Revision of the EU general pharmaceuticals legislation

Feedback from the European Technology Platform on Nanomedicine (ETPN)

Paris, November 7, 2023

Executive summary

The European Technology Platform on Nanomedicine (ETPN) finds the new EU pharmaceutical legislation largely aligned with its objectives of enhancing drug availability, accessibility, and innovation. It commends the efforts to expedite EMA authorization timelines and address drug shortages but suggests greater industrial accountability and supply chain security strategies. The legislation's commitment to sustainability and antimicrobial resistance is supported, yet there is concern over the practical impact and enforcement of such measures.

Notably, the legislation overlooks the specific mention of nanomedicine, which is concerning given the sector's growth and the recent prominence of mRNA vaccines. While nanomedicines must adhere to the same standards as traditional drugs, their omission may suggest an underappreciation of their unique contributions and challenges.

Nanomedicines differ from conventional pharmaceuticals, notably in their potential for reformulating unstable or insoluble drugs and improving pharmacokinetics and toxicity profiles. They do, however, pose regulatory challenges due to their complex composition, characterisation and manufacturing, and the diverse regulatory treatment of their components across regions.

The ETPN advocates for European support in regulatory science and a transparent dialogue between providers and regulators. It regrets the funding cessation for initiatives like the EUNCL that standardised nanomedicine characterization but continues to participate in EU projects like METRINO and NANOSPRESSO-NL for advancement in the field.

There is a consensus among ETPN members on the need for nuanced nanomedicine regulations, with specific protocols and international alignment for fostering global competitiveness. ETPN is ready to contribute to the evolution of such regulations to ensure the continued advancement of nanomedicines.

In conclusion, the ETPN emphasises that the role of nanomedicines should focus on significant medical value, ensuring their place in addressing unmet clinical needs and justifying their future reimbursement. The absence of explicit mention of nanomedicinal products in the revised legislation warrants vigilance, ensuring this is not mistaken for a lack of interest in the field. ETPN seeks to enhance clinical readiness and regulatory guidance for nanomedicines and invites dialogue to shape a resilient regulatory future for medicines in Europe. Contact for further discussion: secretariat@etp-nanomedicine.eu.

ETPN Association
European Technology Platform on Nanomedicine
64-66 rue des archives 75003 Paris France
www.etp-nanomedicine.eu

Full Feedback

About Nanomedicine and the ETPN

Nanomedicine, which involves applying nanotechnologies across healthcare domains, is undergoing rapid expansion and evolution. Its applications, spanning diagnostics, imaging, innovative therapies, and personalised medicine, have yielded over 50 market-ready formulations, with 400+ undergoing clinical trials[1]. While oncology remains a central application area, innovative nanomedicines are providing solutions for a variety of medical conditions. An illustrative example is the efficient nucleic acid delivery in COVID-19 mRNA vaccines. Europe is at the frontline of this transformation, at least partly due to the concerted efforts of the **European Technology Platform on Nanomedicine (ETPN).**

The ETPN was founded in 2005 as an industry-driven initiative in coordination with the European Commission. Today, it comprises over 130 member institutions from 27 countries, representing academia, industry, and healthcare. The ETPN's realm includes nanotherapeutics, medical devices, diagnostics, imaging, and cutting-edge innovations in health. Serving as Europe's nanomedicine think tank, the ETPN propels R&D funding, identifies top nanomedicine advancements, and streamlines their clinical integration, notably by addressing hurdles like GMP manufacturing and regulatory issues Guided by ETPN, Europe has emerged as a fertile ground for nanomedicine's growth, fostering unique academia-SME-industry collaborations. The organisation propels R&D funding and serves as a vital nexus, expediting clinical development of Europe-originated concepts. Learn more: www.etp-nanomedicine.eu.

How do we evaluate the objectives of the revised legislation?

The European Technology Platform on Nanomedicine (ETPN) welcomes the European Commission's ambitious revision of the EU pharmaceutical legislation as a landmark opportunity to enhance the pharmaceutical landscape. In alignment with ETPN's mission to nurture innovation in healthcare technologies, we recognize the revision's potential to catalyse significant advancements in nanomedicine and beyond.

The revision aims to establish a more resilient Europe in the post-COVID era, fostering an environment where pharmaceutical innovation can flourish. This is deeply resonant with our core values, as we advocate for streamlined regulatory pathways that simultaneously uphold the highest safety standards for medicines. The balance sought between reducing administrative burdens and maintaining stringent safety protocols is a critical step towards accelerating clinical development and fostering a robust pharmaceutical ecosystem in Europe.

[1] Germain M, Caputo F, Metcalfe S, Tosi G, Spring K, Åslund AKO, Pottier A, Schiffelers R, Ceccaldi A, Schmid R. Delivering the power of nanomedicine to patients today. J Control Release. 2020 Oct 10;326:164-171. doi: 10.1016/j.jconrel.2020.07.007. Epub 2020 Jul 15. PMID: 32681950; PMCID: PMC7362824.

We commend the objectives of addressing unmet clinical needs, which is a cornerstone of the ETPN's ethos. The focus on harmonisation of legislative and procedural approaches across Member States is particularly salient, promising to mitigate disparities in drug availability and fostering a cohesive European healthcare model.

The initiative to incorporate stakeholder feedback into the legislative process is a constructive approach that ETPN firmly supports. We concur with the European Commission's acknowledgement of specific challenges—such as the needs of patients with rare diseases, the affordability of medicines, and the necessity for greater accessibility across the Union. Such considerations are paramount for ensuring that the legislation not only fosters innovation but also ensures its benefits are broadly and equitably distributed.

Furthermore, ETPN endorses the five key challenges outlined in the new legislation, particularly the reduction of temporal exclusivity to encourage early availability of generics and biosimilars, securing the supply chain to prevent drug shortages, and enhancing the environmental sustainability of medicines. The emphasis on combating antimicrobial resistance and simplifying administrative processes aligns with our vision for a healthtech landscape that is as dynamic as it is regulated.

How well do we think the new legislation aligns with the initially stated objectives?

The European Technology Platform on Nanomedicine (ETPN) recognizes the new EU pharmaceutical legislation as a generally positive step towards aligning with the overarching objectives of enhancing drug availability, accessibility, and innovation within the pharmaceutical sector. The move to streamline regulatory processes and improve the supply chain's robustness reflects a well-intentioned approach to contemporary healthcare challenges. A critical examination of the legislation suggests a well-aligned strategy with the reduction of market exclusivity periods, potentially facilitating earlier access to generics and biosimilars. However, this must be finely balanced to ensure sustained investment in research and development, especially in areas of unmet medical needs.

The ambition to halve the current timelines for the European Medicines Agency (EMA) authorization procedures is a bold and forward-looking objective. It signifies a commitment to improving the efficiency of the regulatory process, which is essential for fostering a dynamic and responsive healthcare ecosystem.

The proactive stance on addressing drug shortages through enhanced reporting obligations and the establishment of an EU-wide catalogue of essential medicines is commendable. Yet, the ETPN encourages a more formidable stance on industrial accountability and a clearer strategy for ensuring secure supply chains, particularly concerning critical dependencies outside of the EU.

Environmental sustainability and the battle against antimicrobial resistance (AMR) are rightly identified as pivotal, and the ETPN endorses the incorporation of these priorities into the legislative framework. Nevertheless, the actual impact of such measures remains to be seen, and the ETPN anticipates a robust mechanism to monitor and enforce these critical objectives.

However, the ETPN notes an apparent disconnect between the legislative text and the explicit support for innovation—especially pertinent given the rapid evolution of medical technologies. The legislation's intent and introductory mentions of innovation must find stronger echoes within the articles of law, thereby providing a firmer foundation for innovative healthcare solutions to thrive.

In conclusion, while the ETPN supports the general direction of the new legislation and its potential to achieve its stated objectives, we remain vigilant regarding its practical application, especially in its ability to encourage and harness the full potential of emerging health technologies.

The Notable Absence of Nanotechnology and Nanomedicine in the proposed revision.

The revised EU general pharmaceuticals legislation presents a notable absence of explicit mention of nanotechnology and nanomedicine. Although many of the nanomedicine products fall under the MDR and/or the ATMP-specific regulation, a very important part of Nanomedicine products - notably most of the well-known drug delivery products (often called "nanomedicines") are regulated as medicinal products. Given the increasingly pivotal role of nanomedicine in healthcare innovation, particularly highlighted by the development of mRNA-based vaccines, this absence seems incongruous.

This absence can be interpreted as an acknowledgment that nanomedicinal products are held to the same stringent safety and efficacy standards as traditional pharmaceuticals, a perspective the ETPN agrees with. Ensuring patient safety and product effectiveness is paramount, and nanomedicines, despite their innovative approach, are not inherently riskier than conventional drugs. They should be regulated with the same rigour, considering each case's unique aspects.
In any case, we hope that this omission does not reflect a gap in recognizing the unique features and challenges associated with these innovative nanomedicinal products. As a leading body in the European nanomedicine community, the ETPN expresses concern over this oversight and its potential to undermine the progression and integration of nanomedicine into the healthcare system.

Nanomedicines show specific advantages & challenges

Nanomedicines stand apart from traditional pharmaceuticals, primarily in their ability to reformulate a wide variety of drugs that are otherwise insoluble or unstable. They also show unique potential in significantly improving pharmacokinetics (PK) and pharmacodynamics (PD), and in modifying the toxicity profiles of drugs to reduce adverse effects and treatment frequency. These key features are instrumental in the development of ground-breaking therapies, notably in the field of mRNA-based vaccines, and more generally for cell and gene therapies, oncology, neurodegenerative diseases, antimicrobial drugs, and rare diseases.

Nevertheless, they present regulatory challenges due to their intricate complex composition, making full characterization exceptionally challenging—far more so than for classical medicinal products. The complexity extends to the nanoparticle excipients which can in some cases play a role in biological activity and require thorough specific characterization, out of the composite nanoparticle. Moreover, the ongoing debates, such as the classification of identical lipid components as excipients

in the EU and active ingredients in the US, underscore the need for harmonised regulatory perspectives[2].

The clear need of guidance and specific support in Nanomedicine

The ETPN emphasises that the composite nature of medicinal products comprising nanoparticles introduces much higher costs in characterization, manufacturing and regulation and longer time for preclinical and clinical development, which would need better support at the European level. We strongly advocate for support to regulatory science, fostering a transparent dialogue between technology providers and regulators.

We deeply regret the end of funding of initiatives like the **EUNCL (European Nanomedicine Characterization Laboratory - https://www.euncl.org/)** inspired by, and in partnership with, the NCI-NCL which was a game-changer in standardising the preclinical characterization of nanomedicine products in Europe.
We continue to support and participate in several initiatives to address these key hurdles and unleash the true power of nanomedicines for patients:

- **The METRINO project (website)** is an ambitious European collaborative initiative aiming to establish Europe as a leader in nanomedicine metrology. Coordinated by the French National Metrology Institute (LNE), the consortium involves multiple partners, with a focus on developing traceable measurement methods and reference materials for assessing the quality of innovative nanotherapeutics. We believe METRINO has the potential to transform the European nanomedicine landscape, ultimately leading to improved patient outcomes and a more competitive European health technology industry.
- **the NANOSPRESSO-NL project (learn more)** is an innovative project funded by the Dutch Research Council, aiming to develop technology for on-site production of nucleic acid nanomedicines in hospital pharmacies. By creating lipid nanoparticles for RNA and DNA delivery, initially targeting orphan diseases, it addresses manufacturing and distribution challenges. The project envisions a machine for single-dose production, enabling personalised treatments for various disorders in a cost-efficient manner. It also intends to analyse the legal and regulatory frameworks to facilitate this localised production method. Coordinated by UMC Utrecht, it gathers a consortium of academic, research, clinical and societal institutions along with co-funding companies. This project especially resonates well with the article #18 on ATMPs in the new general pharmaceuticals legislation: "*Advanced therapy medicinal products that are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, to comply with an individual medical prescription for a custom-made product for an individual patient, should be excluded from the scope of this Directive*".

[2] Hemmrich, E., McNeil, S. Active ingredient vs excipient debate for nanomedicines. *Nat. Nanotechnol.* **18**, 692–695 (2023). https://doi.org/10.1038/s41565-023-01371-w

What could cover a specific regulation of nanomedicinal products in the future?

Among our member institutions, there is quite a clear consensus on the need for nuanced regulation, tailored to the unique characteristics of nanomedicines. The diversity of opinions points towards establishing specific protocols addressing nanomedicine pharmacokinetics (PK) and pharmacodynamics (PD), recognizing the distinct transport mechanisms of nanocarriers, and facilitating in vivo testing to reflect their complex nature. The platform nature of some delivery systems such as Lipid Nanoparticles for nucleic acids could also benefit from better flexibility to accelerate their development.

There is also a clear call for alignment with international standards to foster global competitiveness, alongside a harmonious integration of nanomedicine regulations with the broader nanomaterial knowledge base. This reflects a collective vision for regulations that are robust yet flexible, designed to enhance innovation without compromising safety or efficacy. Such a framework will be essential in ensuring that nanomedicine continues to advance as a cornerstone of modern healthcare, with clear and effective guidance supporting its development and clinical translation. The ETPN is happy to contribute at any step of this potential evolution.

In conclusion

The ETPN, representing a broad spectrum of its members' expertise and insights, asserts that the drive behind nanomedicine innovation should be its medical value and efficacy. Our focus is on fostering the application of nanotechnology where it can offer distinct and tangible benefits, particularly in addressing crucial unmet clinical needs, rather than simply delivering incremental improvements to existing standards of care. Bring Nanomedicine "where it can really make a difference", justifying a proper reimbursement by public health systems undergoing vital financial danger in Europe. In this, we are fully in line with the spirit of the proposed revision of the legislation.

If we totally support the global objectives of the proposed revision, in observing the absence of explicit mention of nanotechnology and its specificities, we remain vigilant. The ETPN will ensure that this omission does not reflect a lack of interest in this crucial sector but rather a confidence that nanomedicinal products can stand firmly within the existing framework, continuing to meet the stringent standards set forth for all pharmaceutical products.

At this stage, our main goal is to foster an improvement of clinical readiness of EU research in nanomedicine. We anticipate actively contributing to the ongoing dialogue to ensure that the innovative potential of nanomedicine is not only recognized but also nurtured within the EU's regulatory ecosystem. In this perspective, further the probable adoption of the current revised legislation, we would urgently call for its translation into practical guidance to help innovators of the field to navigate in the rather complex regulatory complex for medical applications of nanotechnologies and other emerging medical nanotechnologies and efficiently anticipate the regulatory requirements in the very upstream phase of their Research and Development.

We conclude this feedback by recognizing that the path forward is complex and requires continued and transparent collaboration among all stakeholders. ETPN is committed to maintaining an open and constructive dialogue and invites its members and the broader health care community to contact us to further discuss the regulatory issues raised. Shared perspectives and experiences are essential to shaping a robust and resilient medicines regulatory system for the future in Europe.

Together, we can contribute meaningfully to the legislative debate and further ensure that the patients in Europe get equal access to the best innovative solutions coming out of nanomedicine and emerging healthtech in an affordable, and sustainable manner.

For any questions, comments, or suggestions, do not hesitate to contact us:
secretariat@etp-nanomedicine.eu

ETPN Secretariat

Disclaimer

This document represents the collective position of the ETPN, established in response to the European Commission's initiative to revise general EU legislation on medicinal products for human use, as part of the Pharmaceutical Strategy for Europe and lessons learned from the COVID-19 pandemic. Although we seek to reflect a consistent and consensus view of ETPN stakeholders, the opinions and recommendations expressed in this document are advisory and in no way binding on individual ETPN members.