Provisional Translation (as of May 2024)*

Administrative Notice
March 29, 2024

To: Prefectural Health Department (Bureau)

Pharmaceutical Evaluation Division,
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Q & A for "Planning of the Pediatric Drug Development Program during Development of Drugs for Adults"

We have presented the basic concept of planning of the pediatric drug development program during development of drugs for adults in the "Planning of the Pediatric Drug Development Program during Development of Drugs for Adults" (PSB/PED Notification No. 0112-3 issued on January 12, 2024 by the Director of PSB/PED, MHLW. Hereinafter, referred to as "the Director's Notification"). We have summarized Q & A as shown in the attachment, and we ask you to understand it and to cooperate in informing related parties under your administration of this matter.

* This English version of the Japanese Administrative Notice is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

(Attachment)

Q & A for the Planning of the Pediatric Drug Development Program during Development of Drugs for Adults

Q1. Does the Director's Notification mean that it is mandatory to prepare a pediatric drug development plan when developing a drug for adults?

A1. It is just desirable and not mandatory to prepare a pediatric drug development plan.

Q2. Does “drugs with different indications between adults and children (for instance, indications of different types of cancer between adults and children)” include any pediatric cancer in a different type from adults that will be treated with a molecular target drug for cancer and is expected to respond to it in light of its mechanism of action?

A2. Included.

Q3. To have a development plan confirmed by the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) based on the Director's Notification, what concrete procedures are required?

A3. If the drug needs to be confirmed by the PMDA before an approval application for adults is filed, use the PMDA's “Consultation on Confirmation of the Pediatric Drug Development Program (the name is tentative).” If a pediatric drug development plan is confirmed by the PMDA in other face-to-face consultations, the confirmation based on the Director's Notification is regarded as having been made in the face-to-face consultations.

The “Consultation on Confirmation of the Pediatric Drug Development Program (the name is tentative)” is only for confirmation of the development plan. For consultation on the appropriateness of the clinical study design, sufficiency of the clinical data package, etc., the conventional face-to-face consultation services, such as consultation after completion of phase II study for drugs, should be used.

For confirmation by the PMDA after approval application for adults is filed, the pediatric drug development plan should be provided in Module 1.5 of the Common Technical Document (hereinafter, “CTD”) of the approval application documents.

Q4. Is it correct to understand that this notification is applicable to a pediatric drug development plan if the PMDA confirms it before the approval application for additional indication in adults is filed when the drug is developed for the new additional indication in adults?

A4. It is correct. For confirmation by the PMDA on the pediatric drug development plan for drugs with different “indications” between adults and children, the conventional face-to-face consultation services, such as consultation after completion of phase II study for drugs, should be used, instead of “Consultation on Confirmation of the Pediatric Drug Development Program (the name is tentative).”

Q5. For a pediatric drug development plan, isn’t it applicable to the development of pediatric drugs specified in the Director Notification unless the plan provides the contents of conducting clinical trials?

A5. If an appropriate plan can be prepared for approval, it is not always necessary to conduct a new clinical trial. Even if a development plan is made by utilizing real-world data, modeling & simulation, etc., it is regarded as the development of pediatric drugs specified in the Director Notification. Note that for confirmation by the PMDA on the development plan utilizing real-world data, modeling & simulation, etc. without clinical trials, the conventional face-to-face consultation should be used, instead of “Consultation on Confirmation of the Pediatric Drug Development Program (the name is tentative).”

Q6. In the Director's Notification, what is the specific age group expected as children?

A6. It is desirable to develop a plan for the age group in which the need is recognized for each indication to be developed, including newborns. If it is necessary to examine the appropriate dosage and administration by age group in consideration of physical constitution, degree of maturation, etc. among the age groups for which the need of development is recognized, it may be acceptable to develop a drug in a stepwise expansion of the age group. In such a case, the overall picture of the plan including stepwise development should be prepared and confirmed by the PMDA.

Q7. When a pediatric drug (for children aged 10 or 12 years, or older) that can be evaluated together with adults is developed based on "Considerations for the Clinical Evaluation of Drugs in Pediatric Patients (10 or 12 Years of Age and Older) Who Can be Evaluated Together with Adults" (the administrative notice issued by PSEHB/ELD dated June 30, 2020), is it the development of pediatric drugs specified in the Director Notification?

A7. Yes, it is. In this case, if there is another pediatric age group for which the development is considered necessary in addition to the pediatric population to be evaluated together with adults, the entire plan including the development for that age group should be prepared and confirmed by the PMDA.

Q8. The Director's Notification states, "it is desirable to proceed with the development without delay based on the prepared development plan." How long should the development period be?

A8. It is difficult to specify the period across the board, but from the viewpoint of promptly starting the development of pediatric drugs, it is desirable to take the following actions if a dosage form for children different from that for adults is not developed. For actions to be taken when developing a pediatric dosage form, refer to QA9.

- For a development plan requiring the submission of a protocol notification, it is desirable to submit the notification within 2 years after confirmation by the PMDA.
- For a development plan for a clinical trial that does not require the submission of a protocol notification, it is desirable to start the clinical trial within 2 years after confirmation by the PMDA. The start date of a clinical trial in this administrative notice shall be the start date of the implementation period described in the protocol of the clinical trial.
- For development plans without clinical trials (development plans utilizing real-world data, modeling & simulation, etc.), it is desirable to file an approval application in accordance with the plan within 2 years after confirmation by the PMDA.

To have a plan confirmed by the PMDA before an approval application for adults is filed, the confirmation by the PMDA is the record-fixing date of "the conventional face-to-face consultations" or "Consultation on Confirmation of the Pediatric Drug Development Program (the name is tentative)." When a plan is confirmed by the PMDA after an approval application for adults is filed, the confirmation by the PMDA is the approval date.

Q9. The Director's Notification states, "For development of a dosage form for children different from that for adults, the development can take a longer period of time than when the development of a dosage form for children is not necessary." How long should the development period be if a dosage form for children is developed?

A9. It is difficult to specify the period across the board, but from the viewpoint of promptly starting the development of pediatric drugs, it is desirable to take the following actions if a dosage form for children different from that for adults is developed.

- For a development plan requiring the submission of a protocol notification, it is desirable to submit the notification within 3 years after confirmation by the PMDA.
- For a development plan for a clinical trial that does not require the submission of a protocol notification, it is desirable to start the clinical trial within 3 years after confirmation by the PMDA. The start date of a clinical trial in this administrative notice shall be the start date of the implementation period described in the protocol of the clinical trial.
- For development plans without clinical trials (development plans utilizing real-world data, modeling & simulation, etc.), it is desirable to file an application for approval in accordance with the plan within 3 years after confirmation by the PMDA.

To have a plan confirmed by the PMDA before an approval application for adults is filed, the confirmation by the PMDA is the record-fixing date of "the conventional face-to-face consultations" or "Consultation on Confirmation of the Pediatric Drug Development Program (the name is tentative)." When a plan is confirmed by the PMDA after an approval application for adults is filed, the confirmation by the PMDA is the approval date.

Q10. The notification states, "Development to determine appropriate dosage and administration for children." Does it include the case of confirming that the appropriate dosage and administration for children is the same as those for adults? Does this include the case where a clinical trial was conducted on the assumption that the dosage and administration for adults would be different from the appropriate dosage and administration for children, but as a result, the same dosage and administration as those for adults are established for children?

A10. Both are included.

Q11. If the PMDA's confirmation is made in accordance with the Director's Notification, how will the record be kept?

A11. In the record of face-to-face consultation with the PMDA, it is described that the confirmation was made based on the Director's Notification.
(An example of a description in the record of the PMDA consultation)

The pediatric drug development plan in this consultation has been confirmed in accordance with the "Planning of the Pediatric Drug Development Program during Development of Drugs for Adults" (PSB/PED Notification No. 0112-3 issued on January 12, 2024 by the Director of PSB/PED, MHLW").

If an indication for children is approved based on the development plan confirmed by the PMDA, it is also described in the review report for the pediatric indication that the confirmation has been made.
(An example of descriptions in the review report for children: when a confirmation has been made by the PMDA before an approval application for adults is filed)

For this product, the pediatric drug development plan has been confirmed in the face-to-face consultation with the PMDA (Consultation No. ●●●●) in accordance with the "Planning of the Pediatric Drug Development Program during Development of Drugs for Adults" (PSB/PED Notification No. 0112-3 issued on January 12, 2024 by the Director of PSB/PED, MHLW").

(An example of descriptions in the review report for children: when a confirmation has been made by the PMDA after an approval application for adults is filed)

For this product, the pediatric drug development plan has been confirmed by the PMDA in accordance with the "Planning of the Pediatric Drug Development Program during Development of Drugs for Adults" (PSB/PED Notification No. 0112-3 issued on January 12, 2024 by the Director of PSB/PED, MHLW").

When a confirmation is made by the PMDA after an approval application for adults is filed, it is also described in the review report for the indication for adults that the confirmation has been made by the PMDA.

Q12. If a confirmation is made by the PMDA based on the Director's Notification and an approval application for children is filed, is it necessary to describe in the approval application document the fact that the confirmation has been made by the PMDA?

A12. Yes, it is. The Module 1.5 of the CTD, an approval application document, shall

provide the fact that the pediatric drug development plan has been confirmed in the face-to-face consultation with the PMDA (Consultation No. ●●●●) in accordance with the "Planning of the Pediatric Drug Development Program during Development of Drugs for Adults" (PSB/PED Notification No. 0112-3 issued on January 12, 2024 by the Director of PSB/PED, MHLW").

Q13. If a development plan has been significantly changed after confirmation by the PMDA, is it necessary to have another "Consultation on Confirmation of the Pediatric Drug Development Program (the name is tentative)"?

A13. If there is any change in a development plan as shown below, it is acceptable to use the "Consultation on Confirmation of the Pediatric Drug Development Program (the name is tentative)," etc. again for confirmation by PMDA.

- When there is a change in the target age group
- When the schedule of the development plan is significantly changed
- When a dosage form for children is required as a result of the progress of development, although the pediatric dosage form was considered unnecessary

Q14. If a confirmation is made by the PMDA in accordance with the "Planning of the Pediatric Drug Development Program during Development of Drugs for Adults" (PSB/PED Notification No. 0112-3 issued on January 12, 2024 by the Director of PSB/PED, MHLW") before the start of "Consultation on Confirmation of the Pediatric Drug Development Program (the name is tentative)," what should be done?

A14. Use the conventional face-to-face consultation.