Provisional Translation (as of July 2026)*

Considerations for the Clinical Evaluation of Blood Coagulation Factor VIII and Factor IX Products for Pediatric Congenital Hemophilia (Early Consideration)

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Office of Vaccines and Blood Products
Pharmaceuticals and Medical Devices Agency

1. Background and Purpose

There have been growing concerns about the expansion of "drug loss," where drugs approved in the European Union and the United States are not being developed in Japan, which is also an issue for drugs intended for children (hereinafter referred to as "pediatric drugs").

To advance pediatric drug development in Japan without lagging behind other countries, the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA"), during clinical trial consultations for adult drug development, is making efforts to actively check the development status in and outside Japan of a drug being developed, which is expected to be used in children for the diseases and conditions targeted for the drug under development, encouraging the initiation of pediatric drug development in Japan ("Initiatives to Promote Pediatric Drug Development" [PMDA/CPE Notification No. 1618・PMDA/CRS Notification No. 15 dated March 21, 2025]).

When considering pediatric drug development during the adult development stage, inclusion of children of a certain age or older in adult clinical trials is one of the strategies for pediatric drug development. With the objective to streamline and optimize the clinical development of drugs intended for children, considerations for clinical evaluation have been formulated to specify the age groups and diseases in children who can be evaluated together with adults ("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" [Administrative Notice of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated June 30, 2020]). This notification specifies that target diseases whose pathology is similar between children of the target age group and adults or whose pathology is different but may be considered similar for the purpose of clinical evaluation, and states that other diseases not covered in this notification will be discussed in the future as necessary.

In the development of coagulation factor products for congenital hemophilia, the clinical evaluation of many products in children 12 years of age and older has historically and

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

internationally been conducted together with adults. Because of disease rarity, despite the absence of clinical trial results in Japanese pediatric patients at the time of approval, several drugs have been approved for the dosage and administration for children younger than 12 years of age based on clinical trial results in non-Japanese pediatric patients and global clinical trial results including Japanese patients 12 years of age and older. In October 2024, a notification entitled "Basic Principles on Japanese Clinical Trial Data for Drugs for Rare Diseases, etc., for Which Confirmatory Clinical Trials Have Been Conducted Only Overseas" (PMSB/ELD Notification No. 1023-3 dated October 23, 2024) was issued. This specifies that it may be possible in some cases to file an approval application without clinical trial results in Japanese patients, provided that a pivotal clinical trial has been properly conducted overseas, that it is difficult to conduct an additional clinical trial in Japanese patients, and that it is comprehensively determined that the benefits in Japanese patients outweigh the risks based on the available information on the efficacy/safety.

Based on the background above, this document outlines the considerations for the clinical evaluation of blood coagulation factor VIII (FVIII) and blood coagulation factor IX (FIX) products for congenital hemophilia under development in children 12 years of age and older who can be evaluated together with adults, as well as the considerations in children younger than 12 years of age.

These considerations summarize the current fundamental principle of development of FVIII and FIX products for pediatric congenital hemophilia, and the principle shown in the considerations may not be applicable depending on individual cases. In addition, although the principle of these considerations may be applicable to non-factor products, it is recommended to make use of scientific consultations with PMDA to consider individual clinical trial plans at the early stage of development.

The principle presented here is one of the development methods and does not deny other development strategy methods.

Please note that the principle shown in the considerations may change depending on new findings obtained in the future.

2. Congenital Hemophilia

(1) Etiology/Pathology[1),2),3),4)]

Congenital hemophilia is an X-linked recessive inherited congenital bleeding disorder caused by deficiency or dysfunction of FVIII, called hemophilia A, or FIX, called hemophilia B. This disease usually affects males, while females are carriers. It rarely affects females. About 30% are sporadic cases. The incidence of hemophilia A is 1 in 5000 live male births, and the incidence of hemophilia B is about one-fifth that of hemophilia A. According to the nationwide survey on blood coagulation disorder in 2025, the number of

surviving patients with hemophilia A and hemophilia B is 3,813 (including 128 women) and 866 (including 48 women), respectively.

Clinical severity correlates with the level of FVIII or FIX activity, with <1% as severe, ≥1% to <5% as moderate, and ≥5% to <40% as mild. Although the coagulation factors deficient in hemophilia A and B are different, the clinical symptoms are similar. In severe cases, subcutaneous hemorrhage accompanied by hematoma develops repeatedly in the limbs, buttocks, etc. from the late infancy. After infancy, deep hemorrhage in joints, muscles, etc. is common, occurring frequently in large joints, particularly in the knees, legs, and elbows. Hemorrhage repeatedly occurs in the same joints, causing joint deformity and contracture, leading to hemophilic arthropathy. Mouth hemorrhage, gastrointestinal hemorrhage, and hematuria are also observed, and serious hemorrhage can occur in the intracranial region, abdominal cavity, etc. In moderate to mild cases, spontaneous hemorrhage is observed rarely, and this disorder is often diagnosed accidentally based on hemostatic difficulty after tooth extraction, surgery, or trauma, or screening tests.

The advent of new drugs (extended half-life coagulation factor products, non-factor products, etc.) has resulted in increased treatment options and increased implementation rates of regular bleeding control treatment (including prophylactic therapy), thereby extending the average life expectancy of patients with hemophilia. Consequently, it has become a problem that adult patients concomitantly have other conditions such as lifestyle diseases, malignant neoplasms, and renal diseases, which are not directly related to hemophilia. However, deficiency or dysfunction of FVIII or FIX is the major pathological condition in both adults and children, and there seems to be no essential difference in the basic pathological condition.

(2) Treatment strategies[1), 2)]

The basic concept of congenital hemophilia treatment is similar in adults and children. The principle of hemostatic treatment of hemophilia is replacement of deficient coagulation factors, which is achieved by intravenous administration of coagulation factor products in the early stage of bleeding. The products are administered as on-demand replacement therapy (on-demand therapy), preliminary replacement therapy, and prophylactic therapy. Coagulation factor products are broadly divided into plasma-derived products and recombinant products, and recombinant products are further divided into standard half-life products and extended half-life products. Since individual extended half-life factor products have different half-lives of the coagulation factor, it is required to determine the dose and dosing frequency with reference to the package insert. Repeated replacement therapy may cause the development of neutralizing antibodies (inhibitors) to factor VIII or factor IX in 20% to 30% of hemophilia A patients and in 3% to 5% of hemophilia B patients. Once inhibitors develop, it is difficult to control bleeding with conventional factor products

alone. Hemostatic management in patients with inhibitors includes bypassing hemostatic therapy and inhibitor-neutralizing therapy. Bypassing hemostatic therapy is a method to activate the extrinsic coagulation system, thereby stopping bleeding by bypassing the coagulation pathways involving FVIII or FIX. Bypassing hemostatic products include activated prothrombin complex concentrate products (aPCC), recombinant activated factor VII products (rFVIIa), and activated blood coagulation factor VIIa concentrate containing factor X products (FVIIa/FX). Inhibitor-neutralizing therapy is a method to administer a large amount of FVIII products or FIX products, thereby neutralizing the inhibitors present in the blood and further increasing the activity of coagulation factors. Immune tolerance induction therapy is being attempted as another treatment method, where patients with inhibitors are given repeated injections of factor VIII or factor IX to induce immune tolerance of patients with inhibitors, thereby eliminating the inhibitors.

In recent years, periodical prophylactic treatment has become possible by using drugs other than coagulation factor products (non-factor products), such as anti-FIXa/FX bispecific antibodies and anti-tissue factor pathway inhibitor antibodies. All non-factor products are effective for preventing bleeding by regular administration, but they are not intended for hemostasis at the time of bleeding. Therefore, separate hemostatic control using coagulation factor products is required at the time of bleeding and at the time of invasive treatment.

(3) Efficacy endpoint

The therapeutic goal for hemophilia is bleeding control, and the annualized bleeding rate (ABR) is generally used for the clinical evaluation of efficacy in both adults and children.

3. Considerations for the Clinical Evaluation of Pediatric Patients (12 Years of Age and Older) who Can be Evaluated Together with Adults

The notification entitled “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” specifies that children 10 or 12 years of age and older can be evaluated together with adults, provided that the dosage regimen of the drug for children is supposed to be the same as that for adults or within its range, and that the same formulation for adults can also be used for children.

With regard to congenital hemophilia, the European Medicines Agency (EMA) guidelines on clinical trials of coagulation factor products for hemophilia describe an approach to clinical evaluation using the age of 12 as the cutoff.[5),6)] Accordingly, in pivotal clinical trials of FVIII products or FIX products conducted to date, children 12 years of age and older have often been evaluated together with adults.

In view of these situations and in consideration that the etiology/pathology of hemophilia, treatment policy, and efficacy endpoints are similar between adults and children, as described in Section 2 above, and that it is highly likely that FVIII products and FIX products are co-developed internationally while regarding the age of 12 as a cutoff, it is considered appropriate to evaluate children 12 years of age and older together with adults. It may be possible to evaluate children younger than 12 years together with adults. In this case, however, it is necessary to justify the evaluation of children younger than 12 years together with adults in terms of dosage regimen, evaluation method, etc.

When evaluating children together with adults, it is beneficial and worth implementing to obtain information on children, including blood pharmacokinetics, and to perform a subgroup analysis when a sufficient number of participants is obtained.

In the post-marketing setting, appropriate as-needed information collection should be considered for each product.

4. Considerations for the Clinical Evaluation of Pediatric Patients (Younger than 12 Years of Age) who are Not Evaluated Together with Adults

As for multi-regional clinical trials, it is important for Japan to participate whenever possible even if the number of Japanese participants is very small. This is because comparisons of results between the overall population and the Japanese subpopulation can be made to some extent through comprehensive and multifaceted evaluations that also consider clinical perspectives, and also Japan's involvement is of great importance from the perspective of providing information to the medical community, as shown in the notification entitled "Basic Principles on Japanese Clinical Trial Data for Drugs for Rare Diseases, etc., for Which Confirmatory Clinical Trials Have Been Conducted Only Overseas".

For FVIII products and FIX products, however, taking into consideration the findings to date and the reasons shown below and assuming the availability of clinical trial results that include those from Japanese patients 12 years of age and older and the absence of clinically significant differences in efficacy, safety, and other information between non-Japanese patients 12 years of age and older and Japanese patients, it is possible to use the efficacy and safety data in non-Japanese pediatric patients younger than 12 years of age to evaluate the efficacy and safety in Japanese pediatric patients younger than 12 years of age, thereby submitting an approval application without collecting clinical study results in Japanese pediatric patients younger than 12 years of age.

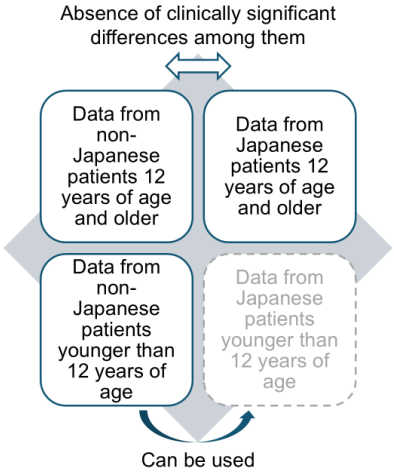
- The epidemiological profile of patients with congenital hemophilia, the etiology/pathology, the concept of replacing deficient coagulation factors for on-demand treatment and prophylaxis, etc. are similar between Japan and overseas. Therefore, intrinsic and extrinsic ethnic factors are not considered to have significant impact on the efficacy and safety of coagulation factor products.

- The doses of FVIII and FIX products are usually specified based on body weight. Therefore, body weight is not expected to have an apparent impact.

If there is no information on Japanese pediatric patients younger than 12 years of age obtained from clinical trials, patient information should be collected shortly after the product launch with the emphasis on the target pediatric population, and the early post-marketing information obtained should be provided to healthcare professionals.

REFERENCE

In the development of FVIII and FIX products for congenital hemophilia, the following prerequisites need to be met:
- **Availability of clinical trial results, including those from Japanese patients 12 years of age and older**
- **Absence of clinically significant differences in efficacy, safety, and other information between Japanese patients 12 years of age and older and non-Japanese patients 12 years of age and older**



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[3] Project entrusted by Ministry of Health, Labour And Welfare. Nationwide Survey of Patients with Coagulation Disorders 2025. Published by Japan Foundation for AIDS Prevention.

[4] Japan Pediatric Society. Diseases-specific Guidelines for Transitional Care: Hemophilia. https://www.jpeds.or.jp/uploads/files/20240318_GL069.pdf (last accessed on May 22, 2026）

[5] Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev. 2)

[6] Guideline on the clinical investigation of recombinant and human plasma-derived factor VIX products (EMA/CHMP/BPWP/144552/2009 rev. 2)