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5.15. FUNCTIONALITY-RELATED CHARACTERISTICS OF EXCIPIENTS

This chapter and the FRC sections in specific monographs are not mandatory and are published for information and guidance.

PREAMBLE

Excipients that have previously been evaluated for safety are used in the formulation of pharmaceutical preparations to bring functionality to the formulation. The intended function of an excipient is to guarantee the required physical and biopharmaceutical properties of the pharmaceutical preparation.

The functionality of an excipient is determined by its physical and chemical properties and, in some cases, also by its content of by-products or of additives used to improve the intended functionality. In addition, the functionality may depend on complex interactions between the constituents of the formulation and stresses related to the process. Excipient functionality can therefore be evaluated only in the context of a particular formulation and manufacturing process, frequently by the use of a number of analytical methods. Knowledge of excipient functionalities may facilitate the application of Process Analytical Technology (PAT).

Certain excipient properties, such as the particle size of an excipient intended for a solid dosage form or the molecular mass of a polymeric material used as a viscosity-increasing agent, may however relate to functionality in a more general sense. Such functionality-related characteristics (FRCs) can be controlled and may be subject to a product-specific quality specification when the pharmaceutical development work has demonstrated their critical role for the manufacturing process and quality attributes of the medicinal product.

Monographs of the European Pharmacopoeia on excipients are designed to ensure acceptable quality for users. Information on the appearance and characters of the excipient, and requirements concerning identity, chemical and microbiological purity and physical characteristics associated with the chemical structure, such as optical rotation, are given in specific monographs and in the general monograph *Substances for pharmaceutical use (2034)*.

FRCs are included in excipient monographs to aid manufacturers of pharmaceutical products in establishing specifications based on standard analytical methods. They provide manufacturers and users of excipients with a common language to support the supply of excipients with specified properties. FRCs may be labelled (in the certificate of analysis, for example) by the excipient manufacturer with a reference to the Pharmacopoeia monograph, thus indicating the method used to test a particular characteristic. The FRC section in specific monographs contains FRCs that are known to have an impact on the functionality of the excipient for the stated uses. The uses and the FRCs listed are not exhaustive due to the multiple uses of many excipients and the development of new uses.

REGULATORY GUIDANCE

According to current regulatory guidelines, for example ICH Q8 Pharmaceutical Development, the marketing authorisation application should discuss the excipients chosen and their concentration, and demonstrate the characteristics that can influence the medicinal product performance and manufacturability relative to the respective function of each excipient. The ability of excipients to provide their intended functionality throughout the intended period of validity of the formulation should also be demonstrated. The information on excipient performance can be used as appropriate to justify the choice and quality attributes of the excipient.

Excipients are normally produced by batch processes, so there is a possibility of batch-to-batch variation from the same manufacturer. Excipients from different sources may not have identical properties with respect to their use in a specific formulation. The inevitable variation in chemical and physical properties is one of the most important input variables that can impact on a pharmaceutical manufacturing process, since excipients typically make up the major proportion of a medicinal product. Many excipients are of natural origin and composed of a mixture of chemically related compounds. Other excipients are made in chemical plants primarily designed for producing chemicals for industries other than the pharmaceutical industry. The excipient manufacturer's process may therefore be focused on the chemical characteristics and some physical properties addressing the manufacturer's primary market. In many cases, the excipient manufacturer has limited knowledge of the pharmaceutical uses of the product.

The key to a successful, robust formulation is to understand the chemical and physical nature of the active substance(s) and the excipients alone, and how their properties interact with other constituents of the formulation and the manufacturing process. During pharmaceutical development, the ingredient properties that are critical to the manufacturing process and performance of the medicinal product are identified. Having identified the critical properties of the excipients, preferably by a risk-based approach, pharmaceutical development may establish the acceptable range of the critical characteristics including both the physical and chemical property variation. The FRCs concerned may not be properties controlled by the excipient manufacturer and are therefore variable. The design of a robust manufacturing process for the medicinal product that limits the effect of the normal excipient variability is preferable.

PHYSICAL GRADES

Excipients that are particulate solids can be available in a variety of physical grades, for example with regard to particle-size distribution, which is usually controlled by the excipient supplier. However, FRCs for these excipients may concern a wide range of properties, resulting from solid-state properties and properties of the particulate solid, which may not be controlled by the excipient supplier.

Examples of solid-state properties to be considered in the development of solid dosage forms include polymorphism, pseudopolymorphism, crystallinity and density. Complementary techniques to study crystalline forms and solvates are given in the general chapters:

- *5.9. Polymorphism*;
- *2.2.34. Thermal analysis*;
- *2.9.33. Characterisation of crystalline and partially crystalline solids by x-ray powder diffraction (XRPD)*;
- *2.2.42. Density of solids*;
- *2.9.23. Pycnometric density of solids.*

Properties of particulate solids include for example particle-size distribution, specific surface area, bulk density, flowability, wettability and water sorption. Depending on the size range, the particle-size distribution can be determined by sieve analysis (see chapter *2.9.38. Particle-size distribution estimation by analytical sieving*) or instrumental methods, for example, *2.9.31. Particle-size analysis by laser light diffraction*. General method *2.9.26. Specific surface area by gas adsorption* is based on the Brunauer-Emmett-Teller

(BET) technique. Methods to characterise flowability and bulk density of powders are described in chapters *2.9.36. Powder flow* and *2.9.34. Bulk and tapped density*. Solid-state properties may impact on the wettability and water-solid interactions of particulate solids. A range of instrumental methods is available for determining these characteristics, for example, techniques to measure the static and dynamic contact angles and the gravimetric vapour sorption and/or techniques of gravimetric analysis.

CHEMICAL GRADES

Excipients that are available in different chemical grades are of natural, semi-synthetic or synthetic origin. Specific monographs usually control the chemical composition of excipients that are composed of a mixture of related compounds, for example, the composition of fatty acids in vegetable oils or surfactants. There are, however, specific monographs in the Pharmacopoeia each describing a class of polymeric materials that may vary in their composition with regard to the structure of homopolymers, block polymers and copolymers, the degree of polymerisation, and thus the molecular mass and mass distribution, the degree of substitution and in some cases even different substituents on the polymer backbone. This variation may, however, have a profound effect on the functionality of the excipient and should be subject to investigations during the pharmaceutical development, preferably to establish the acceptable range of each characteristic being critical to the manufacturing process and performance of the end-product.

While, in the past, the mandatory part of monographs on polymeric excipients may have contained some tests for physical or chemical characteristics, for example, a test for viscosity including acceptance criteria, such tests will gradually be moved to the non-mandatory FRC section, unless the concerned characteristic is an indispensable part of the identification tests. This development should be seen in light of regulatory guidance on pharmaceutical development and the desired regulatory flexibility based on establishing the acceptable range of material properties within the design space. Thus, evaluation of the chemical grades and, when appropriate, the setting of a specification for the critical characteristics, is a part of the pharmaceutical development irrespective of the non-mandatory character of FRCs.

FUNCTIONALITY-RELATED CHARACTERISTICS SECTION IN MONOGRAPHS

Monographs on excipients may have a section entitled 'Functionality-related characteristics'. This section is included for information for the user and is not a mandatory part of the monograph. The section gives a statement of characteristics that are known to be relevant for certain uses of the excipient. The use for which the characteristic is relevant is stated. For other uses, the characteristic may be irrelevant. For this reason, the section should not be seen simply as a supplement to the monograph. It is the responsibility of the manufacturer of the medicinal product to decide how the information on FRCs will be applied in the manufacturing process in light of the use of the excipient and data from pharmaceutical development.

The information on the functionality-related characteristics may be given in different ways:

- name of the FRC;
- name of the FRC and a recommended method for its determination, referring wherever possible to a general chapter of the Pharmacopoeia;
- name of the FRC with a recommended method for its determination and typical acceptance criteria, which may be in the form of tolerances for the nominal value.

A given characteristic may be the subject of a mandatory requirement in the monograph and may also be mentioned in the FRC section. The degree of polymerisation is used in the mandatory Identification section of the monographs on microcrystalline cellulose and powdered cellulose to distinguish the 2 types. The degree of polymerisation of microcrystalline cellulose is not greater than 350, whereas that of powdered cellulose is 440 to 2250. The actual degree of polymerisation is relevant for certain uses and it is therefore also cited as a relevant FRC that the manufacturer of the medicinal product may choose to specify for the grade used of a particular pharmaceutical preparation.

The section on FRCs is intended to reflect current knowledge related to the major uses of an excipient. In view of the multiple uses of some excipients and the continuous development of new uses, the section may not be complete. In addition, the methods cited for the determination of a particular characteristic are given as recommendations for methods that are known to be satisfactory for the purpose, and the use of other methods is not excluded.

INTERNATIONAL HARMONISATION

A number of excipient monographs are subject to international harmonisation among the European, Japanese and United States Pharmacopoeias (see *5.8. Pharmacopoeial harmonisation*). Introduction of the FRC section in the monographs of the European Pharmacopoeia means that the presentation of harmonised monographs differs. Tests for physical and chemical characteristics regarded as functionality-related in the European Pharmacopoeia are, in the 2 other pharmacopoeias, included in the body of the monograph. The different format has no implications on the specification of excipient characteristics for the manufacturer of the medicinal product. Current regulatory guidance recommends the identification and specification of only such critical properties that impact the manufacturing process and the performance of the end-product. The different legal environments of the 3 pharmacopoeias allow for different formats of the monographs without affecting the international harmonisation status.

GLOSSARY

Critical characteristic: any physical or chemical material characteristic that has been demonstrated to impact significantly on the manufacturability and/or performance of the medicinal product.

Design space: the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality.

Functionality-related characteristic: a controllable physical or chemical characteristic of an excipient that is shown to impact on its functionality.

Functionality testing: the direct testing of the concerned function of an excipient in a particular formulation and manufacturing process to verify that the excipient provides the intended functionality.

Performance tests: analytical tests on the critical properties of a medicinal product.

Process robustness: ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.