Provisional Translation (as of June 2023)*

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To: Directors of Prefectural Health Departments (Bureaus)

Director of Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Points to Consider for Quality Assurance and Evaluation of Oligonucleotide Therapeutics

In order to promote the commercialization of innovative drugs, medical devices, and regenerative medical products, the Ministry of Health, Labour and Welfare has been conducting the following projects since fiscal year 2012: (i) Establish the methods of evaluating safety and efficacy based on regulatory science and prepare guidelines at universities/research institutes, etc. where cutting-edge technologies are researched and developed, (ii) Exchange human resources between universities/research institutes, Pharmaceuticals and Medical Devices Agency (PMDA), and the National Institute of Health Sciences (NIHS).

Based on the project, Points to Consider document related to the quality of oligonucleotide therapeutics have recently been formulated as attached, by the Graduate School/School of Pharmaceutical Sciences, Osaka University. Thus, please inform the relevant business operators under your jurisdiction of this document as a reference for the marketing approval application.

Notice

Points to Consider for Quality Assurance and Evaluation of Oligonucleotide Therapeutics

1. This Points to Consider document shows one example of matters to be considered for the quality assurance and evaluation of oligonucleotide therapeutics at present. To select test methods necessary for marketing approval application of oligonucleotide therapeutics, scientific consultation provided by PMDA should be utilized if necessary.

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

2. For the road map of the project Initiative for Accelerating Regulatory Science in Innovative Drug, Medical Device, and Regenerative Medicine, please refer to PMDA's website (https://www.pmda.go.jp/rs-std-jp/facilitate-developments/0001.html).

Attachment

Points to Consider for Quality Assurance and Evaluation of Oligonucleotide Therapeutics

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Introduction

Oligonucleotides are not covered by the existing ICH quality guidelines related to control and specifications of impurities (ICH Guidelines Q3A(R2), Q3B(R2), Q6A, and M7). The principles shown in the existing guidelines for chemically synthesized drugs can be partially applied to chemically synthesized oligonucleotides. However, the existing guidelines for chemically synthesized drugs may be insufficient or may not be applicable, for example, to qualification of impurities or control of oligonucleotide therapeutics for which formation of a higher-order structure is important for the onset of pharmacological activity.

This document focuses on the part related to manufacturing, and specifications of oligonucleotide therapeutics, including control of impurities, which are not covered by the existing guidelines. It is also recommended to refer to other latest guidelines, etc. when preparing an application dossier for a marketing approval application of oligonucleotide therapeutics.

This document has been formulated based on the scientific standards at the time of preparation. Even if the approach differs from that described here, applicants can discuss the applicability of the approach individually with regulatory authorities based on scientific rationale.

Scope

This document covers drugs containing a chemically synthesized oligonucleotide or its conjugate as an active ingredient. These drugs include not only single strands but also double strands and oligonucleotides with higher-order structures. This document does not apply to oligonucleotides conjugated to antibodies, peptides, or other proteins biologically derived or prepared by applying biotechnology, or oligonucleotide therapeutics with complex pharmaceutical characteristics, such as drug products utilizing complex DDS. However, this document can be referred to control of oligonucleotides that are intermediates or drug substances. In addition, this document should not be applied to products containing long-chain polynucleotides which are enzymatically produced, such as mRNA, as an active ingredient.

Definitions of terms and abbreviations

Definition of terms

Annealing

A process involving heating and cooling in general. An annealing process is used to form base pairs from complementary strands.

Counterion

An ion pairing with an active ingredient in case the drug substance is a salt. For example, sodium ion forming a salt with oligonucleotides.

Oligonucleotide therapeutics
Drugs containing a chemically synthesized oligonucleotide (DNA, RNA, and their derivatives) or its conjugate as active ingredients.

Conjugate
To make a covalent bond to another molecule with an expectation of some function. Or a bound drug itself.

Phosphorothioate
A compound in which non-bridging oxygen is replaced by sulfur in the phosphodiester linkage between nucleotides.

Oligonucleotide-related substances
Oligonucleotides other than the active ingredient, which are contained in the drug substance or drug product.

Oligonucleotide-related substance group
A group of oligonucleotide-related substances that have similar physicochemical properties, such as being observed as a single peak in HPLC or LC/MS analysis, and that seem impractical to be controlled separately.

Morpholino oligonucleotide
A non-natural oligonucleotide in which sugars of DNA or RNA are replaced with morpholine rings or their derivatives.

Definition of abbreviations
DDS
Drug delivery system

HPLC or LC
High performance liquid chromatography or liquid chromatography

ICH
The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

MS
Mass spectrometry

1. Drug Substance

1.1. Manufacturing

Manufacturing method and process control

Oligonucleotide elongation is performed by multistep synthesis, and it is recommended to explain how the termination of the reaction is controlled and monitored from the viewpoint of appropriate control of impurities. If an automated synthesizer is used for production, how each synthesis process is monitored and controlled, based on the automatic synthesis system used, should be explained.

For oligonucleotide therapeutics containing a double-stranded oligonucleotide as an active ingredient, annealing is usually performed after the final purification process. Such annealing processes greatly impact the quality of the drug substance and thus require appropriate control. When manufacturing an active ingredient that is a conjugated oligonucleotide or a double-stranded oligonucleotide, the processes or intermediates, such as pre-conjugate intermediates or intermediates before annealing, are highly relevant to critical quality attributes of the final product. It may be easier to evaluate the profile of related substances in such processes or intermediates than that of the drug substance. It may be recommended to establish appropriate tests and acceptance criteria for such critical intermediates in control. It is recommended to explain the monitoring or test methods used for these in-process controls, their appropriateness, acceptance criteria, and rationale. The results of the monitoring of the appropriately controlled manufacturing process can be used as one of the rationales supporting the structural characteristics (e.g., base sequence) of the drug substance.

If it is technically difficult to measure the distribution of stereoisomers of the active ingredient which is a mixture of many stereoisomers derived from oligonucleotides modified with phosphorothioate or morpholino oligonucleotides, the manufacturing process and parameters affecting the stereochemistry of the phosphorus atom should be elucidated and appropriately specified, and the consistency of the distribution of stereoisomers of the active ingredient should be explained.

Control of starting materials

Since impurities in starting materials that will be incorporated into the drug substance are considered to be high-risk factors, the impurity profile of starting materials should be thoroughly examined. In addition, the control of the starting materials should be appropriately established in the control strategy for impurities, in consideration of the facts that opportunities for purification are limited in the manufacture of oligonucleotides compared to small molecules and that the separation and detection of oligonucleotide-related substances are limited in the final product.

It is recommended to outline the manufacturing process of the starting material as it is useful in understanding the control strategy of the starting material.

Manufacturing process development

The background of the examination and changes in the manufacturing process during the development stage, and how the knowledge in the development stage is utilized in the manufacturing

process development should be explained.

If changes are made to the manufacturing process during development, the consistency of the quality should be carefully evaluated and explained based on data. 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 be evaluated based on detailed characterization data and analytical data of critical intermediates in the manufacturing process, and it should be confirmed that the impurity profile is consistent before and after the change in the manufacturing process.

1.2. Characterization

Structural characteristics

Studies performed to assess the structural characteristics of the active ingredient should be presented. Analytical procedures capable of characterizing the structure of the active ingredient should be described in detail. The following elements (1) to (4) are particularly important for the structural characteristics of oligonucleotides and should be considered for the evaluation of the structural characteristics.

(1) Composition and sequence:
The sequence of the oligonucleotide (active ingredient) is a critical characteristic to recognize the target molecule.

(2) Phosphate backbone:
Appropriate implementation of the intended chemical modifications is an important characteristic of oligonucleotides with phosphate backbone modification.

(3) Counterion:
If the active ingredient is accompanied by a counterion, the composition and content of the counterion are important characteristics to characterize the active ingredient.

(4) Higher-order structure and complex:
Higher-order structure or complex formation is a critical characteristic that has a possibility to impact quality. Oligonucleotides may form higher-order structures or complexes depending on (i) the conditions such as salt concentration and temperature and (ii) the base sequence of the oligonucleotide. It is particularly important to evaluate the structural characteristics of each oligonucleotide when the active ingredient has a complex such as a double strand or when the oligonucleotide drug requires the formation of a higher-order structure for the onset of pharmacological activity.

Impurities

It is necessary to present the results of appropriate analysis and investigation for the impurity profile classified by chemical properties as follows.

(1) Oligonucleotide-related substances:

Oligonucleotide-related substances show similar physicochemical properties, and it is often difficult to develop an analytical method to separate all oligonucleotide-related substances from each other. However, the studies conducted to develop analytical methods that can more appropriately evaluate the profile of related substances should be explained.

Individual oligonucleotide-related substances constituting a group of related substances may have different biological characteristics from each other. Still, these oligonucleotide-related substances can be controlled as one group if appropriate. In this case, the results of a multifaceted investigation on what kinds of related substances are contained in each oligonucleotide-related substance group (detailed profile of related substances) should be explained. Although it is not recommended to identify all individual related substances in the related substance group, they should be adequately characterized to explain (i) the consistency of the quality from the development stage and (ii) the comparability of the commercial product to the drug substance and drug product used in pivotal clinical studies in which efficacy and safety are confirmed. As needed, it is recommended to obtain the profile of related substances of intermediates in the manufacturing process and to fully explain the impact on the profile of oligonucleotide-related substances in the drug substance.

If the related substance is expected to have a certain degree of pharmacological activity based on its structure and is present in the drug substance in a sufficient amount to exhibit its efficacy, characterization of the related substance including biological activity should be performed to investigate its impact on the efficacy, as necessary.

Considering the characteristics of oligonucleotides, the application of the ICH Guideline M7 seems to be of little significance for oligonucleotide-related substances. However, 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.

(2) Organic small molecules:

See the ICH Guidelines Q3A(R2) and M7. Although the ICH Guideline M7 does not cover drugs containing an oligonucleotide as an active ingredient, the potential risk of genotoxic impurities (organic small molecules) residing should be evaluated with reference to these guidelines because oligonucleotide therapeutics are manufactured by chemical synthesis.

(3) Residual solvents:

See the ICH Guideline Q3C(R5).

(4) Elemental impurities:
See the ICH Guideline Q3D.

Biological/biochemical characteristics

Regarding efficacy-related characteristics, the binding affinity to target molecules should be provided. If the quality attributes related to the efficacy cannot be sufficiently clarified by physicochemical analysis, a biological or biochemical evaluation should be considered. In particular, oligonucleotide therapeutics that require the formation of a higher-order structure to exert pharmacological activity should be examined for the relationship between physicochemical properties and biological activity or binding affinity to target molecules.

Other physicochemical characteristics

In addition, if there are any other important characteristics from the viewpoint of each mode of action or in the specificity of the active ingredient, such characteristics and evaluation methods should be explained, as with other drugs.

1.3. Control of Drug Substance

Specifications and test methods

The general concept concerning specifications and test methods described in the ICH Guideline Q6A is also applied to oligonucleotide therapeutics. However, existing guidelines for chemically synthesized drugs are sometimes insufficient for establishing the specifications and test methods of oligonucleotide therapeutics, considering challenges such as (i) the limitations of physicochemical analysis for oligonucleotide therapeutics that require the formation of a higher-order structure to furnish pharmacological activity, and (ii) the species specificity for pharmacological effects or adverse effects. Specific specifications and test methods should be established based on the nature of the drug substance, in consideration of the critical quality attributes of the drug substance, characterization, experience, knowledge in the development phase, control in the manufacturing process, etc.

Please refer to the following items for the specifications of the drug substance in oligonucleotide therapeutics. Discussion points specific to oligonucleotide therapeutics are also provided for "items that are usually recommended (no mark)" and "items to be considered, as appropriate (*)." If "items that are usually recommended" are not included in the specifications of drug substances, scientific justification should be provided.

The analytical procedures to be applied to the drug substance as ‘specifications and test methods’ should be appropriately validated as with other types of drugs. See the ICH Guideline Q2(R1) for validation of analytical procedures.

<u>Typical sets of specifications and test methods</u>

(1) Name

(2) Structural formula or rational formula

(3) Molecular formula and molecular weight

(4) Description

(5) Identification

If it is difficult to confirm and assure the identity of the drug substance by a single analytical procedure, it should be considered to combine multiple analytical procedures.

For oligonucleotide therapeutics that require the formation of a higher-order structure to exert pharmacological activity, it may be recommended to establish tests to determine the binding affinity to target molecules, etc.

(6) Purity

Depending on the chemical properties of impurities, they can be classified into several categories as follows.

[1] Oligonucleotide-related substances:

Test method

Oligonucleotide-related substances have similar physicochemical properties, and individual oligonucleotide-related substances may not be separated. Even if it is difficult to separate individual related substances, efforts should be made to establish a test method that enables a more detailed evaluation of the profile of oligonucleotide-related substances based on the results of the characterization of impurities. Multiple analytical procedures should be established when it is useful, such as when the profile of related substances can be better understood.

Specifications of oligonucleotide-related substances

It is not practical to apply the thresholds for reporting, identification, and qualification in the ICH guideline Q3A(R2) to 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.

The level of any oligonucleotide-related substances present in the drug substance that has been adequately tested in non-clinical safety studies and/or clinical studies would be considered qualified. Oligonucleotide-related substances that are also found as significant metabolites in animal and/or human studies would be generally considered qualified.

An oligonucleotide-related substance whose concentration is higher than that present in the drug substance or drug product lot used in 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 related substances possibly contained in the drug substance, it is acceptable to set reporting, identification, and qualification thresholds for individual products according to ICH Guideline Q3A(R2) by giving due consideration to safety, if the threshold can be set at which it can be explained that the secondary pharmacological activity is not expected based on scientific discussions and consideration of the distribution characteristics in the body. In such a case, it is recommended to set the product-specific qualification threshold for impurities based on evidence, by taking into account the properties of oligonucleotide-related substances, experience, and scientific findings in the development stage, dose and target diseases, target patient population, and the risk acceptability for patients.

The above process leading to specification setting and qualification should be described in detail on a scientific basis. 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.

[2] Organic low molecular weight impurities*:
See the ICH Guidelines Q3A(R2) and M7.

[3] Residual solvents*:
See the ICH Guideline Q3C(R5).

[4] Elemental impurities*:
See the ICH Guideline Q3D.

[5] Others*:
Consideration should be made based on the potential impact on safety and efficacy.

(7) Physicochemical properties*

It is recommended to examine the physicochemical properties assuring the quality of the drug substance, based on the characterization.

(8) Water content*

(9) Counterion*

(10) Assay (content)

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.

(11) Biological activity*

If the efficacy cannot be fully assured by other physicochemical measures due to the high complexity of the structure and function of oligonucleotides, a test for biological activity should be included in the specifications.

(12) Others*

Microbiological examination and bacterial endotoxin tests should be considered in consideration of the dosage form and manufacturing process of drug products.

Other tests to assure the quality may be recommended depending on the characteristics of each drug substance.

1.4. Stability of Drug Substance

The ICH Guideline Q1 should be referred to for the stability of drug substances of oligonucleotide therapeutics.

2. Drug Product

For oligonucleotide therapeutics covered by this document, the critical quality attributes of the drug product often overlap those of the drug substance, and thus the section of drug substance should also be considered.

2.1. Manufacturing

The essential manufacturing controls should be in place to assure the critical quality attributes and expected pharmaceutical characteristics associated with the dosage form of the drug product. In addition, if the manufacturing process of the drug product may affect the critical quality attributes of the active ingredient, the key parameters should be appropriately controlled. Oligonucleotides may form higher-order structures or complexes depending on (i) the conditions such as salt concentration and temperature, (ii) physical states such as powder or solution, and (iii) the base sequence of the oligonucleotide. Therefore, especially for oligonucleotide therapeutics that require the formation of a higher-order structure to exert pharmacological activity, it is recommended to carefully evaluate the possibility that the manufacturing process of the drug product may affect the higher-order structure.

2.2. Control of Drug Product

Specifications and test methods

As with drug substance, the general concept described in the ICH Guideline Q6A is also applied to oligonucleotide therapeutics drug products.

Please refer to the following items for the specifications of the drug product of oligonucleotide therapeutics. Points to consider specific to oligonucleotide therapeutics are also described for "items that are usually considered necessary (no mark)" and "tests to be considered, as appropriate (*)." If "items that are usually considered necessary" are not included in the specifications, scientific justification must be provided.

The analytical procedures to be applied to the oligonucleotide drug product for specifications and test methods should be appropriately validated as with other types of drugs. See the ICH Guideline Q2(R1) for validation of analytical procedures.

Examples of items of specifications and test methods

(1) Name

(2) Description

(3) Identification

See Section 1.3. Control of Drug Substance.

(4) Purity

[1] Oligonucleotide-related substances:
See Section 1.3. Control of Drug Substance. Generally, there is no need to test the drug product for impurities that have been confirmed not to be degradation products.

[2] Organic low molecular weight impurities*:
See the ICH Guidelines Q3B(R2) and M7.

[3] Residual solvents*:
See the ICH Guideline Q3C(R5).

[4] Elemental impurities*:
See the ICH Guideline Q3D.

[5] Other impurities*:
Consideration should be made based on the potential impact on safety and efficacy.

(5) Assay (content)
See Section 1.3. Control of Drug Substance.

(6) Biological activity test*

If the efficacy cannot be sufficiently assured by other measures, a test for biological activity

should be established, considering the characteristics of the drug substance and drug product.

(7) Others (drug product testing, etc.)*

Necessary tests should be established according to the dosage form with reference to the Japanese Pharmacopoeia.

2.3. Stability of Drug Product

As with drug substance, the ICH Guideline Q1 should be referred to for the stability of oligonucleotide therapeutics.