청렴韓세상

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Guideline on Evaluation of New Extended Release (ER) Preparations

(Guidance for industry)

MINISTRY OF FOOD AND DRUG SAFETY
National Institute
of Food and Drug Safety Evalution

Cardiovascular and Neurology Products Division
Drug Evaluation Department

This guideline provides the current stance of the Ministry of Food and Drug Safety (MFDS) on evaluation of new extended release (ER) preparations.

This document should be viewed as only recommendations since it is not intended to be legally binding and does not impose any obligations upon industry despite the word 'should' used herein. Besides, since this guidance is written based on the established scientific and technological experiences, and valid laws as of December 22, 2015, its interpretation and application may vary if necessitated by revision of relevant laws and/or new scientific discoveries, etc.

※ An MFDS guidance for industry is a document published to promote understanding of applicable statues or administrative rules in more plain language or to present the current stance of the NFDS, internally and externally, on specific applications or any equivalent ones from industry field with the agency.

※ For any comments or questions regarding this guidance document, please contact the MFDS using the phone numbers provided below.

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Document History

No.	Revision No.	Approval Date	Details
1	B1-2010-2-022	Jan. 2010	Establishment
2	B1-2015-2-040	Dec. 22, 2015	Changing the title of the guideline, clarification of the legal enforceability, standardization of formats, and updating of contact information.
3	Guidance-0184-01	-	Comprehensive revision of registration numbers in accordance with the amendment to the Regulations on the Management of MFDS Guidances and Related Documents (Director for Regulatory Reform and Legal Affairs-No. 3761, May 16, 2017)

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□ Background

○ (Purpose) This guideline is intended to assist the understanding of applicants and aims to ensure consistency in the review process by providing evaluation criteria for the safety and efficacy of extended-release (ER) preparations.

- (Definition) ER preparations are pharmaceutical products designed to control the release rate, release time and release site of the active ingredient, with the aim of reducing the frequency of drug administration or minimizing side effects.

- (Scope) This guideline applies exclusively to **orally administered dosage forms** that contain the same active ingredient as immediate-release (IR) preparations already approved in Korea but have been developed with variations in dosage form, strength, or usage and dosage is different through preparation improvement.

□ Related Regulation

○ Article 5 (1) and Annex 1, Section II. Data Requiring Submission, 7. New dosage form (same route of administration) and Note 8 (b) (**when ER preparations of the same active ingredient are not approved**) of the Regulation for Approvals, Notifications, and Reviews of Pharmaceuticals (MFDS Notice)

- Subparagraph 1, 3, 5 (specifically **absorption and excretion data** under subparagraph c) **6 or data on bioequivalence (BE) study** through 8 in attached data of new drugs, and comparative dissolution study data.

○ In Annex 1, Section II. Drugs Requiring Data Submission of the regulation: 3. New composition of the active ingredient or changes in strength only - New composition (e.g., single-ingredient products to single-ingredient products)

Category \ Submitted data		Document No.*																						
		1	3				4										5			6		7	8
			A		B		A	B	C	D	E	F			A	B	C	A	B		
			1)	2)	1)	2)						(1)	(2)	(3)								
II. Drugs requiring data submission																								
7. New dosage form (same route of administration)																								
New dosage form (same route of administration)		○	×	×	○	×	×	×	×	×	×	×	×	×	×	×	○	○[1)]	×	○	○			
Note		Including submission of comparative dissolution study data																						
3. New composition of the active ingredient or changes in strength only																								
Subject to review	Rationale for exemption (Example of domestic use)																							
Single-ingredient product	Single-ingredient or combination products	○	×	×	○	×	×	×	×	×	×	△	×	×	○[2)]	×	×	○	×	○	○			
Note		Note 1) Data on clinical study results or BE study Note 2) Pharmacodynamics data may be exempted in accordance with Article 28 (4) of the regulation																						

○: Data that must be submitted
△: Data that may be exempted based on the judgment of individual items, as submission is either not meaningful or not feasible
×: Data that is exempted

* Document Number
No. 1: Information on origin or discovery, and pharmaceutical development
No. 3: Information on stability (long-term or accelerated data of the drug products)
No. 4: Information on toxicology (including other toxicological studies, such as local toxicity study: skin irritation)
No. 5: Information on pharmacology (Pharmacodynamics)
No. 6: Information on clinical study
No. 7: Data for foreign usage status
No. 8: Comparative review with similar domestic products and properties of relevant drugs, etc.

□ Considerations for the Development of ER Preparations

○ **Biopharmaceutical characteristics**

- (Elimination Half-Life) Drugs with a prolonged elimination half-life may pose a risk of accumulation.
- (First-Pass Effect) Drugs with a significant first-pass effect are likely to exhibit reduced bioavailability.
- (Adverse Reaction) Excessive drug release may increase the risk of adverse reactions.

※ A review of the relationship between plasma drug concentration or drug concentration at the site-of-action and its clinical effects(efficacy) is required.

○ **Pharmacodynamic characteristics**

- The relationship between the drug and the plasma concentration of the active ingredient, including the API and active metabolites, should be reviewed.
- The average minimum effective concentration and the optimal effective concentration should be identified, along with an investigation of drug concentrations associated with adverse reactions.

○ **Pharmacokinetic characteristics**

- Absorption site, absorption rate, non-linearity, distribution, metabolism, and other related factors should be identified.

○ **Characteristics of candidate drugs for ER preparations**

- Candidate drugs for ER preparations typically have a short half-life and exhibit absorption and elimination rates that are neither too slow nor too fast.

- These drugs exhibit consistent absorption throughout the gastrointestinal tract.
- They possess high potency with low dosage requirements.
- They are characterized by a wide therapeutic index.
- These drugs are primarily intended for chronic diseases rather than acute conditions.
- Drug release acts as the rate-limiting step.

□ Issues

○ For a new ER preparation application, the regulation requires, under Annex 1, the submission of data corresponding to subparagraph 6, which includes either **clinical studies** or **BE studies ;** however :

- there are no criteria for **determining whether the product is subject to** the submission of either clinical studies or BE studies, and
- furthermore, there are no detailed guidelines regarding **the scope of submission** for clinical studies and BE studies.

□ Safety and efficacy Review Approach

○ For a new ER preparation application, data specified in subparagraph 6 (clinical study reports) or BE study reports should be submitted in accordance with Annex 1 of the regulation. The applicable scope is determined based on the flowchart (Attachment 1).

○ The scope of submission of BE studies

- Single-dose administration study, multiple-dose administration study, and food effects study

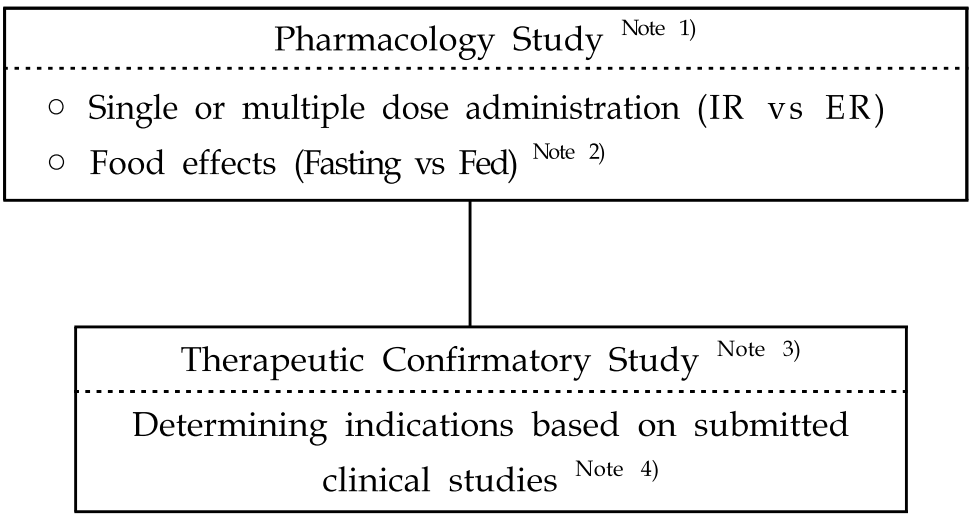
※ Data in accordance with the Standards on Pharmaceutical Equivalence Test (MFDS Notice)

○ The scope of submission of clinical studies

- For clinical pharmacology studies, data on single or multiple dose administration studies, food effects, and therapeutic confirmatory studies

<Attachment 1> Flowchart of Review for New ER Preparations

1) When Submitting Data Related to Clinical Studies



Note 1. Pharmacology studies may reference the Standards on Pharmaceutical Equivalence Test (MFDS Notice).

Note 2. In general, ER preparations may be influenced by food intake; therefore, the study of food effects on bioavailability (single-dose administration study) is required.

Note 3. If dose modification is considered necessary due to differences in exposure between IR and ER preparations during repeated administration, a therapeutic exploratory study(phase 2) may be required to explore the dose-response of the ER preparation.

Note 4. In principle, indications are determined based on the submitted clinical studies. However, for indications within the same therapeutic class, where the mechanism of action is identical to that of the approved IR preparation, all such indications may be accepted.

Example 1) Among the indications already approved for the same IR preparation, postoperative pain and toothache fall under the same therapeutic class for acute pain, while osteoarthritis and rheumatoid arthritis fall under the same therapeutic class for chronic pain.

Example 2) Among the indications already approved for the same IR preparation, alopecia treatments and benign prostatic hyperplasia do not fall under the same therapeutic class.

2) When Submitting Data Related to BE Studies [Note 1)]

BE Study
○ Single-dose administration (IR fasting vs ER fasting vs ER fed) [Note 2)] ○ Multiple-dose administration (IR vs ER)

Note 1. The relationship between plasma drug concentration or drug concentration at the site-of-action and its clinical effects should be established.

Note 2. In general, bioavailability under fasting and fed conditions should be equivalent. The study method may be conducted as a 2×2 crossover design (IR fasting vs. ER fasting, ER fasting vs. ER fed).

※ The fed study should follow the Standard on Pharmaceutical Equivalence Test (MFDS Notice), requiring at least 10 hours of fasting prior to consuming the same high-fat meal (over 900 Kcal with more than 35% from fat content) within 20 minutes and the drug shall be administrated in 30 minutes after the start of the meal.