

Administrative Notice  
June 9, 2022

To: Each 

{	Prefecture	}	Department (Bureau) in charge of hygiene
	City with public health center		
	Special ward		

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

Questions and Answers (Q&A) on "Points to Consider for Quality Assurance and Evaluation of Oligonucleotide Therapeutics"

Considerations for the quality assurance and evaluation of oligonucleotide therapeutics have been notified of "Points to Consider for Quality Assurance and Evaluation of Oligonucleotide Therapeutics" (PSEHB/PED Notification No. 0927-3 issued by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated September 27, 2018) (hereinafter referred to as "Notification of Considerations").

Based on the discussions in the "Study on Quality and Safety Assessment of Antisense Oligonucleotide Therapeutics" (Fiscal year 2018 Research on Regulatory Science of Pharmaceuticals and Medical Devices by Japan Agency for Medical Research and Development), we have compiled a list of questions and answers (Q&A) for the Notification of Considerations as shown in the Attachment. Thus, please inform the relevant business operators under your jurisdiction.

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

## Attachment

### Questions and Answers (Q&A) on "Points to Consider for Quality Assurance and Evaluation of Oligonucleotide Therapeutics"

#### Q1 Section 1.1 in Notification of Considerations

Regarding changes in manufacturing processes in the development stage, Section 1.1 states "When evaluating the comparability associated with changes in the manufacturing process, it may be appropriate to refer to the concept of the ICH Guideline Q5E. In particular, impurities ..." Should the concept of Q5E be applied when evaluating the comparability of impurity profiles regardless of the type of oligonucleotide therapeutics?

A1

Regardless of the type of oligonucleotide therapeutics, the concept of the ICH Guideline Q5E may be appropriate when it is technically difficult to separate, evaluate and control individual oligonucleotide-related substances.

#### Q2 Section 1.2 in Notification of Considerations

(1) Oligonucleotide-related substance, the subsection of Impurities in Section 1.2, states that there is little significance in applying the concept of the ICH Guideline M7, and that "if an oligonucleotide-related substance with a partial structure different from that of the active ingredient is produced, the results of consideration on the genotoxicity risk should be explained according to the degree of concern about the partial structure." Is it correct to understand that, for example, when oligonucleotide-related substances bearing a protecting group are expected to remain, a risk assessment should be performed according to the degree of concern about genotoxicity of the residual protecting group, and the results should be explained in the application dossier?

A2

That is correct.

#### Q3 Section 1.3 in Notification of Considerations

For the specifications of oligonucleotide-related substances, Section 1.3 states "It is not practical to apply the thresholds for reporting, identification, and qualification in the ICH Guideline Q3A(R2) to oligonucleotide-related substances." Is it acceptable to set the threshold for identification at 1.0% for oligonucleotide-related substances, based on (i) oligonucleotide-related substances are similar in characteristics and toxicity to active ingredients, and (ii) 0.1% of small molecule impurities and 1.0% of oligonucleotide-related substances are considered to be equivalent in molar amounts, due to differences in molecular weight?

A3

The identification threshold should be considered on a case-by-case basis depending on the characteristics of each product, taking into account the following:

- The identification threshold should be set at a level sufficiently lower than the established qualification threshold.
  - The qualification threshold should be set in consideration of the characteristics of individual products as described in the Notification of Considerations.
- However, when evaluating the consistency in impurity profiles at the time of change in the manufacturing process, a more detailed characterization may be requested regardless of the identification threshold.

Q4 Section 1.3 in Notification of Considerations

Section 1.3 describes the specifications for oligonucleotide-related substances: "Oligonucleotide-related substances or oligonucleotide-related substance groups (only when it is appropriate to control them as one group) should be analyzed and classified as far as possible. The safety should be evaluated based on the levels of each related substance in the drug substance and drug product used in pivotal clinical and non-clinical studies. And then appropriate limits should be set." For example, with consistently controlling oligonucleotide-related substances as a "group" from non-clinical/clinical batches (drug substance and drug product), is it acceptable to set the acceptance criteria based on the batch analysis results as a "group"?

A4

It is acceptable, if it is assumed that the related substances contained in the oligonucleotide-related substance "group" have been characterized as much as possible and that the consistency of the impurity profile and the appropriateness of controlling them as a group can be explained based on the characterization results, etc.

Q5 Section 1.3 in Notification of Considerations

Section 1.3 describes the specifications for oligonucleotide-related substances as follows: "An oligonucleotide-related substance whose concentration is higher than that present in the drug substance or drug product lot used in previous non-clinical safety studies and/or clinical studies can also be considered qualified based on the actual amount of the oligonucleotide-related substance administered in previous relevant safety studies. If data to qualify the proposed acceptance criterion of oligonucleotide-related substances have not been obtained yet, safety studies to justify such criterion may be needed." For example, is it acceptable to set the specifications based on the maximum amount of each oligonucleotide-related substance (group) contained in the batches used in the toxicity studies? Is it acceptable to set the specifications by considering the amount of each oligonucleotide-related substance (group) during the storage period?

A5

The following description in the Notice of Considerations should be considered:  
"Because the pharmacological activity of oligonucleotide-related substances may be different among species, attention should be paid to the limitation of non-clinical studies

when the safety of oligonucleotide-related substances is evaluated."

In setting the acceptance criteria, it is recommended to consider comprehensively the analytical data of batches manufactured by the proposed commercial process or appropriately designed pilot plant process, and the analytical data of batches used in clinical trials, etc. in addition to non-clinical safety studies and stability studies.

**Q6 Section 1.3 in Notification of Considerations**

Section 1.3 describes the assay (content) as follows: "As stated in the ICH Guideline Q6A, a highly specific assay, which is not affected by impurities, should be established. Considering the complicated profile of oligonucleotide-related substances, multiple analytical methods may be combined as appropriate so that they are totally specific to the drug substance." Is it acceptable to set up the assay (content) using one analytical method?

A6

When a highly specific analytical method can be used, it is not necessary to combine multiple analytical methods.

**Q7 Scope of Notification of Considerations**

The scope is defined as "drugs containing a chemically synthesized oligonucleotide or its conjugate as an active ingredient" Thus, is it acceptable to evaluate the stability of oligonucleotides chemically conjugated with a functional small molecule such as cholesterol or sugar, with reference to the ICH Guideline Q1?

A7

Yes, it is acceptable.

**Q8 Regarding the stability of conjugated oligonucleotides, it may be difficult to evaluate the changes in the oligonucleotide moiety because of conjugation. In this case, is it acceptable to evaluate the stability comprehensively based on the stability of the conjugate part (i.e., the stability of the conjugated oligonucleotide will be evaluated) and the stability of the unconjugated oligonucleotide?**

A8

If the conjugated oligonucleotide is the drug substance, the development of an analytical method capable of appropriately evaluating the stability of the drug substance should be examined. If necessary, it is desirable to utilize consultations provided by Pharmaceuticals and Medical Devices Agency (PMDA).

**Q9 How should impurities be evaluated which are difficult to identify for reasons such as technical inability to separate?**

A9

If it is difficult to identify impurities, consideration should be made to obtain information necessary for the evaluation of the consistency of the impurity profile.