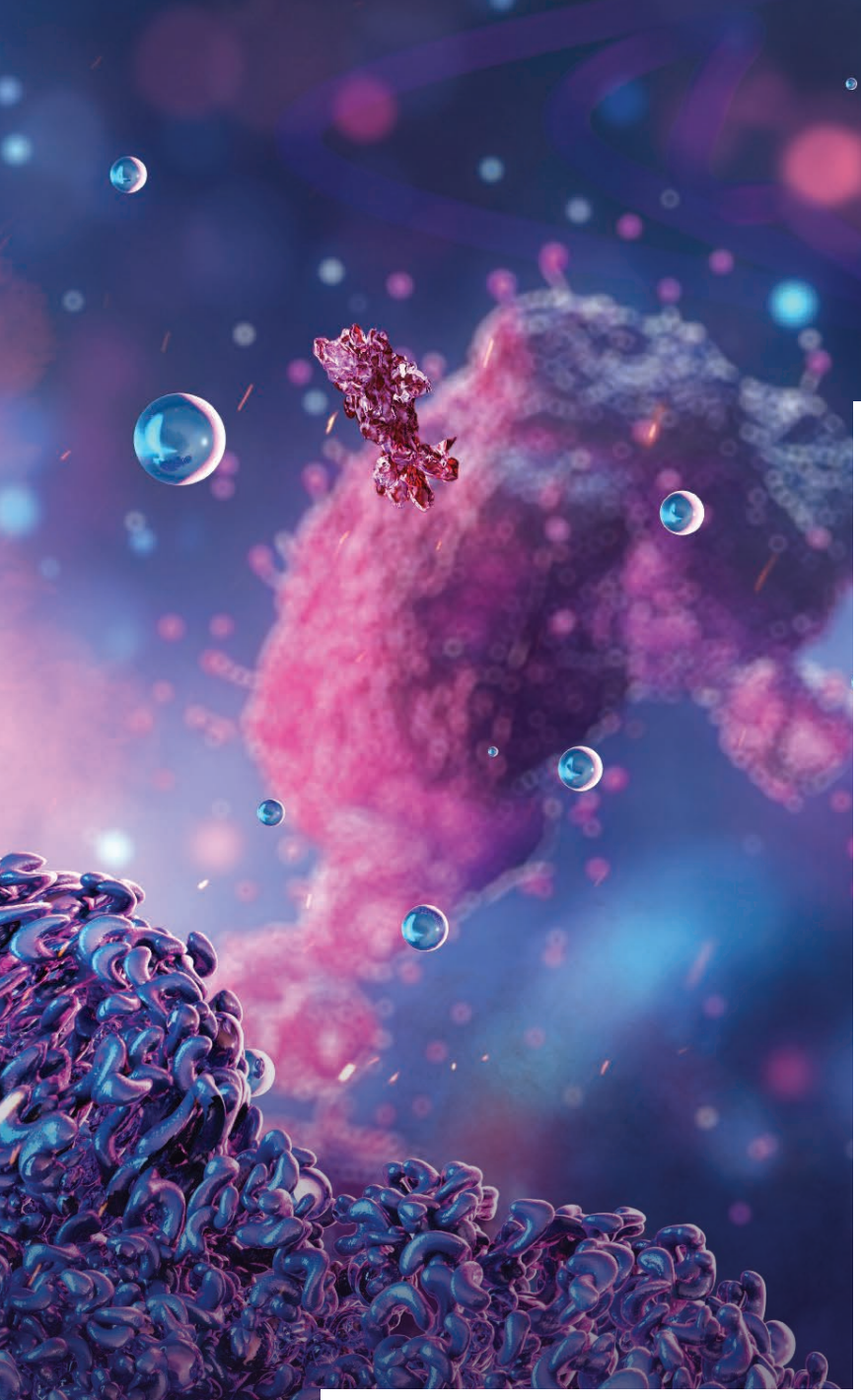


Big picture challenges for biologics

Fouad Atouf, Senior Vice President and Head of the Biologics Program at the United States Pharmacopeia (USP), discusses the biggest issues facing biologics drug production, what is needed to advance the sector and his outlook for the next five years.



What are the major challenges currently impacting the biologics sector?

Manufacturing biologics is more challenging than producing traditional small-molecule drugs owing to their molecular size, sensitivity to environmental conditions and the need for living cells in production. For instance, cell and gene therapies require dedicated facilities, equipment and expertise, which are less common. Ensuring quality and scaling production is a challenge.

Biologic drugs also present distinct safety challenges such as immunogenicity, off-target effects and long-term safety concerns. Regulatory frameworks are adapting to technological advances but for some emerging modalities the existing pharmaceutical regulatory paradigms do not always apply, and new frameworks need to be established.

Lastly, the high cost of production of biologics limits accessibility. Advanced therapies such as CAR-T cells, gene therapies and bispecific antibodies are expensive due to complex manufacturing processes, specialised raw materials, lengthy clinical trials, smaller patient populations and unique handling requirements. Supply chain disruptions, including devices and packaging materials, can further impact availability.

What are some key considerations for industry professionals around mitigating the formation of *N*-nitrosamine impurities in biologics?

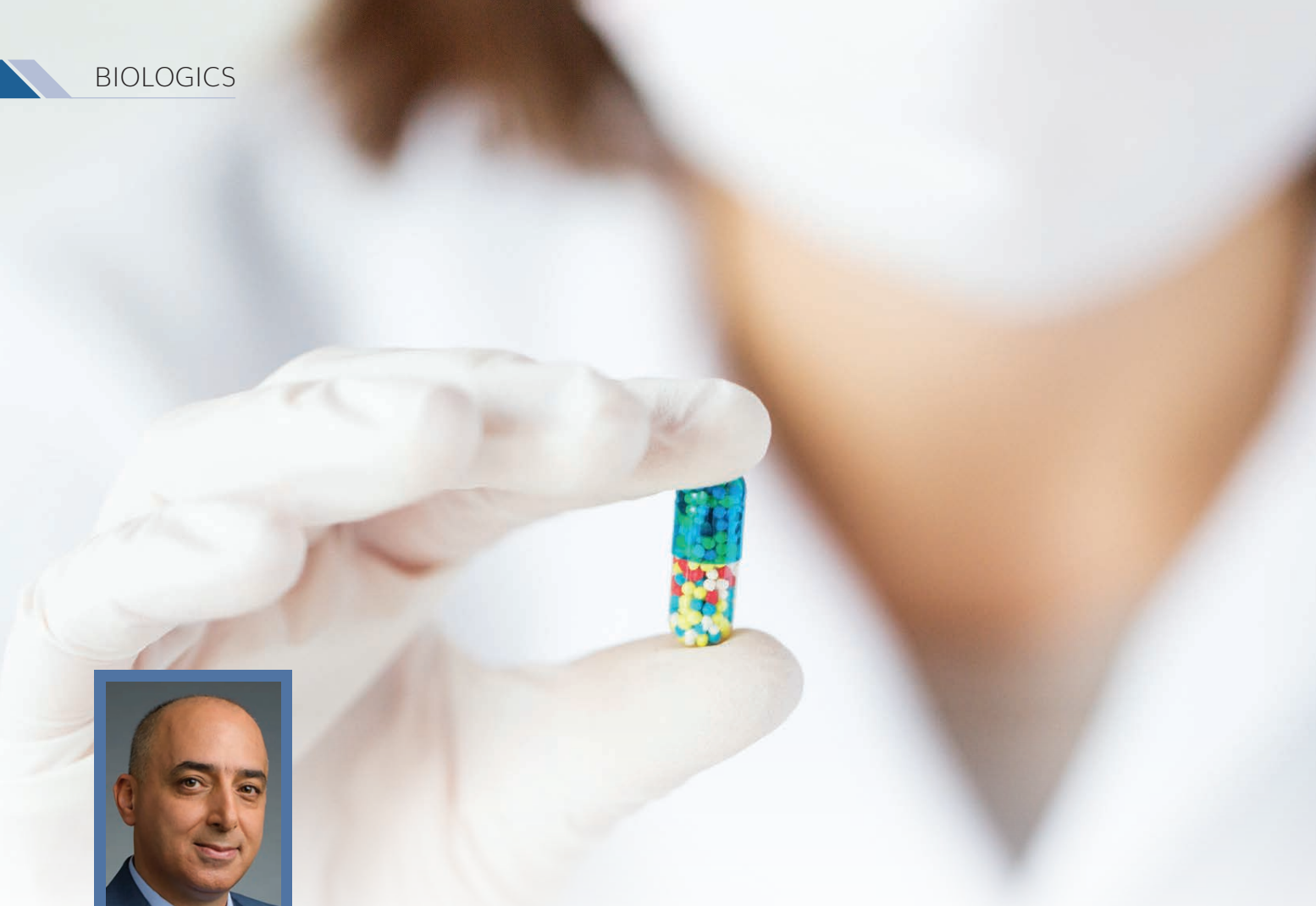
The formation of *N*-nitrosamine impurities in biologics is less prominent than in small-molecule drugs. Proper risk assessment must be made because biological medicines use chemically synthesised materials that can pose a risk, some of the biological manufacturing processes use nitrosating reagents, and some of the primary packaging materials may contain nitrocellulose.[1]

Developers of biological products need to be aware of the risks associated with raw materials and mitigate them as needed. While this risk is low for biologics, risk mitigation approaches should consider the following:

- The use of high-purity grade of reagents and water for the manufacturing, formulation and storage of biologics, minimising the source of potential nitrosating agents such as nitrates
- Biologics are generally stored under acidic conditions and low temperature conditions that do not favour nitrosamine formation
- Low-mass small molecule impurities (from reagents, raw materials and by-products, etc) are cleared during the manufacturing process.

What new biologic modalities do you see emerging in the next five years and why?

Gene-editing technologies and newer methods (base and prime editing) are advancing in precision, efficiency and delivery. Unlike traditional gene therapy, which adds genes, gene-editing therapies can directly repair or deactivate disease-causing genes in situ – a transformative approach for genetic disorders like sickle cell anaemia, muscular dystrophy and cystic fibrosis. »



Fouad Atouf, PhD

Dr Fouad Atouf is Senior Vice President and Head of the Biologics Program at the United States Pharmacopeia (USP). He has been at USP for over 15 years and served in multiple leadership roles developing quality tools for biologics and establishing relevant reference material programmes. In addition to leading the work on compendial standards, Dr Atouf launched and implemented the biologics strategy focusing on technologies to support the manufacturing and testing of biological medicines.

He has implemented new engagement models and collaboration approaches with academia, the biopharma industry and global government agencies. Fouad has a strong background in the regulation and standardisation of pharmaceutical products including biologics and advanced therapies. He holds a PhD in cell biology from the Pierre & Marie Curie University, Paris, France.

Furthermore, cell-based therapies such as CAR-T have shown remarkable results in treating certain blood cancers, paving the way for broader use of engineered cell therapies. Researchers are now developing new cell engineered therapies with reduced side effects and expanding to other cell types aiming to tackle solid tumours, autoimmune disorders and even infectious diseases.

We will also see advances in developing genetically engineered allogeneic cells for treating patients. For cell and gene therapy products we need to be able to bank the cells and offer these as off-the-shelf cell therapies to treat larger populations with more cost-effective approaches.

What excites you about the future of the biologics industry and what is needed to support its advancement?

Biologics can treat patients at the genetic level, not just alleviate symptoms. I am excited about developing tools and standards to reduce complexity and increase confidence in these products for the benefit of more patients.

The future of biologic drug product manufacturing will build on traditional drug development paradigms and leverage emerging technologies to produce new modalities. Creating cell and gene therapies is complex, affecting how we define the critical quality attributes for these products. Standards will enhance our ability to ensure consistent manufacturing and deliver quality therapies and products to patients.

Industry and regulatory stakeholders increasingly recognise that collaboration, transparency, and data- and knowledge-sharing are vital to accelerating development and deployment of advanced biologics treatments. This alignment streamlines development of solutions, avoids duplicative efforts and fosters partnerships with the goal of improving global health.

A system built on open dialogue and scientific collaboration can help improve supply-chain resilience on a global scale and protect the availability of quality medicines across borders and regulatory frameworks, ensuring patients get the treatments they need, when they need them.

As advanced biologic offerings claim an ever-growing share of the medicines market, robust standards are essential to ensure their quality. Throughout the product lifecycle, from R&D to commercialisation, we must critically examine existing systems and leverage all tools to identify gaps in quality and safety. Collaboration enables the creation of new standards and solutions to address these gaps.

Reference

1. Zheng J, Brookes A, Moser J, *et al.* On the Risk of Nitrosamine Contamination During Drug Product Blister Packaging. *J. Pharm. Sci.* [Internet]. 2023; 112(1). Available from: https://www.researchgate.net/publication/372523003_On_the_Risk_of_Nitrosamine_Contamination_During_Drug_Product_Blister_Packaging