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To: Directors of Prefectural Health Departments (Bureaus)

Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)
Director of the Compliance and Narcotics Division, Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare
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Handling of Influenza Vaccines Manufactured Using Strains Other than Those Dispensed by the National Institute of Infectious Diseases (Notification)

Influenza vaccines currently marketed in Japan are manufactured at companies using production strains that have been determined for vaccines of the relevant fiscal year by the Ministry of Health, Labour and Welfare (hereinafter referred to as “MHLW”) and dispensed by the National Institute of Infectious Diseases (hereinafter referred to as “NIID”). For each fiscal year, the production strains are selected from several strains recommended for production in the northern hemisphere by the World Health Organization (WHO) and similar strains (hereinafter referred to as “WHO-recommended strains”) through a review at the NIID and a discussion at the Health Sciences Council. Because the production strains for vaccines of the relevant fiscal year are determined by the MHLW, a change of production strains from the previous fiscal year is exempted from regulatory procedures.

On the other hand, for influenza vaccines manufactured using some WHO-recommended strains outside Japan and imported into Japan, companies will have to select the strains from all the WHO-recommended strains, apart from the above scheme for determination of production strains. However, if the strains of the company’s choice undergo review at the NIID and a discussion at the Health Sciences Council, as done in the above scheme for determination of production strains, a concern would be raised that the influenza vaccines cannot be supplied before the season of influenza epidemic

in Japan.

In view of the concern about influenza vaccines manufactured using vaccine production strains other than those determined by the MHLW and dispensed by the NIID (hereinafter referred to as “influenza vaccines from strains of the company’s choice”), regulatory handling of the above production strains is outlined below. Please understand the content and ensure that all the companies under your jurisdiction are informed.

(1) For a change of production strains for an influenza vaccine from strains of the company’s choice, approval of partial changes in items approved under Article 14, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as “PMD Act”) pursuant to Paragraph 15 of the same article (hereinafter referred to as “partial change approval”) should be obtained.

(2) To ensure that influenza vaccines are supplied before the season of influenza epidemic in Japan, the partial change approval should be obtained promptly. An application to obtain the partial change approval pursuant to Article 14, Paragraph 15 of the PMD Act (hereinafter referred to as “partial change application”) should be submitted by early July at the latest. To contribute to expedited reviews, the partial change application for a change of production strains should not include any changes in items approved for marketing other than those associated with the change of production strains.

(3) A partial change application falls under any of the categories, (10), (10-2), (10-3), and (10-4). The category should be selected in view of whether the product is within a reexamination period, whether the change corresponds to a process change, etc.

(4) For a partial change application, the applicant should submit some of the following data as appropriate at the time of application in consultation with the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”). Even before the partial change application, any data ready for submission should be submitted. Or if submission of the data at the time of a partial change application seems difficult, the applicant should consult with PMDA about timing of the submission in advance. Submission of the data after the partial change application may be allowed in some cases.

- Data on antigenicity of production strains (e.g., similarity of antigenicity between the WHO-recommended strains and production strains, data on gene

sequence)

- Data on product quality after the change of production strains (e.g., results of control tests of the master virus seed [MVS], results of batch analyses during manufacture of the active substance and vaccine product [results of specification tests] and sampling schedule for stability data).
- Other data required at the discussion with MHLW and PMDA

(5) In the following case, administrative processing of the partial change application will generally take 2 months until its approval: the strains used in an influenza vaccine from strains of the company's choice are within a scope of the WHO-recommended strains; and the partial change application for the concerned production strains is submitted to ensure that the vaccine is supplied before the season of influenza epidemic in Japan. However, this period may vary depending on when the data listed in (4) are submitted.

(6) For the partial change application, no GMP compliance inspection specified in Article 14, Paragraph 7 of the PMD Act will be required.

(7) If an individual discussion about timing of application, data to be submitted, etc. is necessary for the partial change application, the applicant should consult with MHLW and PMDA in advance.

(8) For national assay, test reagents and report documents on their preliminary test results should be submitted by the due date designated by NIID. Even if submission of the data is not required, the test reagents should be submitted well in advance before application for lot assay.

(9) If formats of Summary Lot Protocol need to be prepared or changed, the application should be submitted to NIID by around the end of January of the year when the assay is conducted.

(10) For the schedule of application for lot assay for the national assay, a vaccine application plan should be submitted by the due date designated by NIID.