PFSB/ELD Notification No. 0616-1
June 16, 2011

To: Head of Prefectural Health Department (Bureau)

Director of the Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

Handling of Prescription Drugs Having Different Crystalline Forms, etc.

How to handle drug substances in new drugs that exist in multiple crystalline forms (polymorphs) is shown in "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products (PMSB/ELD Notification No. 568 issued by the Director of the Evaluation and Licensing Division dated May 1, 2001)." The points to consider when applying for approval of drugs containing drug substances having different crystalline forms or hydrates/anhydrides (hereinafter referred to as "crystalline forms, etc.") are summarized below. Please inform the relevant business operators under your jurisdiction.

1. Handling of non-proprietary name

It is necessary to clearly distinguish between hydrates and anhydrides when giving non-proprietary names. This rule does not apply to different crystalline forms.

2. Handling of drugs having different crystalline forms, etc. when applying for approval (review)

(1) Basic concept

Different crystalline forms or differences between hydrates and anhydrides are not associated with fundamental differences in the chemical structure, unlike in the case of different salts (acid salts or metal salts) or different esters. Therefore, they should be handled as described below, in principle, even if non-proprietary names are different, when applying for approval (review).

When applying for approval of a new drug product made from a drug substance having a different crystalline form, etc. from that of the drug substance of an approved drug, it should be handled in the same manner as an application for a drug product made from the same active ingredient as that of an approved drug. When switching the drug substance of an approved drug

to a drug substance having a different crystalline form or when adding a drug substance having a different crystalline form from that of the drug substance of an approved drug, it should be handled as a partial change application in principle. When switching to a drug substance of a different hydrate or anhydride, it should be handled in an alternative new approval application in principle.

It should be noted that it is necessary to confirm equivalence in quality, efficacy, and safety to the drug approved as a new drug or equivalent (hereinafter referred to as "original drug") in a new approval application, or to the drug product before change in an alternative new approval application or partial change application.

(2) Data to be attached

When applying for approval of a drug product made from a drug substance having a different crystalline form, etc. from that of the drug substance of an approved drug, it may be necessary to submit additional data depending on the characteristics of each crystalline form, etc., in addition to the data usually required for each type of application.

A separate notification of the guidance on the standard data required will be issued.

(3) Application for approval of generic drugs

When applying for approval of a generic drug, the applicant should submit information on its crystalline form, etc. based on literature information, etc. using an appended form. If the applicant intends to use the master file (hereinafter referred to as "MF") and this information is non-disclosure information, the MF holder (or in-country care-taker if it is a foreign manufacturer) may directly submit the information to the review department of the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as the "PMDA"). In this case, the applicant should request the MF holder after the approval application.

3. Application for non-proprietary naming (JAN)

When the approved drug is an anhydride (or hydrate), an approval application for a hydrate (or anhydride) as an active ingredient usually requires a procedure for non-proprietary naming (JAN) in Japan in advance. For this procedure, see "Handling of Non-proprietary Names" (PFSB Notification No. 0331001 issued by the Director of the Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare dated March 31, 2006). If you have any questions regarding JAN procedure, consult the Division of Pharmacopoeia and Standards for Drugs, Office of Review Management of the PMDA.

Appended form

Reference data on the crystalline form, etc. of the drug substance

1. Information on the application product

Brand name : _____

Name of the active ingredient : _____

Date of application : _____

Name of the applicant : _____

2. Original drug

Brand name : _____

Date of approval : _____

3. Information on the crystalline form, etc.

No.		Proposed drug product	Original drug[*1]
1	Polymorphism	☐ Yes ☐ No ☐ Other	
2	Type of crystals	☐ Crystalline ☐ Amorphous ☐ Other	☐ Crystalline ☐ Amorphous ☐ Unknown
3	Type of crystalline form[*2]		
4	Transition	☐ Yes ☐ No ☐ Other	☐ Yes ☐ No ☐ Unknown
5	Hydrate/anhydride	☐ Hydrate ☐ Anhydride ☐ Other	☐ Hydrate ☐ Anhydride ☐ Unknown
6	Solubility[*3]		
7	Remarks[*4]		

*1: Information on the original drug may be provided to the extent possible.

*2: The type of crystalline form may be indicated by the name or notation considered appropriate by the applicant. In this case, detailed supplement data should be attached as necessary. If a single drug substance is expected to exist in more than one crystalline form, etc., specify the type of each.

*3: Specify the solubility at 37 ± 0.5°C for the pH range of 1.2 to 6.8 and in water.

*4: If "Other" is selected in No. 1, 2, 4, or 5, specify the rationale, etc. For the Master File (hereinafter referred to as "MF"), specify its name, registration number, date of issuance of registration certificate, number of issuances of registration certificate, and which manufacturing method is used (if there are multiple manufacturing methods). If MF registration is pending, indicate the system receipt number.

4. Contact information

Company and department: _____

Person in charge: _____

Phone number: _____

FAX number: _____