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Nanopharmaceuticals: Implications for the European Pharmacopoeia

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KEYWORDS

Nanopharmaceutical, nanoparticle, quality control, pharmaceutical technology.

1. INTRODUCTION

Nanopharmaceuticals are medicinal products containing particles of active pharmaceutical ingredients (APIs), excipients or a combination of these which are produced by nanotechnology and which are nanosized. Nanoparticles can be either pure nanocrystalline particles (usually APIs) or nanostructured particles in which APIs and excipients are combined, such as nanoliposomes, nanopolymeric substances or nanolayered particles. Small particles such as nanoparticles have a much larger surface area per unit mass compared with large particles, with a greater proportion of atoms or molecules at the surface compared to those atoms inside the particle. Nanoparticles may act differently due to their increased surface energy, with effects of quantum physics observed. Therefore, the efficacy and safety of nanoparticles may differ from those of particles of conventional size. For example, the nanopharmaceutical product Doxil, in which the anti-tumour agent doxorubicin is encapsulated in specific nanoliposomes, has a longer circulation time (approx. 4 times longer) in the body than conventional doxorubicin-containing pharmaceutical products, due to the small particle size and specific characteristics of the nanoliposome surface. This longer circulation time has clinical implications regarding the dose to be administered and the side effects which occur. Doxil shows increased skin toxicity but reduced cardiac toxicity compared to conventional doxorubicin products [1].

Nanopharmaceuticals are expected to bring significant advances in the diagnosis and treatment of diseases due to their potentially beneficial effects on, for example, solubility, bioavailability, metabolic clearance, biodistribution and side-effects. For a general introduction to nanotechnology and nanopharmaceuticals, reference is made to recently published literature [2-6]. This paper focuses on the technical quality of nanopharmaceuticals and is intended to stimulate the discussion on the need for specific quality requirements of nanopharmaceuticals and nanoparticles for pharmaceutical use.

2. PHARMACEUTICAL QUALITY

The pharmaceutical quality of a medicinal product is important to ensure that batches released on the market will have the same positive benefit-to-risk ratio compared to batches that were tested clinically. This is not different for nanopharmaceuticals. Indeed, in the past fifteen years several nanopharmaceuticals were granted a marketing authorisation in Europe according to the same legislation as 'conventional' pharmaceuticals [2, 7, 8]. Due to a lack of specific guidance on nanopharmaceuticals, assessment of these products was done on a case-by-case basis. In view of the expected increase in use of nanotechnology in the pharmaceutical industry and taking into consideration the discussions in the scientific and regulatory communities regarding the safety of nanopharmaceuticals and nanoparticles, the development of guidance on specific quality aspects is considered desirable [9-11]. Since nano-aspects may concern APIs and pharmaceutical dosage forms in general, the European Pharmacopoeia (Ph. Eur.) plays a relevant role in setting standards. Currently the Ph. Eur. does not include requirements that are specific to nanopharmaceuticals. We recommend including the relevant quality issues, which are discussed below, in a general monograph on nanoparticles for pharmaceutical use.

2.1. Definition

An internationally accepted definition of nanopharmaceuticals and nanoparticles is currently missing and is essential in determining the applicability of specific regulatory requirements. The main reason for debate is the exact size cut-off point of the particles. Below such a size, particles are considered nanoparticles and pharmaceutical products containing such particles are considered nanopharmaceuticals. Nanoparticles are usually referred to as particles having a size of up to 100 nm [5]. Others have indicated that a size of up to 220 nm is more biologically relevant. However, specific medical effects, such as the ability to cross biological barriers or the passive targeting of tissues, are not strictly

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limited to a size range below 100 nm [2], or even 220 nm. We therefore propose, for regulatory purposes, that nanoparticles are defined as particles of which 95 per cent are at most 1000 nm in size.

2.2. Production

In most general Ph. Eur. monographs, such as the monographs on Products of fermentation (1468) or Radiopharmaceutical preparations (0125), or in specific monographs on APIs, the possible ways of production are mentioned in the section 'Production'. For example, in the monograph on Paclitaxel (1794), three distinct production methods are described (isolation from natural sources or produced by either fermentation or a semi-synthetic process) for which different quality requirements are set. For nanoparticles, several specific methods of preparation may be used which are distinctly different from those used in the production of conventionally sized particles. These production methods can result in different impurity profiles for the APIs. We suggest including a general description of the production of the specific nanoparticles in a general monograph on nanoparticles for pharmaceutical use.

2.3. Characters

Determining the atomic structure at the nanoscale is currently not possible with conventional techniques for bulk chemicals such as X-ray Powder Diffraction, Raman spectroscopy, Nuclear Magnetic Resonance and other spectroscopic techniques [12]. Recommended techniques which are suitable for characterising nanocrystalline particles (pure chemical substances present as nanoparticles) are transmission electron microscopy, atomic pair distribution function method or extended X-ray absorption fine structure [13]. No single technique can yet determine the structure of nanocrystalline particles, so a combination of techniques will be necessary. It is recommended to include a harmonised (set of) possible characterisation method(s), including a general description of these methods in order to have uniform methods for the determination of the atomic structure of nanocrystalline particles. Another issue related to the Characters section in Ph. Eur. monographs is solubility testing and the preparation of solutions for analysis. As the solubility is likely to be affected by the size of the particles, the general requirements regarding solubility might not apply to nanoparticles. This should be addressed in the general monograph on nanoparticles for pharmaceutical use.

2.4. Particle size determination

The particle size of the API in pharmaceutical products may have a large effect on the dissolution and bioavailability, toxicology and kinetics of the product [14, 15]. This is not different for nanoparticles in nanopharmaceuticals. Several pharmacopoeial methods are currently available to determine the particle size and/or size distribution. Most of these methods are however not suitable for nanoparticles: laser light diffraction is only applicable to particles between 0.1 µm and 3 mm [16]. Also the shape of the particles may be relevant to their specific characteristics, for example in the case of carbon nanotubes which are hollow needle-like nanoparticles of which at least one dimension is in the nanoscale. Specific methods of detection which are sensitive to the length or aspect ratio are needed for carbon nanotubes, as these aspects may have the greatest influence on the toxicology [9]. It is therefore proposed to include descriptions of several analytical techniques (such as scanning tunnelling microscopy and atomic force microscopy) in the Ph. Eur. which are suitable for the determination of particle size, particle-size distribution and particle shape of nanoparticles.

2.5. Impurities

Traditionally, the dose of a pharmaceutical product is expressed in weight units such as milligrams and administered in relation to body weight or body surface area. The current limits for impurities in APIs are related to this dose and usually expressed relative to the mass of the API (e.g. in per cent or ppm). Expressing nanopharmaceuticals mostly in weight units is however not considered to be the best unit of measurement. As nanoparticles have a greater surface area per unit mass compared with non-nano or 'bulk' particles, which may have major consequences for efficacy and/or safety, this should be reflected by the unit of measurement [13]. For toxicological research of APIs, it has been stated that the dose should ideally be expressed in mass, surface area and number concentrations of nanoparticles and, optionally, charge [14, 17]. This also applies to the content of impurities present in nanosized APIs and nanopharmaceutical products, as they are also nanoparticles and may be very reactive. This should be reflected in the Ph. Eur. requirements for nanoparticles for pharmaceutical use.

2.6. Labelling

In view of the aforementioned discussion on dose, weight may not be a relevant unit of measurement for labelling. At this moment, it is not clear in which direction the discussion in the scientific field will develop and it is therefore not possible to make any recommendations on how to lay down requirements in the Ph. Eur. for dose labelling. It is however evident that the regulatory authorities, industry, health care professionals and patients should be able to understand the unit of measurement chosen and be able to distinguish between different pharmaceutical products containing the same pharmaceutical substance but with different particles (nano and non-nano).

Currently there are no requirements for nanosized APIs or nanopharmaceutical products to be labelled as such, in contrast to, for example, sterile materials. Clear labelling of nanosized APIs and nanopharmaceuticals is essential in order to avoid confusion and errors when the same material is available with and without nanostructures. This should also be implemented for materials for which Certificates of Suitability of the EDQM are granted. We therefore propose to adopt a new grade of material, for example 'nanosized material'.

3. CONCLUSION

The use of nanoparticles in pharmaceutical products does not only mean that smaller particles are used, but that particles are used which require specific quality requirements. The current monographs in the European Pharmacopoeia do not cover issues specifically related to nanoparticles or nanopharmaceuticals, and are not suitable to guarantee their quality. The

introduction of a general monograph for nanoparticles and nanopharmaceuticals, dealing with the issues as discussed, is therefore recommended. Although several critical quality aspects have been determined, knowledge gaps still remain concerning the toxicological risks associated with nanoparticles. These issues should be solved by further collaboration between the pharmaceutical industry, academia and regulators, and may in the future have further implications for the quality requirements to be set.

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