Nanomedicines & Nanosimilars: Implications for Regulators, Payers, and Prescribers

Summary of Key Discussion Points from DIA Europe 2019

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Nanomedicines and other Non-Biological Complex Drugs (NBCDs) are a growing product class that includes novel technologies and older platforms

- Improved scientific understanding of these compounds has raised new questions regarding testing requirements to properly assess quality, safety, and efficacy.
- These requirements may also apply to products that have been on the market for many years.
- Critical quality attributes and safety parameters must be identified and translated into suitable, validated testing approaches.
- Harmonized regulatory approval pathways for nanomedicines are urgently needed.

Nanotechnology is a dynamic and evolving scientific field that presents numerous opportunities for forward-thinking developers to create innovative new medicines to address unmet needs, improve diagnostics, and unlock the potential of regenerative medicine. 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.[1]

This White Paper, based on a discussion held at *DIA Europe 2019* in Vienna, summarizes the most recent key regulatory and clinical implications of nanomedicines and nanosimilars.

What are Nanomedicines and What Are They Used For?

Although an official definition of nanomedicines by EMA or in EU legislation is missing, these compounds can best be described as the result of the application of nanotechnology to prevent, diagnose, and treat disease. Nanotechnology aims to control the shape, the size, and the characteristics of materials at nanometer scale, which ranges from around 1nm to around 100nm, sometimes even up to 1000nm. At those sizes, nanomedicines have distinctive physicochemical properties with unique implications for the bioavailability and fate of such medicinal products in the body.[2]

Most commonly used for treating various cancers, infections, and blood disorders such as anemia, 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.

Regulatory Challenges

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.

Manufacturers of these products attempt to replicate the processes and technologies used to create the original drug and hope to obtain marketing approval by referencing data from the originator product to demonstrate equivalency. But nanomedicines are quite complex, and unlike generic versions of small molecule drugs, creating exact replicas is impossible. While traditional risk/benefit-based regulatory pathways have typically been sufficient for assessing innovative nanomedicines, current regulatory pathways for generic drugs—which rely solely on demonstrating pharmaceutical equivalence and bioequivalence—cannot properly assess the safety and efficacy of nanosimilars in a clinical setting.

The critical aspect of nanomedicines is that the *process* itself is actually the product. As Hafner and colleagues noted in their 2014 paper, "any variations in the manufacturing process and the formulation may result in a generic product with different physicochemical properties—such as size, size distribution, surface properties, drug loading and release profile, aggregation status, and stability—all of which could lead to a different biopharmaceutical profile with a significant impact on patient safety and efficacy."[3]

With liposomal formulations, for example, small differences in manufacturing steps could produce changes in specific liposome-cell interactions and liposome

distribution characteristics not detectable by conventional bioequivalence (BE) testing. Additional aspects such as materials handling, drug administration, and reactivity of the final product may also modify the safety and efficacy profile. These variances pose challenges not only for regulators, but also for national competent authorities and formulary administrators to determine interchangeability/substitutability between an originator drug and a nanosimilar with marketing authorization.

Regulatory Activities in Europe

The European Medicines Agency (EMA) has long recognized the specific challenges posed by nanomedicines. In a 2006 reflection paper, the agency advised: "in the absence of specific guidance, applicants are encouraged to contact the [agency] from the early stages of the development of their products."[4] Although specific guidance for nanomedicines has not been issued since then, the EMA has been an active leader in facilitating discussion around the challenges presented in reviewing products that apply nanotechnology to medicines. For example:

- EMA established the Ad-Hoc Nanomedicines Expert Group in 2009 to pool quality, safety, and kinetics expertise to help inform evaluation and formulate guidelines.[5] Later that year, the work of this cross-agency group was expanded with the creation of the International Regulators Subgroup on Nanomedicine, an initiative launched jointly by regulators from Canada (Health Canada), Europe (EMA), Japan (Ministry of Health, Labour and Welfare), and the US (FDA).
- In 2010, EMA hosted the first international scientific workshop on nanomedicines in which regulators, academics, and industry representatives from 27 countries met to explore the science of nanomedicines and share their experience at an international level in order to better anticipate future needs.[6] Proposed action items included expanding multidisciplinary regulatory platforms to share experiences, and facilitating early scientific dialogue and knowledge transfer among regulatory, academic, and industrial innovators to identify potential challenges and risks.
- In 2011, EMA established a nanomedicine drafting group tasked with developing a series of reflection papers around nanosimilars and emerging nanotherapeutics. These reflection papers provided the agency's current thinking on issues such as nanoparticles coating and block copolymer micelle medicinal products,[7,8] and two of these papers provided principles for considering nanosimilar-specific issues, recognizing how differences in manufacturing and formulation between the follow-on product and innovator product may substantially modify the drug's safety and efficacy profile.[9,10] In their papers, the drafting group emphasizes the need to create validated analytical techniques for assessing *in vivo* pharmacokinetic and biodistribution studies and encourages developers to seek scientific and regulatory advice in the early stages of development.

Regulatory Activities in the US

FDA has also undertaken a number of initiatives to promote a better understanding of nanotechnology and the regulatory aspects of its application:

- In 2006, the agency created a Nanotechnology Task Force, which released a report the following year intended to address the regulatory challenges that may be presented by products that use nanotechnology.[11]
- In 2014, FDA published a guidance for industry which stated that the agency would consider "both particle dimensions and dimension-dependent properties or phenomena" to determine whether products are nano-engineered.[12] This guidance also noted that "the application of nanotechnology may result in product attributes that differ from those of conventionally-manufactured products, and thus may merit particular examination."
- Additional guidance documents concerning nanomaterials in cosmetics and in animal foods were released in 2014 and 2015, respectively.[12,13]
- Throughout the past decade, the agency has provided product-specific guidances for a handful of follow-on nanomedicines over the past decade, including guidance for follow-on versions of sodium ferric gluconate colloidal complex, iron sucrose, and doxorubicin hydrochloride.[14,15,16]
- A 2018 guidance focused on the unique technical aspects of manufacturing liposome drug products, but did not provide recommendations on clinical efficacy and safety studies; nonclinical pharmacology/toxicology studies; or drug-lipid complexes.[17]

Most significantly, FDA released draft guidance for industry in late 2017 concerning drug products and biologic products containing nanomaterials. The guidance presents general principles and scientific considerations for developing nanomedicines and also includes discussion on potential regulatory pathways and bioequivalence considerations for medicines developed using a reference product (i.e., nanosimilars).[18] The guidance lists eleven risk factors to consider as part of the product's critical quality attributes (CQAs)–such as material structure and function, the complexity of the structure, the effect of

particle size on PK parameters, the predictability of *in vivo* release, and the potential impact of manufacturing changes–but notes that additional risk factors may need to be evaluated during product development. Specifically to nanosimilars, the agency encourages developers to apply a risk-based classification scheme to determine if the product in development will exhibit clinically significant changes in exposure, safety, and effectiveness relative to the referenced listed drug (RLD). The proposed system for sponsors looking to "bridge" performance of an innovator product would place products into one of three risk categories:

- Low risk (for products containing nanomaterials that revert to their molecular constituents immediately after administration);
- Medium risk (for products containing non-targeted nanomaterials intended for systemic action that are administered parentally); and
- High risk (for products containing targeted nanomaterials intended for systemic action and that are administered intravenously).

With potentially significant ramifications, the guidance not only proposes how nanosimilars can be developed along the 505(b)(2) pathway, but also includes discussion for developing nanosimilars using the abbreviated 505(j) pathway for generic drugs. Created for small molecule drugs that are relatively easy to characterize, the 505(j) pathway relies primarily on bioequivalence data and does not require proof of safety or efficacy through clinical studies.

Because nanomedicines are so complex and nearly impossible to replicate reliably, an abbreviated pathway most commonly used for reviewing small molecule generics may not adequately provide enough information to ensure safety, efficacy, and reliability. The guidance itself states that "due to the diversity of nanomaterial formulation, drug release mechanisms, and unique bio-distribution, evidence of comparable PK parameters in blood/plasma in conventional BE studies alone may or may not be sufficient to establish BE of the generic and the RLD depending on the route of administration and nanomaterials employed." As the CQAs for many nanomedicines are still being discussed among the scientific community—including those for older products such as liposomes—the issue of determining bioequivalence of these products along an abbreviated pathway may warrant further consideration by FDA.

However, a recent paper argued that the 505(j) pathway may not be suitable for nanosimilars because "nanomaterial-containing drug products (1) cannot be adequately characterized to support a determination of sameness, (2) will differ as a result of differences in manufacturing process, and (3) have different pharmacokinetic and pharmacodynamic properties as a result of their varying physicochemical characteristics that cannot be determined at the same level of detail as for non-complex small-molecule drug products."[19] FDA's draft guidance is unquestionably a big step forward for advancing discussions around CQAs for nanomedicines, but key questions remain unanswered for the adequate assessment of nanosimilars.

Moving Forward

While FDA's guidance on nanomedicine and nanosimilars is still in draft form, there is still an urgent need for global consensus on how best to assess these innovative and complex products. To address the many unanswered questions, stakeholders should seek agreement and alignment in three essential areas: defining critical quality attributes, establishing common nomenclature, and harmonizing regulatory requirements.

Defining Critical Quality Attributes

Defining CQA's for nanomedicines reliably is often not possible given their size-related physicochemical properties, the current state of knowledge, and the lack of specific guidelines for establishing regulations and standard protocols.[20,21] Ideally, CQAs and testing requirements for nano-specific properties would be harmonized globally, and a suite of validated tests would be available to help sponsors and regulators make informed decisions.

Working toward that goal, the Nanotechnology Characterization Laboratory (NCL) in the United States provides developers with characterization, pharmacokinetic, efficacy, and toxicity testing of potential nano-engineered cancer therapeutics and diagnostics.[22] Similarly—and in partnership with the NCL—the European Nanomedicine Characterisation Laboratory (EUNCL) provides a comparable suite of pre-clinical characterization services, and both organizations work closely with regulatory agencies to help facilitate the translation of nanotechnology for clinical applications.[23]

In an effort to gauge relevance and applicability of methods developed and validated at EUNCL, the European Commission's Joint Research Centre in 2015 surveyed scientists working for agencies involved in the Nanomedicines Working Group of the International Pharmaceutical Regulators Forum (IPRF).[24] For adequate characterization of CQAs, for example, respondents most frequently selected stability, particle size, size distribution, surface properties, and solubility as the most important parameters because these characteristics may influence the pharmacokinetics, biodistribution, and toxicity of the

formulation. The study also confirmed that the EUNCL could best assist regulators by validating test methods and providing scientific advice, and further validated the need for regulatory bodies to share knowledge and harmonize information requirements for nano-specific properties.

Establishing Common Nomenclature

Nanomedicines do not share the same characteristics of either small-molecule drugs or biologics and cannot be categorized under existing terminology. The term Non-Biological Complex Drug (NBCD) was introduced by the scientific community for nanomedicines and other complex therapeutic modalities to enable better communication and coordination of regulatory and reimbursement activities.[25] NBCDs are defined as "a medicinal product, not being a biological medicine, where the active substance is not a homo-molecular structure, but consists of different (closely related and often nanoparticulate) structures that cannot be isolated and fully quantitated, characterized and/or described by physicochemical analytical means. It is also unknown which structural elements might impact the therapeutic performance."[26] Although neither EMA nor FDA currently recognize NBCDs as a distinct class of medicines, both agencies have issued product-specific reflection papers or guidances for NBCDs, and both have granted marketing authorizations for their follow-on versions.

Harmonizing Regulatory Requirements

Although no agency has established a dedicated regulatory framework for nanomedicines and NBCD follow-on products, existing guidelines for the development of biosimilars can serve as instructive models. EMA has worked with biosimilars for more than a decade, has approved the highest number of biosimilars worldwide, and the EU's pharmacovigilance systems have shown these products to be safe with no relevant differences in adverse event severity or frequency.[27] EMA's framework requires a stepwise approach that builds incrementally—from physicochemical characteristics, to pre-clinical *in vivo* studies, to clinical studies, to head-to-head comparison with the originator product—as needed, to demonstrate similarity in quality, safety, and efficacy.[28]

Similarly, FDA's biosimilars guidance also recommends a stepwise approach and emphasizes that sponsors should evaluate "the extent to which there is residual uncertainty about the biosimilarity" of the product and identify actions to address that uncertainty.[29] Under its "totality-of-the-evidence" approach, FDA determines the range of additional studies necessary to demonstrate biosimilarity in a stepwise manner, including detailed structural and functional characterization, animal studies, PK/PD studies, immunogenicity studies, and then comparative clinical trials, if needed.

The same philosophy is echoed in FDA's draft guidance on drugs containing nanomaterials, which acknowledges that a "continual reduction of residual uncertainty" is inherent in the development of nanomedicines. Considering that the CQAs for nanomedicines are not well defined—and that even slight variations in manufacturing can influence a product's biological properties—regulation pathways for NBCDs and their follow-on products should reasonably follow those established for biosimilars.

Conclusion

The first generation of nano-engineered medicines has advanced public health considerably by offering innovative therapeutic interventions for a variety of conditions. Global regulators have thus far assessed nanomedicines under existing regulatory frameworks on a case-by-case basis and, in most cases, have done so with limited tools and insufficient data. With continual advances in nanotechnology and the arrival of next-generation NBCDs and follow-on products, ongoing collaborative efforts between industry, academic, and regulatory stakeholders will be critical to ensure that these therapies are brought to market in a safe and timely way.

Industry	Regulators	All Stakeholders
• Clearer guidance on regulatory requirements • Early dialogue with regulators	• Harmonizing nomenclature and appropriate approval pathways • Updating requirements to better align with state-of-the-art technologies	• Collaboration • Transparency

Figure 1: Advancing development and further clinical use of nanomedicines, nanosimilars, and other NBCDs. What do we need?

References

[1] D'Mello SR, Cruz CN, Chen ML, Kapoor M, Lee SL, Tyner KM. The evolving landscape of drug products containing nanomaterials in the United States. Nat Nanotechnol. 2017 Jul;12(6):523-529. doi: 10.1038/nnano.2017.67. Epub 2017 Apr 24. PMID: 28436961.

[2] Weissig V, Pettinger TK, Murdock N. Nanopharmaceuticals (part 1): products on the market. Int J Nanomedicine. 2014 Sep 15;9:4357-73. doi: 10.2147/IJN.S46900. eCollection 2014. Review. PubMed PMID: 25258527

[3] Hafner A, Lovrić J, Lakoš GP, Pepić I. Nanotherapeutics in the EU: an overview on current state and future directions. Int J Nanomedicine. 2014 Feb 19;9:1005-23. doi: 10.2147/IJN.S55359. eCollection 2014. Review. PubMed PMID: 24600222.

[4] European Medicines Agency. EMEA/CHMP/79769/2006. Reflection paper on nanotechnology-based medicinal products for human use (June 2006); http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069728.pdf

[5] European Medicines Agency. Ad hoc CHMP Expert Group Meeting on "Nanomedicines." Executive Summary. (April 2009); https://www.ema.europa.eu/en/documents/report/ad-hoc-chmp-expert-group-meeting-nanomedicines-29th-april-2009_en.pdf

[6] European Medicines Agency. EMA/559074/2010. European Medicines Agency holds first scientific workshop on nanomedicines. Press release. (September 2010); https://www.ema.europa.eu/en/documents/press-release/european-medicines-agency-holds-first-scientific-workshop-nanomedicines_en.pdf

[7] European Medicines Agency. EMA/325027/2013. Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products (May 2013); https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-surface-coatings-general-issues-consideration-regarding-parenteral-administration_en.pdf

[8] European Medicines Agency. EMA/CHMP/13099/2013. Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products. (December 2013); https://www.ema.europa.eu/en/documents/scientific-guideline/joint-ministry-health-labour-welfare/european-medicines-agency-reflection-paper-development-block-copolymer-micelle-medicinal-products_en.pdf

[9] European Medicines Agency. EMA/CHMP/806058/2009/Rev. 02. Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product. (February 2013); http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/04/WC500105048.pdf

[10] European Medicines Agency. EMA/CHMP/SWP/620008/2012. Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product (March 2015); http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184922.pdf

[11] U.S. Food and Drug Administration (FDA). Nanotechnology: A Report of the U.S. Food and Drug Administration Nanotechnology Task Force. (July 2007); https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf

[12] U.S. Food and Drug Administration (FDA). Guidance for Industry Safety of Nanomaterials in Cosmetic Products. (June 2014); https://www.fda.gov/downloads/Cosmetics/GuidanceRegulation/GuidanceDocuments/UCM300932.pdf

[13] U.S. Food and Drug Administration (FDA). Guidance for Industry Use of Nanomaterials in Food for Animals. (August 2015); https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM401508.pdf

[14] U.S. Food and Drug Administration (FDA). Draft Guidance on Sodium Ferric Gluconate Complex. (September 2018, rev.); https://www.fda.gov/downloads/Drugs/.../Guidances/UCM199635.pdf

[15] U.S. Food and Drug Administration (FDA). Draft guidance on iron sucrose. (November 2013); http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm297630.pdf

[16] U.S. Food and Drug Administration (FDA). Draft Guidance on Doxorubicin Hydrochloride. (September 2018, rev.); https://www.fda.gov/downloads/Drugs/.../Guidances/UCM199635.pdf

[17] U.S. Food and Drug Administration (FDA). Guidance for Industry: Liposome Drug Products Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation Guidance for Industry. (April 2018); https://www.fda.gov/downloads/drugs/guidances/ucm070570.pdf

[18] U.S. Food and Drug Administration (FDA). Draft guidance for industry: drug products, including biological products, that contain nanomaterials. (December 2017); https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588857.pdf

[19] Marden E, Ntai I, Bass S, Flühmann B. Reflections on FDA Draft Guidance for Products Containing Nanomaterials: Is the Abbreviated New Drug Application (ANDA) a Suitable Pathway for Nanomedicines? AAPS J. 2018 Aug 20;20(5):92. doi: 10.1208/s12248-018-0255-0. PMID: 30128758

[20] Hussaarts L, Mühlebach S, Shah VP, McNeil S, Borchard G, Flühmann B, Weinstein V, Neervannan S, Griffiths E, Jiang W, Wolff-Holz E, Crommelin DJA, de Vlieger JSB. Equivalence of complex drug products: advances in and challenges for current regulatory frameworks. Ann N Y Acad Sci. 2017 Nov;1407(1):39-49. doi: 10.1111/nyas.13347. Epub 2017 Apr 26. PMID: 28445611

[21] Soares S, Sousa J, Pais A, Vitorino C. Nanomedicine: Principles, Properties, and Regulatory Issues. Front Chem. 2018 Aug 20;6:360. doi: 10.3389/fchem.2018.00360. eCollection 2018. Review. PubMed PMID: 30177965

[22] Nanotechnology Characterization Laboratory; https://ncl.cancer.gov/

[23] European Nanomedicine Characterisation Laboratory; http://www.euncl.eu/

[24] Bremer-Hoffmann, S, Halamoda-Kenzaoui, B, Borgos, SE. Identification of regulatory needs for nanomedicines. Journal of Interdisciplinary Nanomedicine, 2018; 3(1):4-15, doi: 10.1002/jin2.34.

[25] Crommelin DJ, de Vlieger JS, Weinstein V, Mühlebach S, Shah VP, Schellekens H. Different pharmaceutical products need similar terminology. AAPS J. 2014 Jan;16(1):11-4. doi: 10.1208/s12248-013-9532-0. Epub 2013 Sep 25. PubMed PMID: 24065599

[26] Schellekens H, Stegemann S, Weinstein V, de Vlieger JS, Flühmann B, Mühlebach S, Gaspar R, Shah VP, Crommelin DJ. How to regulate nonbiological complex drugs (NBCD) and their follow-on versions: points to consider. AAPS J. 2014 Jan;16(1):15-21. doi: 10.1208/s12248-013-9533-z. Epub 2013 Sep 25. Review. PubMed PMID: 24065600

[27] European Medicines Agency and the European Commission. Biosimilars in the EU: Information guide for healthcare professionals. (April 2017); https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf

[28] European Medicines Agency. CHMP/437/04. Guideline on similar biological medicinal products (October 2014, rev.); https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf

[29] U.S. Food and Drug Administration (FDA). 2015. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, Guidance for Industry, (Apr. 2015). https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf