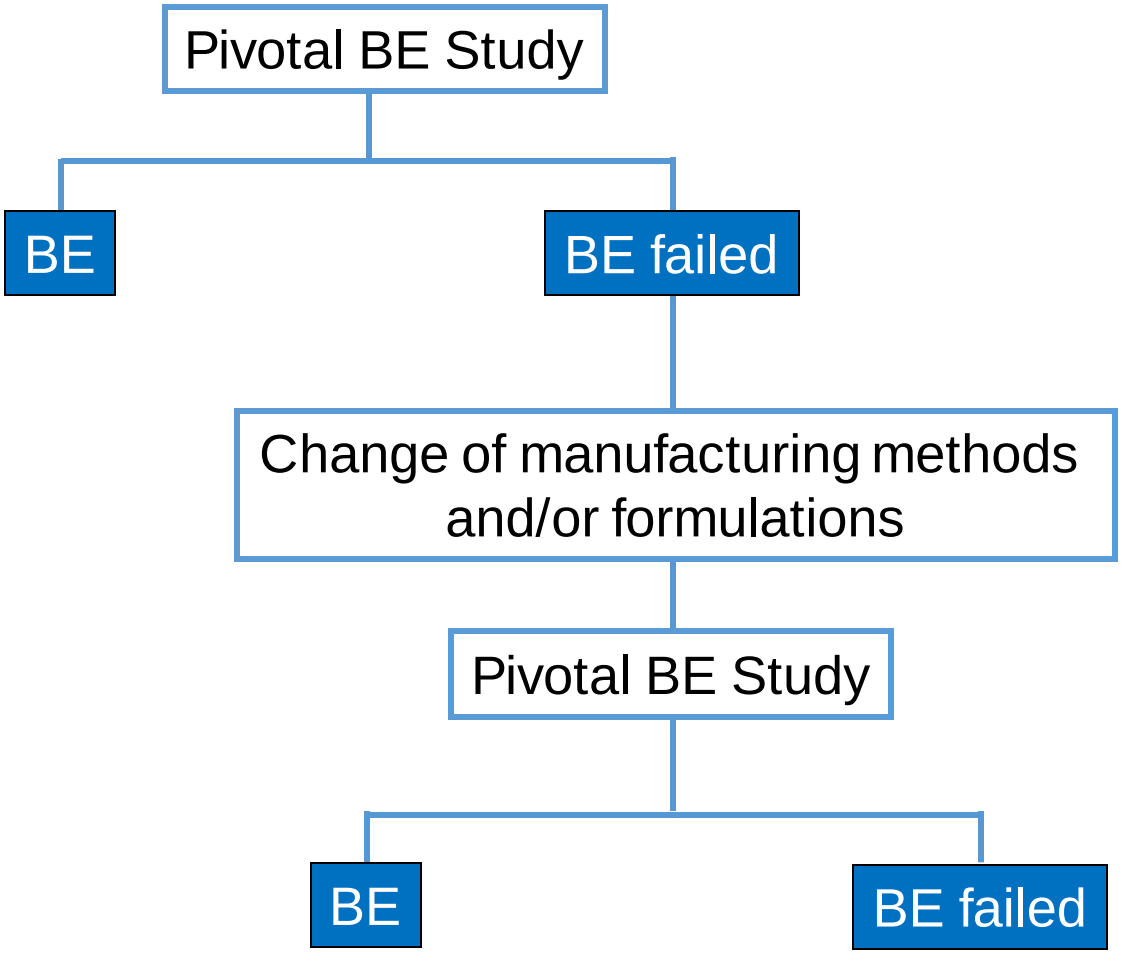
Amendments of Pilot Study and Add-on Study

Current regulation

- ✓ PMDA incorporates the interim analysis for BE study.
- ✓ The sponsors must plan the methodology to control type I error rate at 5% or less.

Amendments of Pilot Study and Add-on Study

Current regulation



Acceptance of BE data of foreign subjects

Foreign subjects

- The data of bioequivalence study against foreign subject are scientifically acceptable.
- If the significant dissolution differences between two products are observed, the subjects for BE study should be Japanese population.

We highly recommend to discuss at face-to-face full consultation meetings in this case.
https://www.pmda.go.jp/english/review-services/consultations/0002.html

Clarify the Requirement of Reference Product

Reference product

- ✓ Domestic original product is required as a reference product for BE evaluations.
- ✓ This decision is strongly tied to the legal aspects.

Conclusions

Take home message

- Modernize and strengthen BE evaluations in Japan (i.e. the incorporation of interim analysis, acceptance of foreign subjects in a BE study, and clarification of the requirement of a reference product modernizes it, and the addition of a fed-state BE study strengthens it).
- Make efforts to harmonise the BE evaluation based on the current scientific rationale for drug development through the ICH activity (e.g. ICH M13 and M9).

Thank you for your kind attention.

Panel Discussion
[Japan]

in APAC 2021

Biowaiver approach

The PMDA accepts the biowaver approach in the following cases for PAC (if some conditions are satisfied).

- BCS based biowaiver
- Formulation change
- Manufacturing site change
- Manufacturing process change

Biowaiver approach

BCS based biowaiver

・The PMDA adopts the BCS based biowaver in accordance with ICH M9 since Dec 2020.

・I have a concern of consistency of results.
Particularly,
Permeability results based on the Caco-2 cell assay may be different between labs.

・ I hope biopharmaceutics classification of the drug substance becomes a same classification all over the world.

Biowaiver approach

Formulation change

The PMDA specifies the levels of formulation changes (i.e., Level A, B, C, D and E).

Also, the PMDA confirms the product characteristics for biowaver of formulation changes (i.e., therapeutic range, poorly soluble or soluble, rapid or non-rapid dissolution)

Biowaiver approach

Formulation change

Table 2. Levels of formulation change for immediate release products

Function of excipient and component	Difference in excipient content compared to BE study strength (%w/w) B	C	D	E
Part : Core				
Disintegrating agents				
Starch	≦3.0	≦6.0	≦9.0	>9.0
Others	≦1.0	≦2.0	≦3.0	>3.0
Binders	≦0.50	≦1.0	≦1.5	>1.5
Lubricants･Polishers				
Stearate salts	≦0.25	≦0.50	≦0.75	>0.75
Others	≦1.0	≦2.0	≦3.0	>3.0
Fluidizing agents*				
Talc	≦1.0	≦2.0	≦3.0	>3.0
Others	≦0.10	≦0.20	≦0.30	>0.30
Diluting agents	≦5.0	≦10	≦15	>15
Others (Preservatives, Sweeteners, Stabilisers etc.) [1)]	≦1.0	≦2.0	≦3.0	>3.0
Sum of absolute values of difference of content (%) of changed components	≦5.0	≦10	≦15	>15
Part : Film coating [2)]				
Sum of absolute values of difference of content (%) of changed components in film coating layer [1)]	≦5.0	≦10	≦15	>15
Rate of change (%) of film coating weight/cm^2 of surface area of core [3)]	≦10	≦20	≦30	>30
Part : Sugar coating				
Sum of absolute values of difference of content (%) of changed components in sugar coating layer	≦5.0	≦10	≦15	>15
Rate of change (%) of sugar coating weight/cm^2 of surface area of core [3)]	≦10	≦20	≦30	>30

Biowaiver approach

Formulation change for IR products
Biowaiver is eligible until Level D change, if some conditions are satisfied.

Level	Therapeutic range	Poorly soluble [1] / Soluble	Rapid [2] /Non-rapid dissolution	Data required
A	Non-narrow			Dissolution specification or multiple dissolution test conditions
B				Multiple dissolution test conditions
C	Non-narrow	Soluble		Multiple dissolution test conditions
		Poorly soluble		Human bioequivalence study
	Narrow	Soluble	Rapid	Multiple dissolution test conditions
			Non-rapid	Human bioequivalence study
		Poorly soluble		
D	Non-narrow	Soluble	Rapid	Multiple dissolution test conditions
			Non-rapid	Human bioequivalence study
		Poorly soluble		
	Narrow			
E				Human bioequivalence study

1) A poorly soluble drug is a drug product for which, when the test is performed at 50 rpm, the average dissolution rate of the comparator product does not reach 85 % within the designated test time in any one of the multi-dissolution media with no surfactant in the medium.
2) Average dissolutions of the comparator and test products reach 85 % at 30 min under all the multi- dissolution conditions.

Biowaiver approach

The PMDA accepts the biowaver approach for PAC.

I believe it is important

・to encourage scientific and risk based approach to BE studies as well as biowaiver.

・ to harmonise the evaluations of bioequivalence/ biowaiver through ICH activity.