

# Nanomedicines and off patent follow-on medicines (nanosimilars) EMA regulatory procedures overview

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## Introduction

The term “nanomedicine” is applied to medicinal products which use nanomaterial and/or nanotechnology for their development and manufacturing. Nevertheless, a uniformly accepted definition for nanomedicines still does not exist, the medicinal products vary largely in type and structure and are used in a multitude of indications for acute and chronic diseases (Mühlebach, 2018).

Nanotechnology in medicines development is a dynamic and evolving scientific field that opens numerous opportunities for forward-thinking developers to create innovative new medicines to address unmet needs, improve diagnostics, and unlock the potential of patient-centric product development. Dozens of nanomedicines are already in clinical use globally, and advances in nanotechnology are contributing to an increase in academic- and industry-led research directed toward developing new nanomedicines for a variety of therapeutic areas. Nanomedicines convey multiple benefits for patients and physicians. For patients, potential advantages include fewer side effects and less frequent dosing. For physicians, nanomedicines can offer a more targeted, more effective, and more personalized intervention, and may also enable treatment with effective drugs that might not otherwise be used due to their high toxicity (Flühmann and Prithviraj, 2019).

Despite their benefits, the size, complexity, and numerous therapeutic applications of nanomedicines presents unique challenges for regulators tasked with assessing the quality, safety, and efficacy of these products. Their properties cannot be fully characterized; even minor changes in manufacturing can influence their biological properties and pharmacokinetic/pharmacodynamic (PK/PD) profiles. And with many first-generation

nanomedicines coming off patent, the arrival of lower cost “nanosimilars” adds to the complexity of regulatory approval (Flühmann and Prithviraj, 2019).

The regulatory framework for nanomedicines presents critical issues that have not been fully resolved, from adopting a definition of nanomedicine that is harmonized at international level, to developing protocols and common guidelines allowing assessment of quality, safety and efficacy of nanotechnology-based products. Furthermore, as manufacturing exact nanosimilars (off patent follow-on medicines) as replicas of nanomedicines is not achievable, therapeutic similarity will need to be shown through clinical evidence based on clear regulatory criteria. In addition, the highest possible manufacturing standards must be guaranteed and included in the license application (EAASM, 2022).

## Materials and methods

Literature review including regulatory legal acts and available publications in peer-reviewed journals.

Key words: *nanosimilars, regulatory, legal acts*

## Results and discussion

In Europe, nanomedicines have no dedicated regulatory pathway and, unlike biologics and despite their complexity, can be approved via the centralized and non-centralized EMA procedures. It should be noted that whilst the centralized procedure is already compulsory in a number of situations, including products containing new active substances (in, for example, the field of oncology and viral diseases), medicines derived from biotechnology processes, such as genetic engineering, advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or

tissue-engineered medicines and orphan medicines, it does not cover all nanomedicines and their follow-on medicines (Klein et al., 2019).

Therefore, these medicines have the potential for being assessed under four different types of procedures: the national procedure, the decentralized procedure, the mutual recognition procedure and the centralized procedure. This leaves the regulatory assessment to national competent authorities (Klein et al., 2019).

These medicines have the potential for being assessed under either full dossier application or “abridged applications” regulated under Article 8 and Article 10 of Directive 2001/83/EC, 12 as amended. Article 10 has three possibilities for abridged applications: 10(1) for generic applications, 10(3) for hybrid applications, and 10(4) for biosimilar applications. Authorization through 10(1) requires the originator-reference product and the generic drug to be the “same,” while 10(4), which applies only to biological substances, allows for small differences between the reference product and the biosimilar if those differences are not meaningful in terms of quality, safety, or efficacy. Of note, abridged applications can be accepted for consideration under the Centralized Procedure (through the EMA) or national procedures, including the Decentralized Procedure and the Mutual Recognition Procedure, depending on the nature of the product and the authorization procedure of the originator (Hussaarts et al., 2017).

In regards to nanosimilars, it is unclear to “generic developers” which abridged application procedures should be followed for follow-on products, e.g. the “generic application” via Article 10(1), requiring only limited quality and bioavailability data, or the “hybrid application” of Article 10(3) requiring additional (pre-) clinical data. Furthermore, the currently applied “case-by-case” approach for regulating follow-on products may lead to differences in the rigorosity to regulate these products (Klein et al., 2019).

In regards to type of marketing authorization application, nanosimilars marketed in EU member states up to 2015 have been approved as generic similars. Since 2015, a totality-of-evidence has been increasingly adopted by EMA, with hybrid pathway. In addition, EMA has released several reflection papers regarding selected nanomedicines and their nanosimilars, such as iron carbohydrate complexes and intravenous (IV) liposomal products, in order to address specific challenges and data requirements for particular products. These reflection papers detail the regulatory requirements for these products, including data requirements based on a stepwise totality-of evidence approach (Hertig et al., 2021).

## Conclusion

Large number of innovative nanomedicines (including the COVID mRNA) go through the centralized procedure for obtaining marketing authorization by default. The gap in the system is that centralized procedure is not compulsory for many nanomedicines (i.e., for other indications), as well as for all follow-on/nanosimilars.

The key for avoiding diverging approaches between Member States, ensuring consistency of scientific evaluation, guarantee of centralized safety monitoring and minimizing adverse events, is development of a clearly defined regulatory pathway by adopting an EMA centralized procedure for nanomedicines and their follow-on medicines. Furthermore, mandatory hybrid pathway for authorization of follow-on products only considered ‘similars’. Alignment of regulation pathways for nanomedicines and follow-on products with those established for biosimilars would ensure that follow-on copies are therapeutically similar to their originator and therefore improve patient safety.

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