Provisional Translation (as of April 2024)*

Administrative Notice
January 16, 2024

To: Pharmaceutical Affairs Section, Prefectural Health Department (Bureau)

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

Questions and Answers (Q&A) for Designation of Orphan Drugs etc.

Handling of the designation of orphan drugs has been shown in "Designation of Orphan Drugs etc." (Joint PSEHB/PED Notification No. 0831-7 issued by the Director, Pharmaceutical Evaluation Division and PSEHB/MDED Notification No. 0831-7 issued by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020, hereinafter referred to as the "Notification by Directors")

With regard to the designation of orphan drugs, "Partial Revision of 'Designation of Orphan Drugs etc.'" (Joint PSB/PED Notification No. 0116-1 issued by Director, Pharmaceutical Evaluation Division, and PSB/MDED Notification No. 0116-1 issued by Director of Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare dated January 16, 2024) has been issued as a result of the review at "Review Committee on Regulatory Affairs to Strengthen Drug Discovery and Development/Ensure Stable Supply." For the Notification by Directors, questions and answers (Q&A) have been compiled as shown in the Appendix. We ask you to understand this compilation and inform related parties under your jurisdiction of this matter.

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

(Appendix)

Questions and Answers (Q&A) for Designation of Orphan Drugs

(Matters related to number of subjects)

Q1
With regard to the number of subjects pertaining to the usage of a drug expected to be used for a short period of time, such as a drug used in treatment, surgeries etc. or a drug used for postoperative complications, is it acceptable to regard the number of subjects who are expected to use the drug in 1 year as 'number of subjects'?

A1
Acceptable.

Q2
With regard to a disease for which standard first-line therapy is established but there are no established standard therapy for patients with insufficient efficacy of the first line therapy, is there any possibility to consider that such restriction of patients is deemed as 'clear medical and pharmaceutical reason' and not 'salami slicing'?

A2
Yes, there is a possibility of designation for such a restricted indication.

Q3
In the case where a drug is expected to be applicable for any stage of treatment from a medical and pharmaceutical perspective, such as the mode of action or the insufficiency of existing therapy, but clinical development is conducted in a stepwise manner from patients who inadequately respond to existing therapy in order to evaluate the efficacy apparently and there are particularly high unmet needs in the portion of target population, is it acceptable to consider such restriction of target population as a proposed indication in the application for designation not 'salami slicing'?

A3
Acceptable.

Q4
In the case where the total number of patients with the target disease is >50,000 but the number of patients requiring treatment with the study drug is limited to a portion of those patients (e.g., treatment is not necessary for patients with mild disease, or the drug is used only for patients who tested positive to a specific gene using companion

diagnostics (CDx) etc.), is it acceptable to consider that counting only the number of subjects to whom the drug will be applied is not deemed ‘salami slicing’?

A4

Acceptable.

Q5

In the case where the total number of patients with the target disease is >50,000 but the treatment with the study drug is applicable only to limited population based on biomarkers etc. for antineoplastic drugs (limited to cases where the limitation is scientifically sound, e.g., expression level of target protein or genetic alteration is biologically significant), is it acceptable to consider that such restriction of target population is not deemed ‘salami slicing’?

A5

Acceptable.

Q6

With regard to ‘the age range (including pediatrics),’ how is it determined whether it is ‘salami slicing’ or not when applying for the designation with dividing age groups?

A6

For instance, cases that are not deemed ‘salami slicing’ include but are not limited to the following:

- The case where the applicant intends to apply for the designation for pediatrics and the target disease occurs mainly in infancy but extremely rarely in adults
- The case where it is considered to be medically and pharmaceutically appropriate to develop a drug with dividing patients into pediatrics or elderly etc., due to the disease concept or treatment algorithm (treatment line and risk classification etc.)
- The case where the applicant intends to apply for the designation for a drug of which tolerability and/or efficacy are different between adults and pediatrics and for which it was considered, at the time of original marketing approval, that a dose-finding study, etc. in pediatrics is required

Q7

What cases are anticipated when the target diseases are restricted based on the “treatment algorithm”?

A7

For instance, the target disease can be restricted when the treatment algorithm differs depending on whether the malignant tumor is resectable or not. However, such a restriction is not limited to this case.

(Matters related to medical needs)

Q8

With regard to “Serious diseases refer to diseases that are fatal as well as lead to the very low quality of life for a long time,” specifically what is anticipated to lead the very low quality of life?

A8

It includes but is not limited to the status in which dysfunction significantly interferes with daily life activities, for instance, visual impairment or disability in motion.

Q9

In the case where the total number of patients with the target disease is <50,000, and where medical needs exist only in a part of the target disease (e.g., patients with a specific gene mutation or with inhibitors etc.) and there are not high medical needs for all of the target disease because existing therapies are sufficient for other part of patients, is it possible to receive an orphan drug designation for the part of the target disease even when marketing application is planned for the overall target disease?

A9

It is possible. If the marketing application is submitted for the overall target disease including designated orphan indication (only in the case where it's impossible to complete clinical data package by clinical trials on the designated orphan indication only), it is subject to priority review (only in the case where the orphan drug designation is deemed subject to priority review.), although it takes the ordinal user fees for marketing application. In so doing, the applicant is required to plan clinical trials adequately so that the efficacy in an orphan-designated population can be appropriately evaluated.

Q10

With regard to the description 'there are approved drugs etc. that are inadequate as treatment/prophylaxis and thus multiple options are clinically needed' in criterion [2], specifically what case does it refer to?

A10

This will be determined case-by-case basis for each target disease.

In the cases where multiple drugs etc. are approved but are not sufficient for the target disease, the criterion shall be considered as satisfied. On the contrary, in the cases where only a single drug etc. is approved, which shows sufficient treatment effect and is considered to satisfy as a therapeutic option to a certain extent, the criterion shall not be deemed satisfied.

Q11

If a drug has a different target molecule, is it deemed to have a new mode of action?

A11

For instance, in case of drugs that show their effects by inhibiting the same signaling pathway even though the direct targets are different, such as drugs acting on a receptor and drugs acting on the ligand of the receptor, but that the difference in the clinical benefit, such as to be effective in patients resistant to existing drugs or safer than existing drugs, cannot be explained, such drugs are not deemed to have a new mode of action.

Q12

With regard to the description ‘High probability of being superior in safety because the safety profile is completely different, for instance, in the case that degree of precautions in the package insert is significantly different (e.g., the boxed warning for the approved indication is different) etc.,’ specifically what cases does it refer to?

A12

It’s assumed a case where there is a certain portion of patients in whom approved drugs are difficult to use for safety reasons but who are expected to be treated with the drug applied for the orphan drug designation. The description ‘degree of precautions in the package insert is significantly different’ is considered to include, but is not limited to, the following examples:

- For approved drugs, safety issue is described in the section “CONTRAINDICATIONS” etc. of the package insert. However, for the drug applied for the orphan drug designation, which is approved by other indications, such safety issue does not exist in “CONTRAINDICATIONS” etc., which indicates a significant difference in the degree of precautions. Besides, for the proposed indication, the safety profile is not expected to be different from that of approved indications.
- For approved drugs, the section “WARNING” etc. in the package insert explains that laboratory tests, observation, premedication or rescue medication are required to prevent or reduce specific adverse reactions. However, these are not expected to be required for the drug applied for the orphan designation.

(Matters related to possibility of development)

Q13

To demonstrate the clinical benefit based on clinical data, are Japanese data required?

A13

It is not required to scrutinize the ethnic differences when evaluating the clinical benefit. If the clinical benefit is demonstrated based on non-Japanese data, the requirements shall be satisfied in principle. However, this shall not apply if there is any strong evidence implying that it is highly probable that the clinical benefit cannot be shown based on Japanese data. In this regard, Pharmaceutical Evaluation Division may issue queries.

Q14

For the outline of a planned clinical studies, is it necessary to describe other indications than the indication applied for the designation of orphan drugs?

A14

It is not necessary.

Q15

With regard to the description ‘the outline of a planned clinical studies to be conducted before the marketing application is clarified,’ specifically what is required to clarify it? Is it necessary to submit the protocol of clinical studies at the time of application for the designation of orphan drugs?

A15

It is not always necessary to submit a protocol of clinical studies. A Gantt chart that shows the process through the marketing approval is sufficient.

Q16

With regard to the description ‘nonclinical studies required to start first-in-human study have been mostly completed,’ is it considered sufficient for the criterion if only a specific costly nonclinical study has not been conducted yet, but all of the other essential nonclinical studies are completed, and the specific nonclinical study is planned after the orphan drug designation followed by a phase I study?

A16

Yes.

Q17

Are orphan drugs designated by route of administration?

A17

The designation of orphan drugs is granted for active ingredients by indication regardless of the route of administration.

Therefore, the number of patients should be estimated without limiting the route of administration in principle.

(Matters related to withdrawal of designation)

Q18

If an orphan-designated drug is found not to satisfy the requirements of orphan drug designation after marketing application, will the designation be withdrawn?

A18

The designation will not be withdrawn in principle after the marketing application (including after the meeting of ‘pre-review consultations for drugs’).

If the evaluation pertaining to the designation criteria is likely to change from that at the time of designation, for instance, a drug in the same class is approved before the marketing application of an orphan-designated drug, the designation holder must consult with Pharmaceutical Evaluation Division.

Q19

If the designation holder recognizes not to satisfy the criteria for orphan drug designation or the criteria for priority review/consultation (i.e., former designation criteria) after the orphan drug designation, what is the holder required to do?

A19

If the holder recognizes not to satisfy those criteria, the holder must promptly notify the Ministry of Health, Labour and Welfare (MHLW) and confirm whether it is possible to maintain the designation or the eligibility for priority review/consultation. In the case the holder believes there is no change in the status that has satisfied the criteria for orphan

drug designation or priority review/consultation, it is not necessary to confirm with the MHLW. However, if the MHLW finds that the criteria may not be satisfied, the MHLW may issue queries to the designation holder.

(Matters related to priority review/consultation)

Q20

For a drug that is deemed ineligible for priority review/consultation and is designated as an orphan drug at an early stage of the development, if the designation holder would like to apply for priority review/consultation based on additional data at the late stage of the development, what procedures are provided to change the eligibility for priority review/consultation?

A20

The designation holder can use '*consultation on drug product eligibility for priority review (orphan) (tentative)*' or '*consultation on drug product eligibility for priority review (with pre-application consultation for drugs) (orphan) (tentative)*' by 40 working days prior to the marketing application. If the designation holder wishes to use both of pre-application consultation for drugs and '*consultation on drug product eligibility for priority review (with pre-application consultation for drugs) (orphan) (tentative)*', they are expected to request the consultations simultaneously.