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To: Prefectural Health Department (Bureau)

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

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

With the objective to further streamline and optimize the clinical development of drugs for the pediatric population, the following considerations have been compiled to outline the age groups and diseases in pediatric patients who can also be evaluated together with adults as per the Attachment. We ask you to ensure that relevant Marketing Authorization Holders placed under your administration are informed of this document.

Note that the considerations compiled in the Attachment represent general principles at present and in some cases, may not be applicable depending on individual cases.

Considerations for the Clinical Evaluations of Drugs in Pediatric Patients (10 or 12 Years of Age and Older) Who Can be Evaluated Together with Adults

I. GENERAL

1. Background and Purposes

In the course of pharmaceutical development, the development of pediatric dosage is usually preceded by the development of corresponding adult dosage. In addition, it is often difficult to make progress on the development of pediatric dosage for several reasons, such as the difficulty in conducting clinical trials and the small market scale. Under such circumstances, the development of dosage needed by pediatric patients often cannot make the desired progress, and there are some unapproved drugs for pediatric dosage that are being clinically used by pediatric patients.

Among the pediatric dosage of drugs established on the basis of pediatric clinical studies, there exist cases where the use in children of, e.g., 12 years of age and older has been approved with the same dosage as that of adults. With the exception of diseases with many pediatric patients, available information about pediatric use is limited for reasons such as only open-label uncontrolled trials have been conducted and/or only a small number of pediatric patients have been enrolled in clinical studies. As for diseases with many pediatric patients, there are cases in which, in spite of the same target disease, different pediatric age categorizations have been defined for various drugs. Distinct age group categorizations have been used in clinical studies for different drugs, resulting in a situation in which caution is required when those drugs are used in clinical practice.

From a global perspective, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) developed guidelines for clinical studies in the pediatric population, which cover potential issues that could occur at the initiation phase of planning a development program, initiation of clinical studies, study types, and age categorizations among others.[1),2),3)] To facilitate the development of pediatric drugs, the U.S. Food and Drug Administration (U.S. FDA) issued a draft guidance on oncology clinical trials last year that states that adolescents should be included in adult clinical trials when the target malignancy has similar pathological and biological characteristics among adults and adolescents with respect to the clinical evaluation of antineoplastics.[4)]

Base on this background, with the objective to further streamline and optimize the clinical development of drugs for the pediatric population, the present considerations have been compiled to outline the age groups and diseases in pediatric patients who can be evaluated together with adults.

Note that the compiled considerations represent general principles at present and in some cases, may not be applicable depending on individual cases. Furthermore, this does not demand for pediatric patients to be evaluated together with adults in clinical evaluations for all drugs used to treat the target diseases. The completion of adult trials and clinical use of

drugs for adults should not be delayed due to planning of pediatric development.[1)]

2. Target Age Group

In the present Considerations, the target pediatric age group is such that: (1) The exposure levels of the drug considered are supposed to be similar to those in adults, (2) the dosage of the drug for the pediatric patients is supposed to be the same as that for adults or within its range (e.g., the adult regimen has multiple dose levels including the pediatric dose), and (3) the same formulation for adults can also be used for the target age group.

Some reports show that major drug-metabolizing enzymes and transporters generally have no significant differences in their expression levels among children of 10 years of age and older and adults.[5),6),7),8),9),10)] The study report that the level of renal function in children of 10 years of age and older does not differ from that in adults.[10)] Surveys indicate that the pediatric population of 10 or 12 years of age and older in Japan may include a subpopulation of a certain size whose physique is within the variation range for adults.[11)]

Given the above, the target pediatric age group in the present Considerations will, in principle, be that of 10 or 12 years of age and older. Specific target age groups, however, will be discussed for each target disease because they should be determined according to the target disease/condition as well as the characteristics of the drug. The final decision to include a pediatric population in an adult clinical study should, however, be justified for each individual drug, as described in "8. Considerations for the Development of Individual Drugs," because interindividual differences in growth may be large for the target pediatric age group.

It should be noted that inclusion of children younger than 10 years of age in adult clinical studies may also be possible, depending on the characteristics of drugs, such as dosing regimen and safety margin. If pediatric population of a younger age group are to be included, the rationale such as the evaluation method should be explained.

3. Target Diseases

The present Considerations apply to diseases such that their pathology in the pediatric population of the target age group is similar to that in adults, or although it may be different, it should be regarded as similar to that in adults for the purpose of clinical evaluation. Many diseases may fall into this category, but in the present Considerations we deal with type 2 diabetes mellitus, familial hypercholesterolemia, allergic diseases, antimicrobials/antivirals, and hematopoietic malignancy. Other diseases will also be discussed in the future as necessary.

Note also that the present Considerations presuppose that the same efficacy endpoints can also be used equally in the target pediatric patients as in adults because those pediatric patients are to be enrolled in adult clinical studies. For any endpoints which may be impacted by the patients' comprehension, the relevant target age group should be carefully assessed.

4. Clinical Studies Enrolling Pediatric Patients

The present Considerations apply to pediatric patients for whom the dosing regimen is supposed to be the same as that for adults or within its rage and for whom the formulation for adults can also be used. These Considerations are therefore assumed to apply, in principle, to confirmatory or long-term clinical studies after the efficacy and safety of the drug in adults have been evaluated in exploratory studies to establish a dosage.

On the other hand, taking into account the diversity of clinical development programs, the principles in the present Considerations may also be applicable to some exploratory studies. However, in case a pediatric population is to be included in those exploratory studies, its appropriateness must be examined and explained.

Prior to enrolling pediatric subjects in a clinical study, exclusion of children of markedly short stature and/or low body weight should be considered for safety. Safety measures related to secondary sexual characteristics, such as exclusion of prepubertal children, should also be considered as necessary.

Prior to enrolling pediatric subjects in a long-term clinical study, possible impacts on their growth and development during the study period should also be carefully considered.

5. Collection and Provision of Information in Post Marketing Phase

The nature of the information that can be obtained from pre-marketing clinical studies varies depending on whether conducting pediatric studies is difficult for various reasons due to the target diseases or pathology (e.g., type 2 diabetes mellitus) or possible as there exist a certain number of pediatric patients (e.g., allergic rhinitis).

In the former case, because of limited pre-marketing information on the target pediatric population, additional patient information should be collected shortly after the product launch with the focus on the target pediatric population, and the early post-marketing information obtained should be provided to healthcare professionals. In this case, collection of safety information should be of particular focus. For some target diseases, special approach should be considered such as starting the use of the drug only in selected medical institutions during an early post-marketing phase and then expanding on a step-by-step basis. Information on the target pediatric population should also be provided through the labeling by stating that available information regarding the population is limited at the time of marketing approval, and the information obtained thereafter should be promptly and surely delivered to healthcare professionals.

In the latter case, in which a certain level of information on pediatric patients has been obtained before product launch, appropriate as-needed information collection should be considered for each product.

In addition, active collaboration with related academic societies and efforts to be made by physicians and pharmacists are important to ensure that pediatric drugs are properly used and relevant safety information is collected.

6. Ethical Requirements

When conducting pediatric studies, special considerations are required such as protecting the right of the pediatric subjects, protecting from avoidable risks and minimizing pain. Pediatric studies must be planned and conducted in accordance with the relevant ICH guidelines.[1),2),3)] The present Considerations are therefore assumed to apply, in principle, to clinical studies after the drug has been evaluated in exploratory studies in adults to determine a clinical dosage that is expected to be efficacy and has a tolerable safety profile.

It is needless to say that informed assent suitable for the patients' age/comprehension should be obtained.

7. Relationship to the ICH Guidelines Regarding Studies in the Pediatric Population[1),2),3)]

The ICH has laid down basic principles concerning the clinical evaluation in the pediatric population, which include those regarding "Extrapolation in Pediatric Drug Development" (extrapolation of adult or other data to the pediatric population).[3)] Currently, efforts are ongoing to develop a more detailed guidance.

The present Considerations do not take the standpoint of the "Extrapolation in Pediatric Drug Development" but support the idea that, by choosing an appropriate pediatric age group for selected diseases/conditions, it is possible to generalize the clinical evaluation of drugs for the diseases/conditions in a manner that allows conducting the clinical evaluation in children of the relevant age group and adults combined. However, the basic principles regarding the similarities among diseases/conditions here do not differ from the general concept considering the ICH's "Extrapolation in Pediatric Drug Development."

8. Considerations for the Development of Individual Drugs

Even if the present Considerations categorize the target disease for pediatric development to be evaluated in combination with adults, it would be necessary to establish a rationale to explain the development method for the pediatric regimen for each individual drug since the safety profile and available information differ depending on the drug.

The rationale for the adopted development approach should be explained before initiating a clinical study and at the time of marketing application. Items to be considered are as follows:

- Impacts on Growth and Development in Nonclinical Studies
  Nonclinical studies in juvenile animals, though not required generally to initiate a study in children of 12 years of age and older, should be conducted if available data are considered to be insufficient to initiate a pediatric study.[13),14)]
- Appropriateness of Dosage
  - ✓ Explain the impacts of physique or body weight on the absorption, distribution, metabolism, and excretion of the drug in children of the target age group, using existing data from completed studies including nonclinical studies and adult pharmacokinetics studies.

- ✓ Clarify the reason for determining that the drug could be administered to the target population using the same dosage as adults based on the pharmacokinetics, pharmacokinetics/pharmacodynamics (PK/PD), and exposure-response relationship of the drug. This may include examination by means of computer simulation.

- Special Population Requiring Careful Administration
  Consider limiting the use according to body height and/or body weight if the drug must be administered with care in children with a physique deviating from the standard range, such as children with short stature or low body weight.

References:

1) ICH Harmonised Tripartite Guideline, Clinical Investigation of Medicinal Products in the Pediatric Population, PMSB/ELD Notification No. 1334, issued by Director of Evaluation and Licensing Division (ELD), Pharmaceuticals and Medical Safety Bureau (PMSB), Ministry of Health and Welfare, dated December 15, 2000.
2) Questions and Answers on the ICH Harmonised Tripartite Guideline, Clinical Investigation of Medicinal Products in the Pediatric Population, Administrative Notice issued by the ELD, Pharmaceutical Bureau, Ministry of Health, Labour and Welfare (MHLW), dated June 22, 2001. (in Japanese)
3) ICH Harmonised Guideline, Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population, E11(R1), PSEHB/PED Notification No.1227-5, issued by the Director of Pharmaceutical Evaluation Division (PED), Pharmaceutical Safety and Environmental Health Bureau (PSEHB), MHLW, dated December 27, 2017.
4) Consideration for the inclusion of Adolescent Patients in Adult Oncology Clinical Trials, Guidance for Industry, March 2019; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Oncology Center of Excellence (OCE)
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11) 2018 School Health Statistics (School Health Statistics Investigation Report), March 25, 2019, Ministry of Education, Culture, Sports, Science and Technology (in Japanese)
12) ICH Harmonised Tripartite Guideline, “Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals”, M3(R2), PFSB/ELD Notification No. 0219-4 issued by the Director of the ELD, Pharmaceutical and Food Safety Bureau (PFSB), MHLW, dated February 19, 2010.
13) Guidelines for Nonclinical Safety Studies in Juvenile Animals for Pediatric Drugs, PFSB/ELD Notification No.1002-5 issued by the Director of the ELD, PFSB, MHLW, dated October 2, 2012. (in Japanese)
14) “Questions and Answers on the Guidelines for Nonclinical Safety Studies in Juvenile Animals for Pediatric Drugs”, Administrative Notice issued by the ELD, PFSB, MHLW, dated October 2, 2012. (in Japanese)

II. CONSIDERATIONS FOR INDIVIDUAL DISEASES

1. Type 2 Diabetes Mellitus

(1) Pathology

The incidence of pediatric type 2 diabetes mellitus (T2DM) in Japan is reported higher than in Caucasian populations in Europe and the United States. The annual rate of detecting T2DM by school urine test or DM screening in Japan has been reported to be 2.5-3.5/100,000 children. As for the distribution of onset age, the incidence of T2DM by age increases from 9 years of age (0.5/100,000 children) and reaches its peak at 14 years of age (2.5/100,000 children).[1)] It has also been reported that complications develop earlier in pediatric patients with T2DM than in those with T1DM.[2)]

According to the Report of the Committee on the Classification and Diagnosis Criteria of Diabetes Mellitus, which was published in 1999 by the Japan Diabetes Society, diabetes mellitus is defined as "A disease group characterized by chronic hyperglycemia occurring as a result of insufficient insulin activity, involving various characteristic metabolic abnormalities. Both genetic and environmental factors are involved in its onset. Persistence of metabolic abnormality for a long period easily results in the onset of specific complications and also promotes arteriosclerosis. Diabetes mellitus shows a broad spectrum of pathology ranging from being asymptomatic to ketoacidosis or coma, depending on the severity of the metabolic abnormality."

In particular, T2DM is characterized by impaired insulin secretion and decreased insulin sensitivity, and accounts for the majority of DM cases in Japan. The magnitude of the two factors differs in individual cases, and there exist several types including one consisting of cases in which impaired insulin secretion is dominant and another consisting of cases in which insulin resistance is dominant and relative shortage of insulin is involved. The function of pancreatic beta cells is conserved to some extent in patients with T2DM.

In pediatric patients with T2DM, obese patients with insulin resistance is observed more often than in adult patients with T2DM.[3),4)] The median age at the diagnosis of pediatric T2DM is 11.9 years of age, and it has been reported that T2DM is diagnosed at a higher age even in children if obesity exists.[4)] In spite of these, the pediatric and adult populations are similar in that impaired insulin secretion and insulin resistance are the main etiologies of T2DM, and therefore no essential differences may exist in the pathologic foundation of T2DM between adult and pediatric patients.

(2) Treatment in Clinical Practice

The section of "Diabetes Mellitus in Childhood and Adolescence" in *Clinical Practice Guidelines for Diabetes Mellitus, 2019* (ed. Japan Diabetes Society, Nankodo, Tokyo, 2019) states that due to the absence of subjective symptoms, it is common that pediatric patients with T2DM leave their disease untreated or discontinue their treatment; that complications are more common in pediatric T2DM than in pediatric T1DM[5)]; and that glycemic control is achieved with diet/exercise therapy alone in 60-70 % of pediatric patients with T2DM and the remaining

patients receive drug therapy in Japan.

A survey of medical treatments for pediatric T2DM in Japan[6] reports as follows:

- In case the HbA1c level at the time of diagnosis of DM is low, an alpha-glucosidase inhibitor is used.
- In case it is moderate, metformin or a sulfonylurea is used.
- In case it is high, insulin is used.
- Metformin is safe and effective in T2DM patients with obese
- Many patients who have started their treatment with monotherapy eventually use combination therapy or insulin monotherapy.

The situation concerning the medical treatments for pediatric T2DM may be the same as that for adult T2DM in that drugs are selected on the basis of conditions of individual patients.

Currently, metformin and glimepiride are the only oral hypoglycemic agents with their pediatric dosages being approved in Japan. For metformin, its dosage is indicated for pediatric patients of 10 years of age and older, while for glimepiride, the section of "Pediatric Use" in the labeling states that the safety in children younger than 9 years of age has not been established, although no age categories have been indicated for its dosage.

(3) Rationale for Including Children in Adult Studies

In the Japanese population, pediatric T2DM differs from adult T2DM in that the proportion of obese patients with insulin resistance tends to be higher in pediatric patients than in adult patients. The pediatric and adult populations are, however, similar in that impaired insulin secretion and insulin resistance are the main etiologies of T2DM, and therefore no essential differences may exist in the pathologic foundation of T2DM between adults and children.

The goal of treating Diabetes is to control blood glucose. In the clinical evaluations, using of efficacy measures such as HbA1c as the primary endpoint and blood glucose as a secondary endpoint has been recommended rather than using different efficacy measures for different pathologic backgrounds of individual patients. This is because the fact that its pathology is characterized by multiple contributing factors including the factors such as impaired insulin secretion and increased insulin resistance, though are different for each patients, are common to all patients, and because the treatment goal for DM is glycemic control, which can be clinically evaluated by assessing the effects of the drug on glycemic control.

Taken together, these facts indicate that to evaluate the efficacy of drugs in the pediatric population, assessing the efficacy of drugs on glycemic control may be sufficient as is in adults, even if the contributions of impaired insulin secretion and insulin resistance differ to some extent between pediatric and adult patients. It can therefore be evaluated the efficacy of drugs for DM in a single population consisting of pediatric patients of a certain age group and adults is possible.

(4) Target Age Group

As described in “I. GENERAL - 2. Target Age Group,” the present Considerations apply, in principle, to children 10 or 12 years of age and older, a pediatric population for whom the dosage is supposed to be the same as that for adults or within its range and for whom the formulation for adults can also be used. For T2DM, the group of 10 years of age and older may be reasonable as the target pediatric age group considering its pathology and onset age. Given that the incidence of pediatric T2DM has been reported to increase from 9 years of age, inclusion of children younger than 10 years of age in adult studies may also be possible, depending on drug characteristics such as dosage and safety margin. If children younger than 10 years of age are included, the rationale including the evaluation method should be explained. For dose-adjustable drugs such as GLP-1 receptor agonists or for drugs such as SGLT 2 inhibitors which may affect the patients’ growth such as bone metabolism, it may be required to examine which age group could be included for each individual drug.

(5) Clinical Evaluation Methods

The present Considerations apply, in principle, to the clinical evaluation of drugs in a pediatric population for whom the dosage is supposed to be the same as that for adults or within its range, conducted after the adult regimen is established. These consideration assume that pediatric clinical data for the drugs are mostly collected from confirmatory or long-term studies.

It is not mandatory to perform subgroup analyses for the pediatric population in confirmatory clinical trials, given that the foundations of the etiology of T2DM are the same for adults and children and that the dosage for target age group is supposed to be the same as the adult dosage or within its range. Nevertheless, it is useful to collect pediatric information including pharmacokinetic data and/or to perform subgroup analyses if a certain number of pediatric subjects have been accrued; pediatric patients should therefore be included in confirmatory and long-term studies.

The adverse event of hypoglycemia may occur at a higher frequency in pediatric patients than in adults because of a larger interindividual variability in physical activity; caution should be exercised if children are included in an adult study.

(6) Collection of Post-Marketing Information

Because available pediatric data before marketing approval are limited, post-marketing surveys should be conducted in an early post-marketing phase with the focus on the target pediatric population, and the results obtained should be provided to healthcare professionals.

(7) Other Considerations

The positioning of proposed drug should be explained to support its marketing application because children with T2DM should be treated like adults with pharmacotherapy if glycemic control cannot be achieved with diet/exercise therapy alone and the priority of pharmacotherapies varies according to patient characteristics such as insulin resistance.

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2. Familial Hypercholesterolemia

(1) Pathology

Familial hypercholesterolemia (FH) is a genetic disorder caused by mutations in the low-density lipoprotein (LDL) receptor and its related genes. FH is inherited in an autosomal dominant manner; the disorder is called heterozygous FH if the causative mutations exist in one allele, or called homozygous FH if the causative mutations exist in both alleles. FH is characterized by hyper-LDL cholesterolemia, tendon xanthoma, and early-onset coronary artery disease (developed at men younger than 55 years of age or women younger than 65 years of age). In patients with FH, arteriosclerosis develops more rapidly with severer organ involvement, compared with patients with hyper-LDL cholesterolemia having no genetic basis. Postmortem macroscopic observations in the Bogalusa Heart Study[1)] and the Pathological Determinants of Atherosclerosis in Youth (PDAY) study[2)] have also proved that arteriosclerotic changes are already seen in childhood. In particular, in patients with homozygous FH, arteriosclerotic diseases such as coronary arteriosclerosis/aortic valve disease rapidly develop starting from childhood. In general patients with heterozygous FH, arteriosclerotic cardiovascular disease develops in middle aged people, although a Dutch study in children with heterozygous FH revealed that arteriosclerosis rapidly develops from around 10 years of age and that the progress of the conditions could be inhibited with statin therapy.[3)]

In summary, FH, a disorder caused by mutations in relevant genes, has continuous pathology among adult and pediatric patients, and the involvement of hyper-LDL cholesterolemia is common to both groups of patients.

(2) Treatment in Clinical Practice

Studies have shown that hyper-LDL cholesterolemia continues to be an independent risk factor of arteriosclerosis from childhood and many children with heterozygous FH already experience progression of increased carotid intima-media complex thickness during a later school period.[4)] In recent years, many guidelines of countries outside of Japan point out the importance of starting treatment during childhood for prophylaxis of future cardiovascular events.[5),6),7)]

The Pediatric Familial Hypercholesterolemia Clinical Practice Guide 2017[8)] states that "Once diagnosed with FH, the patient should be instructed to modify his/her lifestyle as early as possible and make efforts to reduce arteriosclerosis risks including those to lower the LDL-cholesterol level. If results from the lifestyle modification is insufficient, pharmacotherapy should be considered at a recommended 10 years of age." As for pharmacotherapy for heterozygous FH, the Guide instructs that "Statin should be used for first-line treatment and should be initiated from the minimal dose. If sufficient efficacy is not obtained with statin therapy alone, consider (1) increasing the dose of the same statin, (2) changing statins to a more potent one (and increasing the dose), and (3) adding another lipid-lowering agent." For patients with homozygous FH, the Guide states that "At first, statin therapy should be initiated, and then the dose should be increased to a maximal tolerable dose. After approximately one month, the

efficacy of the statin therapy should be determined; if it is insufficient, LDL apheresis should be initiated, and in parallel, the efficacy of non-statin agents (e.g., ezetimibe, resins, probucol, PCSK9 inhibitors) should be examined."

(3) Rationale for Including Children in Adult Studies

In Japan, FH is diagnosed according to different criteria for adults (Table 1) and children (Table 2). Adult and pediatric patients are, however, similar in that abnormal lipid metabolism due to mutations in the LDL receptor and its related genes is the essential condition for FH, and therefore the foundations of the disorder may not essentially differ between adults and children.

Table 1. Diagnostic Criteria for Heterozygous FH in Adults (15 years of age and older)

1. Hyper-LDL cholesterolemia (LDL-C level ≥180 mg/dL when untreated)
2. Tendon xanthoma (tendon xanthoma in the knees, the elbows, or the back of the hands; or thickened Achilles tendon) or cutaneous tuberous xanthoma
3. History of FH or early-onset of coronary artery disease in first- or second-degree relatives

Table 2. Diagnostic Criteria for Heterozygous FH in children (younger than 15 years of age)

1. Hypercholesterolemia: LDL-C level ≥140 mg/dL when untreated (when total cholesterol ≥220 mg/dL, measure the LDL-C level)
2. History of FH or early-onset coronary artery disease in first- or second-degree relatives

In both adult and pediatric patients, treatment for hypercholesterolemia aims at lowering the blood LDL cholesterol level to prevent arteriosclerosis and subsequent cardiovascular events. In clinical evaluations, the decrease in LDL cholesterol level from baseline has been used as the primary endpoint because the LDL cholesterol level has been established as a surrogate marker for cardiovascular events. Although the specific values are different for the two groups, management targets for the blood LDL cholesterol level have also been established for both adult and pediatric patients. Taken together, these facts indicate that assessing the LDL cholesterol lowering effect may be sufficient to evaluate the efficacy of drugs for both adult and pediatric patients, leading to the conclusion that evaluating the efficacy of a drug for FH in a single population consisting of children of a certain age group and adults is possible.

(4) Target Age Group

The Pediatric Familial Hypercholesterolemia Clinical Practice Guide 2017[8)] states that "Once diagnosed with FH, the patient should be instructed to modify his/her lifestyle as early as possible and make efforts to reduce arteriosclerosis risks including those to lower the LDL-cholesterol level. If results from the lifestyle modification is insufficient, pharmacotherapy should be considered at a recommended 10 years of age."

As described in "I. GENERAL - 2. Target Age Group," the present Considerations apply, in principle, to children 10 or 12 years of age and older, a pediatric population for whom the dosing

regimen is supposed to be the same as that for adults or within its range and for whom the formulation for adults can also be used. As the Pediatric Familial Hypercholesterolemia Clinical Practice Guide 2017[8)] instructs that "If results from the lifestyle modification is insufficient, pharmacotherapy should be considered at a recommended 10 years of age," the age group of 10 years of age and older may be appropriate for inclusion in adult studies. As described in "I. GENERAL - 4. Clinical Studies Enrolling Pediatric Patients," however, it is recommended that pubertal stages including the development/maturation of secondary sexual characteristics should also be considered, as necessary. It should be noted that inclusion of children younger than 10 years of age in adult studies may also be possible, depending on drug characteristics such as dosing regimen and safety margin. If younger pediatric patients are to be included, the rationale including the evaluation method should be explained.

(5) Clinical Evaluation Methods

The present Considerations apply, in principle, to the clinical evaluation of drugs in a pediatric population for whom the dosing regimen is supposed to be the same as that for adults or within its range, conducted after the adult regimen is established. These considerations assume that pediatric clinical data for the drugs are mostly collected from confirmatory or long-term studies.

It may be reasonable to evaluate the efficacy and safety of drugs for FH with pediatric patients 10 years of age and older being included in adult studies, given that the foundations of the etiology of FH are the same for adults and children, that the same endpoints can be used for the two populations, and that a pediatric age group such that the dosing regimen is supposed to be the same as that for adults or within the range of it is to be included. In clinical evaluations, it is therefore not mandatory to perform subgroup analyses for the pediatric population. Nevertheless, it is useful to collect pediatric information including pharmacokinetic data and, if a certain number of pediatric subjects have been accrued, to perform subgroup analyses for the pediatric population alone; pediatric subjects 10 years of age and older should therefore be included in confirmatory and long-term studies in adults. The fluctuation range of LDL-C level in childhood should be kept in mind, and it should also be considered whether factors regarding the subjects' development including growth and pubertal stages should be assessed.

(6) Collection of Post-Marketing Information

Because available pediatric data before marketing approval are limited, post-marketing surveys should be conducted at an early post-marketing phase with the emphasis on the target pediatric population, and the results obtained should be provided to healthcare professionals.

(7) Other Considerations

As for pitavastatin, which is currently approved in Japan for the treatment of children with familial hypercholesterolemia, the dosage and administration requires that the drug must be

administered with care because in children, the frequency/intensity of daily activity can be higher than in adults, and muscle disorders may tend to easily occur. Therefore, it should be kept in mind that there may be unique characteristic which need to be taken into account for each individual drugs when considering the development of pediatric indications.

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3. Allergic Diseases

3-1 Bronchial Asthma

(1) Pathology

Asthma is a disease of which the essential nature is chronic inflammation of the airway, characterized by some clinical symptoms including reversible airway narrowing (wheezing, dyspnea) and coughing.[1)] Pathologic changes in the airway include infiltration of inflammatory cells including eosinophils, lymphocytes, and mast cells, vasodilation, and mucosal/submucosal edema. Structural changes include airway abrasion, hyperplasia of goblet cells, hyperplasia of the submucosal gland, neovascularization, hyperplasia of subepithelial fibers (thickening of the basement membrane), and hyperplasia of the airway smooth muscle.[1)]

Although asthma has many possible causes and exacerbation factors, and manifests itself in many different ways, it is generally classified into two types, the atopic type, characterized by detection of ambient allergen-specific IgE antibodies, or the non-atopic type, characterized by the lack of detection of the IgE antibodies. Among the childhood-onset cases, the atopic type is more common, while among the adult-onset cases, more non-atopic cases exist.[1)] Childhood-onset asthma develops by 6 years of age in 80-90 % of patients, and if not controlled during adolescence, is highly likely to persist until adulthood.

In summary, although asthma has different distributions of disease types in adult and pediatric patients, the two populations are similar in that the etiology is attributable to chronic inflammation of the airway. This airway inflammation may be caused by direct actions of various inflammatory cells including eosinophils and of inflammatory mediators and cytokines released by tissue constituting cells such as airway epithelial cells, fibroblasts, and myofibroblasts; or by actions mediated by other cells, the nervous system, or adhesion molecules.[1)]

(2) Treatment in Clinical Practice

For asthma, the management goals are the same for adults and children; they are (1) to control symptoms (i.e., to maintain a state that is free from asthmatic attacks and symptoms) and (2) to avoid future risks (e.g., to reduce the decline in respiratory function over time, or to prevent asthma).[1),2)]

Treatments for asthma are classified into two large groups; the group of *controllers* used in patients without symptoms or exacerbations to achieve certain management goals such as maintaining respiratory function, or the group of *relievers* used to primarily relieve symptoms such as dyspnea when acute exacerbation (attack) occurs. The treatment with controllers basically consists of 4 stages of different intensities, although the drugs used and their doses could vary accordingly.[1)] For pharmacotherapy of asthma, drugs that can reduce airway inflammation and dilate the airway are used. These basic strategies are the same for children and adults.

(3) Rationale for Including Children in Adult Studies

Although asthma occurs due to various causes and has different distributions of disease types for children and adults, it develops as a result of chronic inflammation of the airway in both children and adults. In addition, adult asthma cases include childhood-onset cases, which require treatment from adolescence to adulthood.

The goals of pharmacotherapy are to reduce airway inflammation and dilate the airway in both children and adults. In principle, drugs intended to treat asthma are evaluated in clinical studies with the main focus on asthmatic symptoms and respiratory function.

For bronchodilators such as short-acting beta 2 agonists (SABAs), treatment effects as a reliever are represented by improvements in airway obstruction. For evaluations in adults, FEV_1 is used as a good efficacy measure.

For controllers, treatment effects are assessed in terms of improvements in asthmatic symptoms, and in particular, acute exacerbation is an important measure. To evaluate controllers, assessments solely by means of respiratory function tests such as FEV_1 are not sufficient, and symptoms such as acute exacerbation also need to be evaluated using appropriate measures.

In children, the use of a respiratory function test such as FEV_1 as the primary endpoint requires care because skill levels concerning the testing technique affect the validity of the assessment.[1)] In addition, when using a patient-reported outcome such as symptom scores as the primary endpoint, consideration regarding the feasibility and appropriateness of the self-assessment is required based on children's mental and psychological development. Thus, although some considerations are required when conducting clinical evaluation in children, the same efficacy measures as in adults can be used in children 10 or 12 years of age and older.

Thus, it may be possible to develop asthma drugs with pediatric patients of a certain age or older together with adult patients.

It is worth mentioning that the European Medicines Agency (EMA)'s guideline defines three age groups of children, younger than 6 years of age, 6 to 12 years of age, and 13 to 17 years of age, and states that pediatric trials are required unless conducting no pediatric trials is justified, and that adolescents may be included in adult confirmatory trials if the pharmacokinetics are similar in adolescents and adults.[3)] In Japan, some of the asthma drugs that have recently been approved also for pediatric use were evaluated for pediatric patients 12 years of age and older together with adults in the same clinical trials.

(4) Target Age Group

As described in "I. GENERAL - 2. Target Age Group," the present Considerations apply, in principle, to children 10 or 12 years of age and older, a pediatric population for whom the dosing regimen is supposed to be the same as that for adults or within its range of it and for whom the formulation for adults can also be used.

In principle, the age group of 12 years of age and older may be reasonable as the target pediatric age group for asthma drugs, given that there are many younger pediatric patients as

indicated by the fact that the disease develops by 6 years of age in 80-90 % of childhood-onset cases, and therefore development of pediatric regimens for a wide range of age groups is required, and that in recent years, drugs may be developed based on global studies. It should be noted that inclusion of children younger than 12 years of age in adult studies may also be possible, depending on drug characteristics such as dosing regimen and safety margin. If pediatric patients younger than 12 years of age are included, it should be justified with respect to the evaluation method and others.

(5) Clinical Evaluation Methods

The present Considerations apply, in principle, to the clinical evaluation of drugs in a pediatric population for whom the dosing regimen is supposed to be the same as that for adults or within its range, conducted after the adult regimen is established. These considerations assume that pediatric clinical data for the drugs are mostly collected from confirmatory or long-term studies.

For asthma, because pediatric patients of 12 years of age and older do comprise a population of a certain size, a certain number of pediatric patients of this age group should be included in an adult confirmatory study to collect information on the pharmacokinetics, efficacy, and safety of the drug before the launch of products. In particular, for drugs such as topical drugs that have limitations in constructing a theory to support their efficacy on the basis of their pharmacokinetics, information regarding efficacy and safety from clinical studies is more important. Because it may be possible to evaluate the pediatric subjects 12 years of age and older similarly to adult subjects, statistical tests in the pediatric population alone may not be mandatory. Nevertheless, it is useful to evaluate the efficacy, safety, and pharmacokinetics in children 12 years of age and older vs. adults by performing subgroup analyses as much as possible to confirm the appropriateness of the determined regimen. In addition, collecting long-term safety information in children is also useful, and long-term studies should also include pediatric patients 12 years of age and older.

(6) Collection of Post-Marketing Information

In principle, for asthma drugs, efficacy and safety data in the pediatric population are collected to some extent from clinical studies and evaluated during the drug application review process. For post-marketing surveillance, therefore, the type and scope of information required should be determined for individual drug according to available premarketing information.

(7) Other Considerations

In the adolescent population (children 12 years of age and older), decrease in treatment adherence has been observed[2)]; caution should be observed with respect to its possible impacts on the appropriateness of their inclusion in clinical studies and on efficacy evaluation. For example, in the placebo arm of a clinical study in refractory patients, treatment adherence may

improve after joining the study in pediatric patients. This may lead to a placebo effect lager than that in adults and result in difficulties in securing the consistency of study results.

References:

1) Japanese Society of Allergology. Asthma Prevention and Management Guideline 2018 (in Japanese)
2) Japanese Society of Pediatric Allergy and Clinical Immunology. Japanese Pediatric Guideline for the Treatment and Management of Asthma 2017 (in Japanese)
3) Guideline on the clinical investigation of medicinal products for the treatment of asthma. CHMP/EWP/2922/01, 2015

3-2 Allergic Rhinitis

(1) Pathology

Allergic rhinitis (AR) is a type I allergic disease in the nasal mucosa, of which major symptoms generally include paroxysmal repetitive sneezing, (watery) rhinorrhea, and nasal congestion. It is characterized by increased serum-specific IgE antibody level, increased local mast cells, increased local and blood eosinophils, and increase in nonspecific hypersensitivity of mucous membrane among others.[1)] Furthermore, AR can be classified into perennial AR and seasonal AR (e.g., pollinosis).

During childhood, AR patients often experience allergic dermatitis prior to the onset of AR and then their symptoms lead to the complication. Pediatric AR cases are also frequently complicated with bronchial asthma. Dermatitis and bronchial asthma may resolve spontaneously around 11 or 12 years of age, but AR self-cure relatively infrequently and may persist until much later.

In summary, AR is a type I allergic disease of the nasal mucosa and its etiologies may be the same for adults and children.

(2) Treatment in Clinical Practice

Treatment approaches for AR include communication between the patient and healthcare professionals, antigen elimination and avoidance, pharmacotherapy, allergen immunotherapy, and surgical therapy. The drug classes used for pharmacotherapy include chemical mediator antireleasers, receptor antagonists, Th2 cytokine inhibitors, and steroids.

A treatment for perennial AR is determined according to the combination of the disease type and severity, and although this cannot be done in a uniform manner, the Practice Guideline for the Management of Allergic Rhinitis in Japan[1)] provides the following selection criteria:

<table>
<tr><td>Severity</td><td>Mild</td><td colspan="2">Moderate</td><td colspan="2">Severe</td></tr>
<tr><td>Type</td><td></td><td>Sneezing/rhinorrhea type</td><td>Nasal congestion type or complete type consisting mainly of nasal congestion</td><td>Sneezing/rhinorrhea type</td><td>Nasal congestion type or complete type consisting mainly of nasal congestion</td></tr>
<tr><td rowspan="4">Treatment</td><td>(1) 2nd generation antihistamine
(2) Antireleaser
(3) Th2 cytokine inhibitor
(4) Steroid for nasal spray

One of the four, (1), (2), (3), and (4)</td><td>(1) 2nd generation antihistamine
(2) Antireleaser
(3) Steroid for nasal spray

One of the three, (1), (2), and (3); or (3) in combination with (1) or (2), as necessary.</td><td>(1) Antileukotriene
(2) Anti-PGD2/TXA2
(3) Th2 cytokine inhibitor
(4) 2nd generation antihistamine
(5) Steroid for nasal spray

One of the five, (1), (2), (3), (4), and (5); or (5) in combination with (1), (2), or (3), as necessary.</td><td>Steroid for nasal spray
+
2nd generation antihistamine</td><td>Steroid for nasal spray
+
Antileukotriene or anti-PGD2/TXA2

OR

2nd generation antihistamine/vasoconstrictor

Use, as necessary, a vasoconstrictor for nasal application during the first 1 or 2 weeks of treatment only.</td></tr>
<tr><td></td><td></td><td></td><td colspan="2">Surgery if the case is of the nasal congestion type accompanied by morphological abnormality of the nasal cavity.</td></tr>
<tr><td colspan="5">Allergen immunotherapy</td></tr>
<tr><td colspan="5">Elimination and avoidance of antigens</td></tr>
</table>

As for the treatment for pollinosis, the Guideline recommends choosing drugs according to the predicted pollen count in the season, and the disease type and severity while the symptoms are most severe, as shown in the following table.

<table>
<tr><td>Severity</td><td>Initial Therapy</td><td>Mild</td><td colspan="2">Moderate</td><td colspan="2">Severe</td></tr>
<tr><td>Type</td><td></td><td></td><td>Sneezing/ rhinorrhea type</td><td>Nasal congestion type or complete type consisting mainly of nasal congestion</td><td>Sneezing/ rhinorrhea type</td><td>Nasal congestion type or complete type consisting mainly of nasal congestion</td></tr>
<tr><td rowspan="5">Treatment</td><td rowspan="3">(1) 2nd generation antihistamine
(2) Antireleaser
(3) Antileukotriene
(4) Anti-PGD2/TXA2
(5) Th2 cytokine inhibitor
(6) Steroid for nasal spray

For the sneezing/rhinorrhea type, use (1), (2), or (5). For the nasal congestion type or the complete type consisting mainly of nasal congestion, use one of the four, (3), (4), (5), and (6).</td><td rowspan="2">(1) 2nd generation antihistamine
(2) Antireleaser
(3) Antileukotriene
(4) Anti-PGD2/TXA2
(5) Th2 cytokine inhibitor
(6) Steroid for nasal spray

One of the six, (1)-(6).
If treatment was started with one of the five, (1)-(5), add (6) as necessary.</td><td rowspan="2">2nd generation antihistamine
+
Steroid for nasal spray</td><td>Antileukotriene or anti-PGD2/TXA2
+
Steroid for nasal spray
+
2nd generation antihistamine

OR

2nd generation antihistamine/vasoconstrictor
+
Steroid for nasal spray</td><td rowspan="2">2nd generation antihistamine
+
Steroid for nasal spray</td><td>Antileukotriene or anti-PGD2/TXA2
+
Steroid for nasal spray
+
2nd generation antihistamine

OR

2nd generation antihistamine/vasoconstrictor
+
Steroid for nasal spray

Use, as necessary, a vasoconstrictor for nasal application during the first 1 or 2 weeks of treatment only.

In case of intense symptoms, prescribe an oral steroid for 4-7 days.</td></tr>
<tr><td colspan="2">An antihistamine for ophthalmic application or an antireleaser</td><td colspan="2">An antihistamine for ophthalmic application, an antireleaser, or a steroid</td></tr>
<tr><td colspan="4"></td><td colspan="2">Surgery if the case is of the nasal congestion type accompanied by morphological abnormality of the nasal cavity.</td></tr>
<tr><td></td><td colspan="5">Allergen immunotherapy</td></tr>
<tr><td></td><td colspan="5">Elimination and avoidance of antigens</td></tr>
</table>

The Guideline states that the drug therapy for pediatric patients basically follows that for adults, but half of the adult dose should be used for elementary and junior high school students. With regard to steroids, nasal spray should be administered with care and oral steroids should be avoided as much as possible in children.

On the other hand, for some drugs recently approved for pediatric use, the approved dosage for children 12 years of age and older is the same as that for adults.

(3) Rationale for Including Children in Adult Studies

Allergic rhinitis is a type I allergic disease of the nasal mucosa and its etiologies in children are considered to be the same as in adults. Childhood-onset AR resolves relatively infrequently and at older ages. If AR remains unresolved during childhood, treatment will be required from adolescence to adulthood. The pharmacotherapy for pediatric patients basically follows that for adults.

When using a patient-reported outcome such as a symptom score as the primary endpoint for clinical evaluation, the differences in the feasibility and appropriateness of the self-assessment between pediatric and adult patients must be considered, taking into account the children's psychiatric and mental development. In children 10 or 12 years of age and older, however, the use of the same efficacy measures as in adults may be possible.

Thus, development of drugs in pediatric patients (children 10 or 12 years of age and older) together with adults may be possible.

A guideline of the EMA states that for the development of immunotherapies for general pediatric patients, the efficacy and safety must be evaluated in the pediatric population, but adolescents can be included in adult clinical studies.[2)] Some drugs that have recently been developed in Japan were evaluated in pivotal studies enrolling children 12 years of age and older together with adults.

(4) Target Age Group

As described in "I. GENERAL - 2. Target Age Group," the present Considerations apply, in principle, to children 10 or 12 years of age and older, a pediatric population for whom the dosing regimen is supposed to be the same as that for adults or within its range and for whom the formulation for adults can also be used.

In principle, the age group of 12 years and older may be reasonable as the target pediatric age group for AR drugs, given that there are many younger pediatric patients. Therefore development of pediatric regimens for a wide age range is required, and that in recent years, drugs may be globally developed. It should be noted that inclusion of children younger than 12 years of age in adult clinical studies may also be possible, depending on the drug characteristics such as dosing regimen and safety margin. If pediatric patients younger than 12 years of age are included, the rationale including the evaluation method should be explained.

(5) Clinical Evaluation Methods

The present Considerations apply, in principle, to the clinical evaluation of drugs in a pediatric population for whom the dosage is supposed to be the same as that for adults or within its range, conducted after the adult dosage is established. These considerations assume that pediatric clinical data for the drugs are mostly collected from confirmatory or long-term studies.

For AR, because pediatric patients 12 years of age and older do comprise a certain size of the population, a certain number of pediatric patients of this age group should be included in an adult confirmatory study to collect information on the pharmacokinetics, efficacy, and safety

of the drug before product launch. In particular, for drugs such as topical drugs that have limitations in the interpretation based on pharmacokinetics, information regarding the efficacy and safety obtained from clinical studies is more important. Because the pediatric subjects 12 years of age and older can be evaluated similarly to adult subjects, statistical significance for the pediatric population alone are not mandatory. Nevertheless, it is important to evaluate the efficacy, safety, and pharmacokinetics in adults vs. children 12 years of age and older by performing subgroup analyses as much as possible to confirm the appropriateness of the determined dosage. In addition, even in children, collecting long-term safety data is useful, and long-term studies should also include pediatric patients 12 years of age and older.

(6) Collection of Post-Marketing Information

In principle, for any AR drug, efficacy and safety data in pediatric patients are to some extent collected from clinical studies and are evaluated during the drug application review process. For post-marketing surveillance, therefore, the content and range of required information should be determined for each individual drug, taking into account the available premarketing information.

(7) Other Considerations

Oral steroids for AR should be avoided in children as much as possible, as cautioned in the Japanese guideline. To develop steroids for AR, its appropriateness should be carefully reviewed taking into account the impact of possible adverse reactions and others.

References:

1) Practice Guideline for the Management of Allergic Rhinitis - Allergic Perennial Rhinitis and Pollinosis (PG-MARJ) 2016 (version 8) (in Japanese)
2) Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. CHMP/EWP/18504/2006, 2008

4. Antimicrobials and Antivirals

(1) Relationship to Existing Guidelines

For the clinical evaluation of antimicrobials, an administrative notice, Guideline for the Clinical Evaluation of Antimicrobial Drugs[1)] has been issued. This Guideline gives instructions to refer to the relevant ICH guidelines regarding the development in the pediatric population.

The Science Board of the Pharmaceuticals and Medical Devices Agency has just complied a guidance document, "On the Clinical Evaluation of Anti-Infective Drugs Against Drug-Resistant Bacteria", which states that in developing pediatric dosages the possibility of including an older pediatric population in adult studies should be considered taking into account the characteristics of the target disease and of the drug to be developed.

The present Considerations explain what should be considered when clinical evaluation is conducted with pediatric patients enrolled in adult clinical studies, in accordance with the above mentioned guideline or guidance documents.

(2) Pathology of Infectious Diseases

In infectious diseases, pathogenic microorganisms (e.g., bacteria, viruses) invade the human body passing through its barriers, colonize and proliferate at the invasion site and/or remote organs. In addition, the immunologic responses to the virus proliferation occurs at the infectious site, resulting in cellular injury. Therefore, if children are already in a similar developmental stage to adults at the infectious site or the site of tissue injury, the etiology of the infectious disease in those children may be similar to that in adults. It should, however, be kept in mind that children might have different patterns of pathology from adults depending on the body's defense mechanism acquired as a result of past infections.

(3) Rationale for Including Children in Adult Studies and Target Age Group

The chemotherapy for infections is intended to inhibit the infectious and/or proliferative mechanism of the pathogenic microorganisms, and the etiology of infections and action mechanisms of drugs in children are similar to adults. Therefore, from the viewpoint of the drug efficacy against pathogens, it may be possible to develop anti-infective drugs in children together with adults. It should, however, be kept in mind that even if drugs are designed to exert their effects on microorganisms, their clinical effects might differ depending on the acquired biological defense mechanisms.

As described in "I. GENERAL - 2. Target Age Group," the present Considerations apply, in principle, to children 10 or 12 years of age and older, a pediatric population for whom the dosage is supposed to be the same as that for adults or within its range and for whom the formulation for adults can also be used..

With regard to anti-infective drugs, in principle, the age group of 12 years of age and older may be reasonable as the target pediatric age group with following reasons: younger children are also affected, development of pediatric dosages for a wide age range required, and recently

drugs may be developed globally. It should be noted that inclusion of children younger than 12 years of age in adult studies may also be possible, depending on the drug characteristics such as dosage and safety margin. If pediatric patients younger than 12 years of age are to be included, the rationale including the evaluation method should be explained.

For example, with regard to antiviral drugs against influenza, drugs inhibiting the activity of influenza neuraminidase or cap-dependent endonuclease which are required for viral replication are currently approved in Japan. The etiology of influenza virus infection and the mechanisms of action of anti-influenza virus drugs on the virus are considered to be similar among children and adults. On the other hand, the acquired immunity against the influenza virus may vary depending on the history of past infection, but children 10 or 12 years of age and older are generally assumed to have a past history of influenza virus infection, and thus may be evaluated for efficacy in a similar manner to adults.

Anti-influenza virus drugs recently approved for pediatric use in Japan were evaluated in adult pivotal trials with pediatric patients 10 or 12 years of age and older enrolled.

Regarding the development of anti-influenza virus drugs, the U.S.FDA's guidance points out the possibility that the immunocompetence acquired through past infection might affect the pathology of influenza virus infection among children vs. adults as well as the possibility that virus shedding might differ in children vs. adults; in particular, for children younger than 12 years of age, it states that studies for clinical efficacy measures and for safety should be conducted. On the other hand, for adolescents, it states their inclusion in the adult clinical studies may be possible, depending on the pharmacological action of individual drugs.[2)]

As for antimicrobials, the EMA and the U.S.FDA have expressed the following principles regarding pediatric clinical evaluations.

The EMA considers that efficacy results for antimicrobials in adults may be extrapolated to children of all ages except for some cases, and states that in many cases pediatric studies are required only for the evaluation of pharmacokinetics.[3)]

Regarding the clinical evaluation of antimicrobials against hospital-aquired pneumonia, the U.S.FDA's guidance states that the extrapolation of efficacy results in adults to children may be in general acceptable, but pediatric clinical studies may be required for determining an optimal dosage and for evaluating safety.

(4) Clinical Evaluation Methods

The present Considerations apply, in principle, to the clinical evaluation of drugs in a pediatric population for whom the dosage is supposed to be the same as that for adults or within its range, conducted after the adult doage is established. These Considerations assume that pediatric clinical data for the drugs are mostly collected from confirmatory or long-term studies.

For infectious diseases, the size of patient population varies depending on the disease, and the necessity for pediatric clinical data should be considered for each disease. In general, for an infectious disease for which pediatric patients 12 years of age and older comprise a certain size

of the population, information regarding the pharmacokinetics, efficacy, and safety of drugs should be collected before product launch by enrolling a certain number of pediatric patients of the target age group in an adult confirmatory study. In this case, because it may be appropriate to evaluate the pediatric subjects 12 years of age and older similarly to adult subjects, statistical significance in the pediatric population alone may not be mandatory. Nevertheless, it is important to evaluate the efficacy, safety, and pharmacokinetics in adults vs. children 12 years of age and older by performing subgroup analyses as much as possible to confirm the appropriateness of the dosage determined. In addition, if the drug is supposed to be administered for a long period of time and a long-term study is planned to be conducted, collecting long-term safety information in pediatric patients may be useful, and the long-term study should include children 12 years of age and older.

Even for infectious diseases with clinical studies for which it may not be possible to enroll a certain number of pediatric patients 12 years of age and older, clinical studies should include those pediatric patients because collecting pediatric information including pharmacokinetic data may be useful to review the appropriateness of the dosage.

(5) Collection of Post-Marketing Information

For antimicrobials and antivirals, pediatric data obtained from clinical studies varies depending on the target disease. For the antimicrobials/antivirals for which a certain level of pediatric data regarding the efficacy and safety is obtained from clinical studies and reviewed during the drug application review process, the content and range of the information to be collected by post-marketing surveillance should be determined for individual drug, taking into account the available premarketing information.

On the other hand, for antimicrobials/antivirals with limited premarketing pediatric efficacy and safety data obtained from clinical studies, post-marketing surveys should be conducted with the emphasis on the target pediatric population, especially regarding the safety, and the results should be provided to healthcare professionals quickly once they are obtained.

(6) Other Considerations

The antimicrobials/antivirals should be carefully used considering that the prevention of emergence of resistant bacteria/viruses is important regardless of pediatric use. The positioning as an antimicrobial or antiviral agent should be clearly characterized for the drug being developed.

References:

1) Guideline for the Clinical Evaluation of Antimicrobial Drugs, PSEHB/PED Notification No. 1023-3 issued by the Director of the PED, PSEHB, dated October 23, 2017. (in Japanese)
2) Guidance for Industry Influenza: Developing Drugs for Treatment and/or Prophylaxis. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), April 2011

3) Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements. EMA/CHMP/187859/2017,2018
4) Guidance for Industry, Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), May 2014

5. Hematopoietic Malignancy

(1) Relationship to "the Guidance for the Clinical Evaluation of Antineoplastic Drugs in Pediatric Malignancy"[1)]

For the development of pediatric antineoplastic drugs, "the Guidance for the Clinical Evaluation of Antineoplastic Drugs in Pediatric Malignancy" points out the following:

If the target protein expression or the target genetic mutation also exists in the corresponding pediatric malignancy, developing drugs intended to modify the target molecule simultaneously adults and children in Japan is recommended.

If the pathology of the pediatric malignancy is similar to that of the corresponding adult malignancy, it is recommended to consider the inclusion of pediatric patients in adult studies when planning a development program in adults. In this case, however, the appropriateness of evaluating adult and pediatric patients in the same study should be carefully considered.

The Considerations take into account the principles presented in the aforementioned Japanese guidance, and set the target on hematopoietic malignancies, and provide considerations for the clinical evaluation of drugs in pediatric patients who can be evaluated together with adults.

Application of the principles in the present Considerations to solid malignancies and brain tumors may also be possible depending on their pathology and/or the mechanism of action of the drug considered. In this case, the rationale for including pediatric patients in adult clinical studies should be explained including the pathology of the malignancy.

(2) Pathology

Hematopoietic malignancies are categorized into various types depending on what kind of cells they are derived from. Although some commonly occur with unknown cause, accumulating evidence indicates that some hematopoietic malignancies including Philadelphia chromosome-positive acute lymphocytic leukemia (Ph+ ALL), acute myeloid leukemia (AML), and some malignant lymphomas have generally the same etiology and pathology in children and adults.

For example, acute lymphocytic leukemia (ALL) develops as a result of neoplastic transformation of the lymphocyte precursor cells that have been determined to differentiate to the B or T/NK lineage during the course of differentiation in both children and adults. In particular, in Ph+ ALL and MLL-associated ALL, which results from the reciprocal translocation involving the KMT2A (MLL) gene on the chromosome 11 and a gene on another chromosome, their characteristic chromosomal abnormalities may be the cause of the disease.

Studies have shown that chronic myelogenous leukemia (CML) may develop because of the BCR-ABL1 chimeric gene product, a constitutively activated tyrosine kinase, produced as a result of a translocation involving the chromosomes 9 and 22 in cells at a level of pluripotent hematopoietic stem cells.

Even for hematopoietic malignancies of unknown cause, their essential nature is that mutated hematopoietic stem cells repeatedly differentiate and/or proliferate which leads to inhibition of normal hematopoiesis to produce functional cells (e.g., erythrocytes, neutrophils, platelets, etc.), resulting in conditions such as anemia and infections, and/or accumulated cells before intermediate steps of differentiation infiltrate in organs and cause impairments; this nature may be common to all hematopoietic malignancies.

(3) Treatment in Clinical Practice

Dosages and combination therapies for the treatment of hematopoietic malignancies are investigated to improve treatment outcomes for each of the various disease types.

For example, for the treatment of ALL, the patient's risk is categorized according to factors such as age, white blood cell count, immunological category, and chromosomal/genetic abnormalities to select their therapy. For the treatment of Philadelphia chromosome-negative (Ph−) ALL, studies indicate that pediatric dosages provide significantly better outcomes in adolescents and younger adults than adult dosages; clinical practice guidelines for pediatric leukemia/lymphoma also recommend pediatric dosages for the treatment of ALL in adolescents/younger adults. As for Ph+ ALL, although combination chemotherapies with imatinib are recommended in both children and adults, their pediatric dosages have not been approved in Japan.

For CML, the recommended treatments when newly diagnosed are tyrosine kinase inhibitors (TKIs) for both children and adults. Although TKIs have been administered to pediatric patients using the standard adult regimen, nilotinib is the only TKI for which the pediatric dosage has been approved in Japan.

(4) Rationale for the Appropriateness and Necessity of Including Children in Adult Studies

Although hematopoietic malignancies are classified into various types depending on what kind of cells they are derived from, and those of unknown cause are also common, the essential nature that mutated hematopoietic stem cells repeatedly differentiate and proliferate and as a result, cause a variety of impairments is common to all hematopoietic malignancies in adults and children. The goal of pharmacotherapy is therefore to lead the neoplastic cells to death, even if the specific pharmacologic action differs depending on the drug's mechanism of action, and therefore the efficacy evaluation of drugs in children may be the same as in adults.

On the other hand, for dosages, which are closely related to the efficacy and safety of pharmacotherapies of hematopoietic malignancies, studies indicate that their tolerability to adverse reactions can vary depending on the patient's age. Thus, dosages should be determined with caution.

However, due to the limited number of pediatric cases of hematopoietic malignancies, it is often difficult to conduct pediatric studies to collect evidence for the appropriateness of the dosage and for the efficacy and safety of the treatment.

Because of these situations, consideration for the possibility of including pediatric patients in adult studies is recommended after reviewing its scientific reasonability based on the etiology of the hematopoietic malignancy and the drug's mechanism of action.

For example, the pediatric dosages of TKIs for the treatment of CML and Ph+ ALL, the hematopoietic malignancies of known cause, have been determined to coincide with the respective adult dosages.

The U.S.FDA has published a draft guidance that states that adolescents should be included in adult studies that evaluate drugs for the treatment of malignancies of which pathological and biological characteristics in adults and adolescents are similar.[2)]

(5) Target Age Group

As described in "I. GENERAL - 2. Target Age Group," the present Considerations apply, in principle, to children 10 or 12 years of age and older for whom the dosage is supposed to be the same as that for adults.

Because hematopoietic malignancies are life-threatening and could develop during early childhood, new drugs are also needed for the treatment of patients younger than 10 or 12 years of age. In principle, however, the age group of 12 years of age and older may be reasonable as the target pediatric age group to be included in adult studies because, although the aim of pharmacotherapies for hematopoietic malignancies is eradicating neoplastic cells, the cause of the neoplastic transformation has not been elucidated in many cases and the efficacy, safety, and dosages of any drugs should be evaluated with caution.

Inclusion of children younger than 12 years of age in adult clinical studies may, however, be possible, if the developed drug has a mechanism of action which is as clear as in the TKIs that inhibit a constitutively activated tyrosine kinase in patients with CML, a malignancy of known cause, and has a safety profile which is expected to be similar to that in adults on the basis of safety data in adults collected during an early development phase and the safety information regarding drugs in same class. If children younger than 12 years of age are included in an adult clinical study, safety characteristics specific to children should be investigated in, e.g., juvenile animal studies.

It should be noted that, for the development of antineoplastics, the U.S.FDA provides basic principles on the enrollment of adolescents and children 2 years of age and older in adult clinical studies, dividing the clinical development into two stages, the early clinical development and the late clinical development, and dividing pediatric patients into two age categories, from 2 to 11 years of age, and from 12 to 17 years of age.[3)]

(6) Clinical Evaluation Methods

The present Considerations apply, in principle, to the clinical evaluation of drugs in a pediatric population for whom the dosage is supposed to be the same as that for adults or within its range, conducted after the adult dosage is established.

Although hematopoietic malignancies are classified into various types depending on what kind of cells they are derived from, and those of unknown cause are also common, the goal of pharmacotherapy is to lead the neoplastic cells to death, even if the specific pharmacologic action differs depending on the drug's mechanism of action. If the target malignancy is likely to have the same pathology in children and adults and if the pediatric dosage is supposed to be the same as that for adults or within its range, efficacy evaluation will be similar in children and adults; thus it may be reasonable to evaluate the efficacy and safety of the drug in a similar manner as in adults in a pediatric population of a certain age range such as 12 years of age and older. In the clinical evaluation, it is therefore not mandatory to perform a subgroup analysis for the pediatric population. Nevertheless, it is useful to collect pediatric information including pharmacokinetic data and to perform, if a certain number of pediatric subjects have been accrued, subgroup analyses for the pediatric population; pediatric subjects 12 years of age and older should therefore be included in adult clinical studies.

For the development of individual drugs, however, if the pediatric dosage has been determined to be the same as or within the range of adult dosage, the decision should be scientifically explained with respect to whether a variable dosage based on tolerability is necessary or not and others.

(7) Collection of Post-Marketing Information

Including children 12 years of age and older in adult studies may be reasonable if the pathology of target disease is similar or is considered similar for the purpose of clinical evaluation of the drug between children and adults. However, in general, as for hematopoietic malignancies, the number of pediatric patients enrolled in a clinical study is expected to be small because of their rarity. If this is the case, 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. In addition, taking a special approach should be considered during the early post-marketing phase, such as starting the use of the drug at limited medical sites and then expanding the use step by step.

Hematopoietic malignancy is a life-threatening disease, and it is an area where improvement of treatment outcome is always required. Hence, even if a drug has been approved for pediatric use after evaluation of efficacy and safety by including pediatric patients in an adult study, continued exploration of better dosages may be required for some of those drugs.

(8) Other Considerations

Antineoplastics do not necessarily take the general development stages of Phase 1, Phase 2, and Phase 3, but the drug application can be submitted for filing with only data from a Phase 2 study, and without waiting for the completion of a Phase 3 study. For the development of antineoplastics, new development approaches such as those using master protocols are explored. To include pediatric patients 12 years of age and older in an adult clinical study during a stage

in which a dosage for adults has not yet been established, its appropriateness should be explained for each individual drug, taking into account its development program and/or the study objectives.

References:

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3) Cancer clinical trial eligibility criteria: minimum age for pediatric patients guidance for industry draft guidance; U.S. Department of Health and Human Services, Food and Drug Administration, Oncology Center of Excellence (OCE), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), March 2019