IFAPP TODAY

The Global Pharmaceutical Medicine Journal

INTERNATIONAL FEDERATION OF ASSOCIATIONS OF PHARMACEUTICAL PHYSICIANS AND PHARMACEUTICAL MEDICINE

THIS ISSUE INCLUDES:

APCR Joins IFAPP: Returning as the National Member Association Representing Physician Clinical Researchers

The **International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine** (IFAPP) is pleased to welcome the **Academy of Physicians in Clinical Research** (APCR, https://apcrnet.org/) as its newly elected National Member Association (NMA). The APCR is the only professional academy within the American Medical Association (AMA) federation dedicated to physician researchers. Its mission is to provide **Advocacy**, promote **Career Growth**, and encourage **Education** among physician clinical researchers to nurture the most trustworthy clinical research ecosystem in the United States and beyond.

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APCR Academy of Physicians in Clinical Research

APCR's re-engagement after many years will help grow the network of associations of pharmaceutical physicians globally. In this article, a brief overview of the recent APCR 2025 Annual Meeting is provided.

Building Strong Foundations for a Resilient US Clinical Research Ecosystem: The 2025 Annual Meeting

APCR members gathered together once again at the **2025 Annual Meeting** in Chicago (October 24–25). The program featured excellent speakers to guide discussions on the foundational issues physician clinical researchers need to navigate.

Dr. Jack Resneck, Jr. (UCSF; Chair of Council, World Medical Association) delivered a timely keynote on the **recent revisions to the Declaration of Helsinki**. Highlighting its 60th anniversary, Dr. Resneck detailed the shift from "subjects" to "participants" and the new mandate for meaningful community engagement in study co-creation. He urged APCR members to join the upcoming 2026 revisions of the **Declaration of Taipei**, which governs the ethical use of identifiable data and biological materials.

Continuing the focus on the future, **Dr. Sheuli Porkess** (President, Faculty of Pharmaceutical Medicine, United Kingdom) presented on **Artificial Intelligence (AI) and the Future of Clinical Trials**. While AI promises smarter protocol design and faster recruitment, Dr. Porkess reminded attendees that investigators remain the ultimate "human-in-the-loop," responsible for mitigating algorithmic bias and ensuring participant safety under Good Clinical Practices.

A highlight of the meeting was the **Mansfield Memorial Lecture** delivered by **Dr. Elena Rios**, Founder and President of the **National Hispanic Health Foundation** (NHHF). Dr. Rios outlined NHHF's strategy to increase Hispanic participation in clinical trials by developing a clinical trials workforce that includes Hispanic physician clinical researchers.

Cutting-Edge Research and Collaboration

The meeting also showcased practical innovations in the field:

- **Digital Health**: Dr. Jackson Snyder explored using Digital Health Technologies (DHTs) for remote, real-world data acquisition.
- **Big Data**: Dr. Naveen Baskaran demonstrated how **EPIC Cosmos** leverages large-scale EHR data to accelerate discovery.
- **Hospitalist Research**: Dr. Ramesh Adhikari provided a roadmap for conducting research within hospital settings.

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The Poster Session further highlighted multidisciplinary work from investigators nationwide, offering practice-impacting ideas across genomics and therapy.

Networking and Leadership

The Friday program concluded with a memorable reception at the AMA Headquarters, where attendees enjoyed skyline views and networking opportunities. A Saturday morning member session moderated by **Dr. Santosh Basapur**, a human centered systems designer, helped in creating novel ideas to advance physician clinical researchers in all parts of the research ecosystem to feel a strong sense of belonging in APCR.

The meeting served as the formal transition of leadership from **Dr. Raj C. Shah** to the incoming President, **Dr. Monish Sheth.**

The APCR looks forward to learning and contributing to the growth of the mission of the IFAPP in 2026. If any member of IFAPP has or is transitioning to a role in the United States, please feel free to connect with us (info@apcrnet.org). Please think of us as your home away from home.

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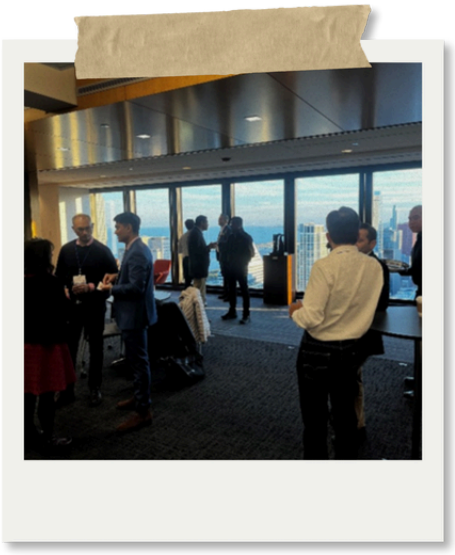
Thank you to Dr. Shah



Friday reception view

Dr. Sheuli Porkess, President of the Faculty of Pharmaceutical Medicine, United Kingdom

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New IFAPP Board Member: Dr Monika Boos

During the General Assembly on 28 Nov 2025, I was elected as the Scientific Chair of the new IFAPP Pharmacovigilance Working Group (PVWG) and thus have become a member of the IFAPP Board of Officers.

I am a physician (MD) with a PhD in Clinical Pharmacology and hold a Master's Degree in Pharmaceutical Laws. I have been working in clinical safety and post-authorisation safety for more than 20 years, assuming various roles for development compounds and established products in national, European and international working environments, including the role of European Qualified Person for Pharmacovigilance (EU QPPV) and Head of Global Pharmacovigilance.

Even beyond my day-to-day professional responsibilities, I am committed to my particular field of expertise within Pharmaceutical Medicine, e.g., as a trainer/lecturer, author or former IFAPP National Member Association Board Member/Pharmacovigilance Group lead.

As the initiator and founder of IFAPP's Pharmacovigilance Working Group (PVWG), I have been leading this initiative right from the beginning in 2023 (when it was started as a pilot). Considering, however, that a group flourishes primarily through its members, I am delighted about the other very experienced and highly motivated Pharmacovigilance and Patient Safety Experts who have joined this initiative so that the PVWG currently represents six countries in three IFAPP Regions (Europe (Greece, Spain, Germany), USA and Japan).

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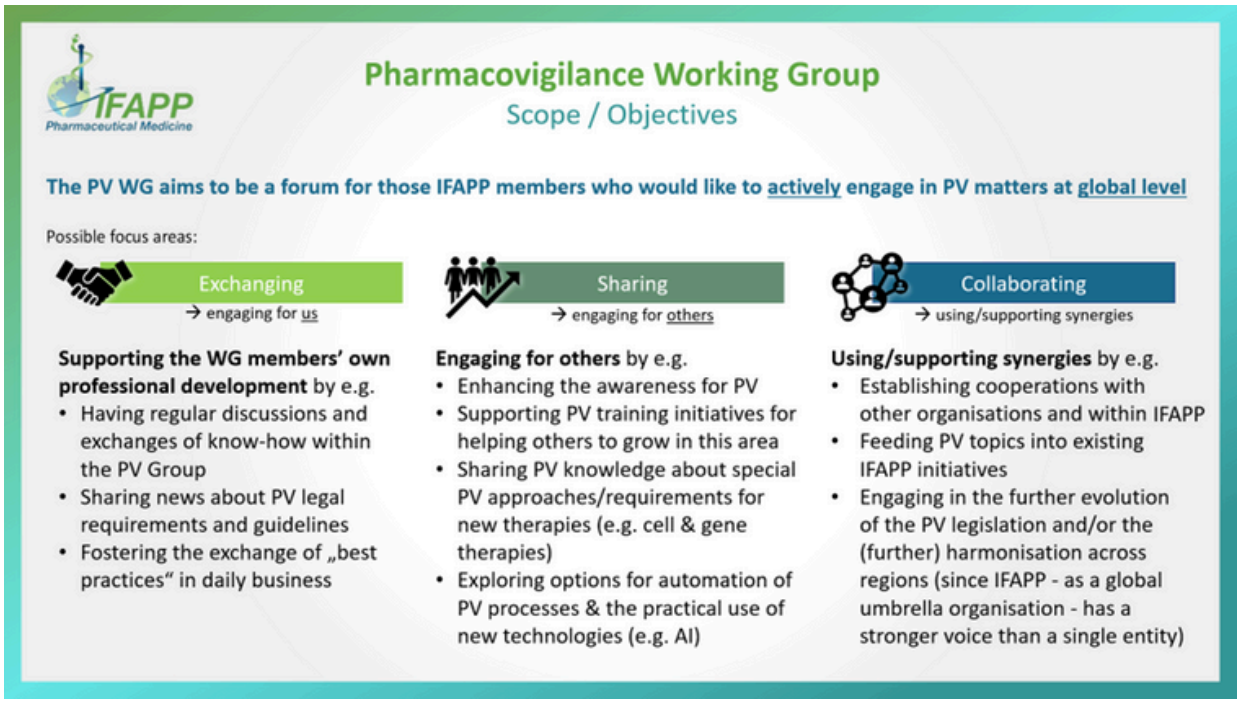
The PVWG aims to be a forum for those IFAPP members who would like to actively engage in PV matters at a global level in order to create additional value for themselves, for the IFAPP members and for the professional discipline Pharmacovigilance and Patient Safety as such.



Within the WG, the members with their diverse backgrounds may benefit from regular interactions by exchanging knowledge and sharing best practices. By engaging in PV education and training the WG will help others to grow in this area (particularly as solid skills/qualifications are considered key for performing a high-quality job). Facilitating patient engagement (incl. patients, physicians, pharmacists, students, caregivers and others) will play a major role for activities by the group members as well, in particular as patients and their well-being are in the centre of any PV activity.

Sharing know-how about special PV approaches/requirements for new therapies (e.g., cell and gene therapies, including their harmonisation efforts/needs across regions/countries) within and beyond the group will also be subject to the WG discussions and actions. The same applies for exploring options for the automation of PV processes and the practical use of new technologies (e.g., artificial intelligence). And by leveraging the international umbrella organisation, even the further PV legislation evolution might be supported by the WG (in close collaboration with other IFAPP WGs and initiatives).

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More information about the PVWG, including its scope and objectives can be found here: https://ifapp.org/working-group/pharmacovigilance/

Anyway, as done in the past already (e.g., in editions no. 46/2024, 47/2024, 48/2024 or 56/2025), the PVWG will continue to report about planned/accomplished activities or to address current topics of interest in the IFAPP TODAY.

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Individual IFAPP Affiliate, Chair of IFAPP's PVWG

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AMIFE'S 50th Anniversary: ICOMEM Interviews the President, Dr Susana Gómez-Lus Centelles

"We demand new career paths for doctors beyond the hospital"

The **Association of Medicine of the Pharmaceutical Industry in Spain (AMIFE)**, celebrated its 50th Anniversary on 27 November 2025 at the Official College of Physicians of Madrid (ICOMEM), focusing the event on a key demand: to give visibility to the multiple professional opportunities that exist for doctors beyond clinical practice.

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The President of AMIFE, Dr **Susana Gómez-Lus Centelles**, highlighted that " many doctors associate their career exclusively with the hospital and are not always aware of the wide variety of roles that exist in industry, research, regulation or the management of scientific knowledge."

During her speech, Dr Gómez-Lus defended the strategic value of non-clinical medical departments within pharmaceutical companies, as they are "a key element in strategic decision-making, in the generation of evidence and in the connection between science and the real needs of patients."

“Medicine isn’t practiced only in the hospital,” she stated. “It’s also practiced by promoting research, ensuring the safety of treatments, and bringing innovation to those who need it. Young doctors should know that there’s a vast, dynamic, and profoundly medical professional world waiting for them.”

The event included an interactive format with live questions from the audience, which revealed a growing interest in and knowledge of these career paths. Even so, some responses highlighted the need for continued efforts in outreach and training.

In addition to the Master's programme, AMIFE promotes conferences, workshops and collaborations with universities through its training group, to bring the reality of the industry closer to students, residents and active professionals.

“We want to show that there are diverse and very valuable ways to contribute to health beyond clinical practice ” Dr Gómez-Lus concluded. “AMIFE is here to help you discover them.”

Interview with Dr Susana Gómez-Lus:

Today AMIFE participated in the ICOMEM 50th anniversary event. What does this celebration mean to you and to AMIFE?

Celebrating AMIFE's 50th anniversary at ICOMEM has profound significance. It is a recognition of half a century of dedicated work focused on quality research, professional development within the sector, and collaboration between medicine and industry.

For me, it is a moment of pride and gratitude: pride for what AMIFE has built over these years, and gratitude towards all the people and institutions such as ICOMEM that have accompanied this journey.
This anniversary symbolises not only our history, but also the strength of a community that continues to evolve and looks to the future with the same commitment to rigour, ethics, and innovation with which it was born.

During the event, the important role of non-clinical medical departments was highlighted. Do you think doctors in general are aware of these career paths?

In general, I think they are still not well known enough. Many doctors associate their careers exclusively with clinical practice and are not always aware of the wide variety of roles that exist in industry, research, regulation, or the management of scientific knowledge.

Medical departments offer very valuable opportunities to contribute to health from another perspective: developing evidence, ensuring the safety of medicines, driving innovation, and connecting science with the real needs of patients.
There is still work to be done to raise awareness of these alternatives and to ensure that professionals understand that their training and clinical experience can have a significant impact beyond the healthcare setting. AMIFE wants to continue helping to spread this knowledge further.

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You have repeatedly defended the strategic value of medical departments in the industry. What role do these professionals actually play within pharmaceutical companies?

Medical departments play an absolutely strategic role within pharmaceutical companies. They are the point where science is integrated with clinical practice and where it is ensured that all decisions, from drug development to real-world use, are based on evidence, ethics, and a patient-centred approach.

These profiles offer three major benefits:

1. Scientific rigour and credibility: they ensure that medical information is sound, transparent and aligned with the real needs of healthcare professionals and patients.
2. Connection with the healthcare system: they are the ones who understand the clinical context and can translate that reality to the company to better guide research, strategy and priorities.
3. Long-term vision: They contribute to identifying therapeutic opportunities, unmet needs, and areas where innovation can have the greatest impact.

In short, medical departments are no longer support areas: they are a key element in strategic decision-making and in building a relationship of trust between industry, healthcare professionals and society.

Today's event used an interactive format, with live questions for the audience. What conclusions did you draw about the attendees' level of knowledge in these areas?

Interaction with the audience allowed us to confirm a growing interest in and increasingly solid understanding of the role of non-clinical medical departments. Many attendees demonstrated familiarity with these functions and their impact on research and healthcare practice.

However, it also became clear that there is still room for further dissemination and training. Some responses reflected doubts about the scope of these roles, the necessary skills, or professional development opportunities.

Besides the Master's programme, what other actions is AMIFE taking to raise awareness and promote these career paths?

In addition to the Master's programme, AMIFE has working groups, specifically the university training group, which promotes and raises awareness of career opportunities in medical departments. We organise conferences, workshops, and roundtables that bring the realities of the industry closer to students, residents, and practicing professionals.

The goal is clear: to show that there are diverse and very valuable ways to contribute to health from beyond clinical practice.

What message would you like to convey today to young doctors who may not yet be aware of these career paths beyond the hospital?

My message is to keep an open mind and explore all the ways your vocation can have an impact on. Medicine isn't practiced only in the hospital: it's also practiced by driving research, ensuring the safety of treatments, generating evidence, or helping to bring innovation to patients responsibly.

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Medical departments offer real opportunities to add value, grow professionally, and stay connected to science and patient needs. If you're curious, learn more, ask questions, and reach out to those who work in these fields.

A vast, dynamic, and deeply medical professional world awaits you. And AMIFE is here to help you discover it.

Source: El Viernes Newsletter, The Official College of Physicians of Madrid (ICOMEM)

Published on 15 January 2026

When Mechanism Becomes Evidence: The FDA's Plausible Mechanism Pathway and the Future of Rare Disease Development

For decades, regulatory science has relied on a familiar evidentiary hierarchy. Randomised trials, population-level statistics, and reproducibility across large cohorts have defined what it means to demonstrate safety and effectiveness. This framework has served medicine well. But in rare and ultra-rare diseases, particularly monogenic, rapidly progressive, and paediatric conditions, it increasingly fails the patients it was designed to protect. Small populations, biological heterogeneity, ethical constraints, and the urgency of irreversible disease progression make traditional development paradigms impractical and, in some cases, impossible.

Against this backdrop, the US Food and Drug Administration (FDA) has articulated what may be one of the most consequential regulatory shifts in decades. In a recent New England Journal of Medicine article, FDA leadership described a plausible mechanism pathway for drug and biologic development (1). Rather than abandoning rigour, the pathway reflects a deliberate re-weighting of evidence. It places greater emphasis on biological plausibility, mechanistic sufficiency, and natural history grounded clinical interpretation when conventional trial structures cannot reasonably be executed.

This evolution is particularly relevant for pharmaceutical physicians working in gene therapy, gene editing, and other precision modalities, where the mechanism is not simply supportive of efficacy but foundational to it.
In many rare diseases, especially severe childhood-onset genetic disorders, the evidentiary expectations embedded in conventional drug development are mismatched to clinical reality. Randomised controlled trials may be infeasible due to population size alone. Placebo control may be ethically untenable in conditions with predictable and devastating natural histories or complex routes of administration. Even well-designed single-arm studies can struggle to demonstrate statistical certainty when patient numbers are counted in the single digits.

The absence of traditional trial structures does not imply an absence of knowledge. In monogenic disease, the causal link between genotype, molecular dysfunction, and phenotype is often well established. Natural history, when rigorously characterised, can be remarkably consistent. In such settings, the central question shifts. It is no longer whether a therapy demonstrates population-level statistical significance, but whether intervention at a defined biological node plausibly alters the expected disease trajectory in a clinically meaningful way. This is the core logic of the plausible mechanism pathway (1).

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As articulated by FDA leadership, this pathway is not intended as a relaxation of regulatory standards. It is a reframing of what constitutes persuasive evidence when traditional approaches are impractical. Several principles define this framework. There must be a clearly defined molecular or cellular abnormality that is causally linked to disease. This pathway is not designed for syndromic diagnoses or poorly understood polygenic conditions. It is grounded in diseases where the biological defect is known.

The therapeutic intervention must act proximally on that defect. Treatments that exert broad or downstream effects without a clear mechanistic link to the inciting pathology are unlikely to qualify. The closer the intervention is to the causal mechanism, the stronger the plausibility argument becomes.

A well characterised natural history is essential. The FDA places substantial weight on understanding how disease unfolds in the absence of intervention, allowing treated patients to be interpreted against a credible counterfactual rather than an artificial control arm. Evidence of target engagement or biological activity, when feasible, further strengthens the case. While invasive confirmation such as tissue biopsy may not always be possible, converging data from biomarkers, model systems, or pharmacodynamic signals can support mechanistic claims.

Finally, there must be a clinically meaningful deviation from the expected disease course. Improvement need not be dramatic, but it must be durable, coherent with the proposed mechanism, and sufficient to exclude regression to the mean or spontaneous fluctuation. This framework does not bypass evidence generation. It reallocates evidentiary weight towards biological coherence when statistical certainty is unattainable.

It is worth emphasising that many of these evidentiary elements are not themselves novel. The FDA has long considered biomarkers, mechanistic data, external controls, and natural history in rare disease development, and approvals based on surrogate or intermediate endpoints are well established. What is different here is not the individual tools, but the explicit way in which senior FDA leadership is reframing their collective acceptability. The plausible mechanism pathway represents a shift in emphasis and transparency, elevating biological coherence and mechanistic sufficiency from supportive evidence to a central organising principle for regulatory judgement when traditional trial paradigms are not feasible.

The case of Baby K.J., an infant with carbamoyl phosphate synthetase 1 deficiency treated with a patient-specific in vivo base editing therapy, illustrates the pathway in practice (2). The disease mechanism was unequivocal. The intervention was precisely targeted to the causal mutation. The natural history of untreated disease was well documented. Post-treatment clinical improvement was aligned with biological expectations (2). Importantly, the case also illustrates a broader regulatory insight. Individualised therapies can generate generalisable knowledge. While each intervention may be bespoke, repeated success across patients using a shared technological platform can establish confidence in the process itself.

In this sense, the FDA is signalling openness to approving not only individual products, but platforms, provided that the underlying science, manufacturing controls, and clinical logic are sufficiently robust. This reasoning extends beyond gene editing alone. Antisense oligonucleotides, RNA-based therapies, gene replacement approaches, and other precision modalities may also qualify when they directly address a defined molecular defect.

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Rare diseases, particularly fatal or severely disabling paediatric conditions, are the natural proving ground for this framework. In these settings, the cost of inaction is high, and the limitations of traditional development models are most acute. The FDA has been explicit that it intends to prioritise such conditions, while leaving open the possibility that similar principles could extend to more common diseases with substantial unmet need. At the same time, the pathway is deliberately constrained. Its integrity depends on disciplined application. Broad extrapolation to conditions with ambiguous mechanisms or heterogeneous biology would undermine its credibility and risk patient harm.

The plausible mechanism pathway does not exist in isolation. It sits alongside other recent FDA initiatives aimed at modernising therapeutic development for rare diseases, including the Rare Disease Endpoint Advancement framework (4) and related Rare Disease Evidence Principles or RDEP (3). Rather than functioning as a new endpoint qualification programme or regulatory shortcut, RDEP is best understood as an early alignment mechanism. It provides a structured opportunity for sponsors and the FDA to agree, before pivotal development, on what constitutes sufficient evidence of effectiveness in settings where conventional trial designs are not feasible.

Under RDEP, the statutory standard for safety and effectiveness does not change. What changes is the transparency around how different forms of evidence may be weighed. Mechanistic data, relevant nonclinical models, pharmacodynamic signals, rigorously collected natural history, and external or self-controlled comparators can all contribute to a coherent evidentiary package (3), underpinned by effectiveness established based on one adequate and well-controlled single-arm trial when randomised controls are impractical. In this way, RDEP complements the plausible mechanism pathway by clarifying evidentiary expectations early, reducing downstream uncertainty, and anchoring regulatory judgement in biological coherence rather than trial architecture alone.

Taken together, these initiatives suggest a broader regulatory evolution towards process-based reasoning. Rather than evaluating isolated data points, the FDA is increasingly focused on the coherence, reproducibility, and scientific integrity of an entire development approach.

For pharmaceutical physicians, this shift carries practical implications. Development strategies must increasingly be built around rigorous natural history studies, mechanism- driven endpoint selection, and early integration of biomarker logic. Regulatory engagement becomes less about negotiating trial size and more about aligning on biological narratives, uncertainty, and risk tolerance.

At the same time, the plausible mechanism pathway places significant responsibility on clinicians, sponsors, and regulators to exercise judgement. Overconfidence in mechanism, insufficient post-marketing follow-up, and inequities in access remain real risks. The FDA has emphasised that approvals under this framework will be coupled with ongoing evidence generation and that tolerance for uncertainty will remain proportional to disease severity and therapeutic benefit. What is clear, however, is that the agency is signalling a willingness to evolve.

By formalising a path for individualised and mechanism-defined therapies, the FDA is not only addressing an immediate need in rare disease but also establishing a regulatory foundation that could enable personalised therapeutic development more broadly. Other regulators are already watching closely. The United Kingdom, for example, has announced plans to explore a dedicated pathway for individualised genetic therapies (5), reflecting growing international recognition that traditional development paradigms are poorly suited to this class of medicines.

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For patients with rare and devastating diseases, and for the physicians who care for them, this shift offers a pragmatic and scientifically grounded path forward. In certain contexts, mechanism is no longer simply supportive of evidence. It becomes evidence itself.

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The Potential and Reality of RNA-Based Drugs: an Opportunity not to be Missed

(Abbreviations below)

From scientific breakthrough to therapeutic platform

The revolution of RNA-based drugs stems from a pioneering discovery: introducing modified bases into RNA made it possible to overcome its intrinsic instability and pronounced immunogenicity. This breakthrough – achieved through the work of Katalin Karikó and Drew Weissman, awarded the 2023 Nobel Prize in Medicine– laid the scientific foundations that enabled the rise of companies such as Moderna and BioNTech, ultimately leading to the development of mRNA vaccines against SARS-CoV-2. These vaccines provided the clearest proof of principle: RNA was no longer merely an experimental concept but a therapeutic platform capable of altering the course of a global pandemic.

Vaccines, however, represent only the tip of the iceberg. Pharmacological research is rapidly expanding the range of RNA-based approaches designed to selectively modulate gene expression. The potential is considerable: RNA enables strategies to regulate not only the synthesis and function of virtually any protein, but also the activity of non-coding RNAs, such as microRNAs, which play a central role in the regulation of intracellular pathways.

For pharmacologists, this means confronting a new class of therapeutics that does not conform to the paradigms of small molecules or biologics. Pharmacokinetic and pharmacodynamic profiles differ, safety models evolve, delivery requirements change, and even clinical and regulatory development pathways are being redefined. This transformation could be one of the most significant revolutions in contemporary medicine.
RNA has proven its capacity to become a therapeutic approach. From mRNA vaccines to ASOs and siRNAs now in clinical practice, reality has surpassed expectations. As new therapeutic areas and emerging platforms open unprecedented possibilities, there are many challenges - stability, safety, delivery, and manufacturing - that must be rigorously addressed.

For the pharmacology community, the task is clear: understand these evolving paradigms and help guide RNA technologies towards effective clinical and societal impact.

The landscape of RNA-based therapeutics: mechanisms, technologies and delivery

RNA molecules currently in development or already in clinical practice can be grouped into three major functional categories: i) gene expression inhibition; ii) functional addition or replacement; and iii) emerging platforms.

The inhibitory logic is the most clinically advanced. This group includes antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs), with multiple approved drugs already in use. Nusinersen marked a breakthrough in spinal muscular atrophy by modulating SMN2 splicing, while patisiran and vutrisiran pioneered RNA interference for transthyretin amyloidosis. Inclisiran introduced a new model for managing hypercholesterolemia, enabling sustained LDL cholesterol reduction with just two administrations per year.

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AntagomiRs, designed to inhibit pathologically overexpressed miRNAs, represent an intriguing conceptual extension. Rather than targeting single genes, they aim to rebalance entire regulatory networks. Although still experimental, they hold a great potential, particularly in cardiovascular and oncological fields, though clinical data remain preliminary.

A defining feature of these molecules is that their pharmacokinetics largely depend on the delivery system: intrathecal administration to reach the CNS (nusinersen), subcutaneous administration with GalNAc for hepatic targeting (inclisiran, lumasiran), or intravenous administration with lipid nanoparticles (mRNA vaccines, patisiran). In many cases, the route of administration and delivery technology effectively define the PK profile.

Among RNA-based therapeutics aimed at functional addition or replacement are therapeutic mRNAs, which gained global visibility with SARS-CoV-2 vaccines. The same technology is now evolving towards personalised vaccines targeting tumor neoantigens and applications in genetic and respiratory diseases. Their hallmark feature is controllable transience: protein expression lasts only a limited time, allowing modulation of both intensity and duration of the effect.

miRNA mimics seek to restore the activity of microRNAs whose expression is reduced, thereby influencing entire biological networks. Conceptually powerful, these molecules nonetheless face safety and specificity challenges, exemplified by the early termination of MRX34 clinical development. Despite encouraging preclinical antitumor activity, human trials revealed limited efficacy and unexpected adverse events, particularly immune- and liver-related.

Alongside established strategies, new technologies are emerging and may define the next generation of RNA-based therapeutics. Circular RNAs (circRNAs), which are more stable than linear mRNAs, promise prolonged expression and reduced immunogenicity. ADAR-based RNA editing allows reversible corrections at the RNA level without altering DNA and has already shown early clinical results in rare genetic diseases.

Aptamers, already tested in ophthalmology with pegaptanib, act as “nucleic acid antibodies”, binding protein targets with high specificity. Their potential also extends to delivery applications. Long non-coding RNAs (lncRNAs), while still in early research phases, are emerging as regulators of great interest in oncology and neurology. Self-replicating RNA (srRNA) vectors represent another frontier: once inside cells, they self-amplify and drive sustained production of natural RNAs, resulting in more intense and longer-lasting therapeutic effects.
Although RNA’s therapeutic potential is enormous, its clinical use presents challenges that directly affect pharmacokinetics, pharmacodynamics, and safety. RNA is naturally unstable, and its duration and efficacy depend on chemical modifications and formulation strategies. Biodistribution often concentrates in the liver and kidneys, while access to tissues such as the CNS, heart, or muscle requires specialised delivery systems.

Despite significant advancements, immunogenicity remains a concern. Off-target effects, especially for network-modulating strategies such as microRNAs, represent another critical issue. Safety must therefore be assessed not only at the level of individual targets but in terms of global biological modulation.

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Delivery remains the true frontier of RNA therapeutics. Lipid nanoparticles, GalNAc conjugates, and innovative vectors make tissue targeting possible and effectively define the PK/PD behaviour. Here, the route of administration becomes a principal determinant of exposure and therapeutic response.

Manufacturing poses additional complexities: unlike traditional small molecules, RNA therapeutics require elaborate synthesis and purification processes with strict quality controls (length, purity, secondary structure). These requirements translate into high costs and scalability challenges with direct implications for patient access.

Another key opportunity lies in combinations with other drug classes. RNA therapeutics can be paired with small molecules or biologics to enhance efficacy, extend durability, or reduce toxicity through complementary mechanisms.

Clinical reality: approvals and expanding therapeutic areas

Beyond mRNA vaccines, the number of RNA-based drugs in clinical practice remains limited but is steadily increasing – currently including around ten ASOs, several siRNAs, and two approved aptamers. Although still a young pipeline, the pace of development is accelerating.

The first approved RNA-based drug was fomivirsen (Vitravene) in 1998 for cytomegalovirus retinitis in HIV-positive patients. Although later surpassed, it demonstrated the feasibility of translating RNA molecules into clinical care. Since then, ASOs have rapidly evolved: nusinersen reshaped the natural history of spinal muscular atrophy, and volanesorsen has shown efficacy in familial chylomicronemia syndrome by reducing apo CIII synthesis and plasma triglycerides.

The siRNA field made a decisive step forward in 2018 with the approval of patisiran for transthyretin amyloidosis. Subsequent developments expanded rapidly into cardio metabolism: inclisiran revolutionised LDL-cholesterol management by improving adherence through twice-yearly dosing. Other examples include givosiran, indicated for acute hepatic porphyria, and lumasiran for primary hyperoxaluria, both delivered via GalNAc conjugates.

Aptamers, though less prominent today, remain historically important. Pegaptanib, approved in 2004 for age-related macular degeneration, was the first RNA therapeutic to reach patients.

RNA therapeutics are now entering the metabolic field as well. Beyond hypercholesterolaemia and acute hepatic porphyria, RNA targeting obesity and metabolic dysfunction are advancing into clinical development, with the first trials launched in Europe. Parallel research is expanding mRNA-based cancer vaccines and exploring approaches to slow neurodegenerative disease progression.

These examples confirm that RNA technologies have moved beyond the laboratory and into clinical reality. For pharmacologists, this means engaging with therapeutics that combine innovative mechanisms, unprecedented PK/PD profiles, and administration modalities that reshape clinical practice.

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Looking ahead: opportunities and responsibilities

Europe has historically contributed to RNA research, both academically and industrially. Numerous research groups have developed advanced core technologies, from chemical modifications to delivery systems, and today the continent hosts a growing number of biotech companies dedicated to RNA therapeutics.

Public investment has played a decisive role in advancing biotechnology. The Human Genome Project, for instance, enabled transformative progress through large-scale public funding. In this context, the recent $500 million reduction in U.S. funding for mRNA vaccine research is concerning but could become an opportunity: if Europe chooses to fill this gap strategically, it could strengthen its leadership and accelerate RNA-platform development.

RNA-based drugs represent a distinct therapeutic class: unlike traditional drugs, they can be designed to recognise nucleotide sequences, RNA secondary structures, or entire regulatory networks, expanding the landscape of pharmacological targets far beyond proteins alone. This versatility opens the door to disease-modifying approaches capable of rebalancing the molecular architecture underpinning complex conditions – from rare genetic disorders to oncology and metabolic diseases.

As RNA technologies continue to evolve, the challenge for the pharmacological community is to accompany this transformation with rigorous science, clinical insight, and responsible innovation. The progress achieved so far is only the beginning: RNA is set to reshape therapeutic strategies in ways we are only beginning to understand. The task ahead is to ensure that this potential translates into meaningful, safe, and accessible benefits for patients worldwide.

Abbreviations:

ADAR – Adenosine Deaminase Acting on RNA: enzyme family enabling targeted RNA editing without altering.
Apo CIII – Apolipoprotein C-III: key regulator of triglyceride metabolism; therapeutic target in metabolic disorders.
ASO – Antisense Oligonucleotide: short synthetic nucleic acid designed to modulate gene expression by binding target RNA.
circRNA – Circular RNA: covalently closed RNA molecules with enhanced stability and prolonged expression.
CNS – Central Nervous System.
GalNAc – N-Acetylgalactosamine: ligand enabling targeted delivery to hepatocytes via ASGPR.
HIV – Human Immunodeficiency Virus.
LDL – Low-Density Lipoprotein: major cholesterol-carrying particle in plasma.
LDL-C – Low-Density Lipoprotein Cholesterol: cholesterol content within LDL particles.
lncRNA – Long Non-Coding RNA: long regulatory RNA molecules involved in gene expression control.
LNP – Lipid Nanoparticle: lipid-based carrier used to encapsulate and deliver RNA therapeutics.
mRNA – Messenger RNA: RNA molecule carrying genetic information for protein synthesis.
miRNA – MicroRNA: small non-coding RNA regulating multiple intracellular pathways.
PD – Pharmacodynamics: study of a drug's effects on biological systems.
PK – Pharmacokinetics: study of drug absorption, distribution, metabolism, and excretion.
RNA – Ribonucleic acid.

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SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2: virus responsible for COVID-19.
siRNA – Small Interfering RNA: double-stranded RNA mediating sequence-specific gene silencing.
SMN2 – Survival Motor Neuron 2: gene whose splicing is therapeutically modulated in spinal muscular atrophy.
srRNA – Self-replicating RNA: engineered RNA capable of intracellular self-amplification.

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The authors will be happy to provide a list of literature references upon request which can be sent to secretariat@ifapp.org

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IFAPP Free Webinar

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2026
IFAPP *Free webinar*

The webinar will be given by **Todor Darakchiev**, M. Pharm., Head of Division Medical Devices Department, Market Supervision and Inspections,, Bulgarian Drug Agency (BDA), who will examine the background, scope and implementation of the Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices, repealing Directive 98/79/EC and Commission Decision 2010/227/EU.

Regulation (EU) 2017/746 lays down the rules concerning the placing on the market, making available on the market, or putting into service of in vitro diagnostic medical devices for human use and accessories for such devices in the European Union. This Regulation also applies to performance studies concerning such in vitro diagnostic medical devices and accessories conducted in the European Union.

Todor Darakchiev is Head of Division "Medical Devices" in the department Market Supervision and Inspections at the BDA. He has been working in the field of medical devices regulation since he started to work for the BDA in 2000. During his career in the BDA he gained regulatory experience as a chief expert for issuing of marketing authorisations of medical devices (till 2006), and as a chief inspector for medical devices and medicinal products (since 2007). Todor Darakchiev participates in the meetings of the EU Competent Authorities for Medical Devices as BDA representative. During the period 2007 – 2017 he attended several workshops for medical devices organised by TAIEX (1). In the beginning of the Bulgarian EU membership, he was a member of a working group responsible for transposition of the European legislation for medical devices. From 2011 to 2012 Todor Darakchiev participated in an interdepartmental project "Creation of digital database of medical devices paid with public resources" as a coordinator. After adoption of the EU Regulations for Medical Devices and In vitro Diagnostic Devices he was designated as a member of the Medical Device Coordination Group (MDCG) in the EU. Todor Darakchiev has also become a member of a working group for amendment of the Bulgarian Law on Medical Devices in connection with the implementation of the new legislation in the sector.

(1)TAIEX: Technical Assistance and Information Exchange, a key European Union instrument for institutional capacity-building worldwide, providing targeted and rapid support to public administrations in EU candidate countries and beyond

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Click here to register for this webinar.

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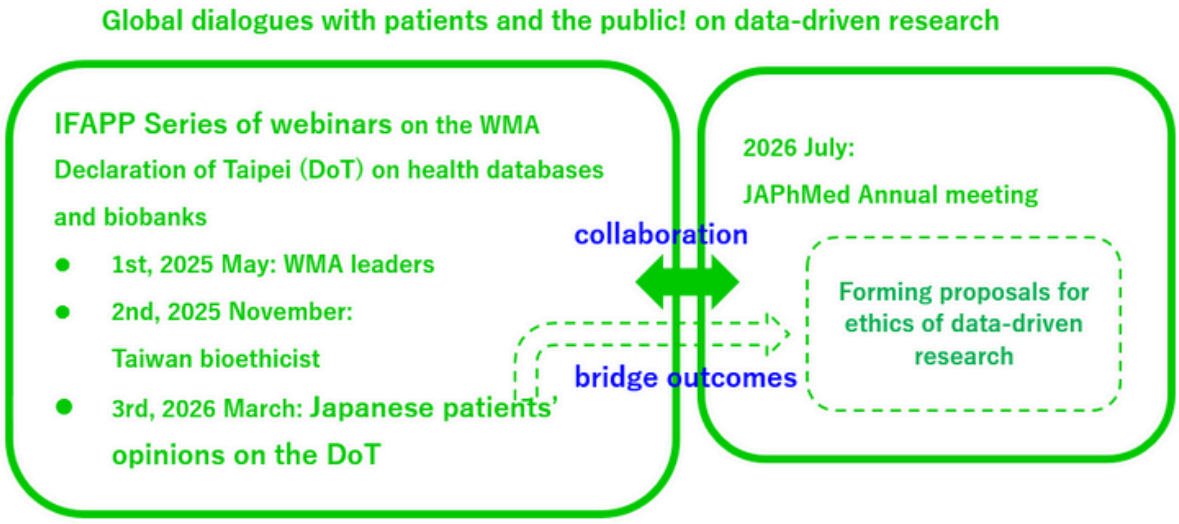
Dialogue with Patients and the Public on Data-driven Research

The third webinar in the series of Ethics in Data-driven Research will be held on **23 March 2026** and is a collaborative initiative between JAPhMed, the Japanese National Member Association of IFAPP, a Japanese patient and public group, and IFAPP. The Bioethics Working Group of Ji4pe (the Japanese Institute for Public Engagement) has expressed the opinions of patients and the public towards the 2024 revision of the World Medical Association (WMA)'s "Declaration of Helsinki". The WMA has started the revision process for the Declaration of Taipei (DoT) on Health Databases and Biobanks, with the planned adoption in October 2027. Consequently, IFAPP has organised a series of webinars inviting leaders from the WMA (1) and a bioethicist from Taiwan to discuss the DoT. This third session invites a patient group to present their opinions on the DoT for raising discussions with experts of Pharmaceutical Medicine. Outcomes from this webinar will be bridged to the JAPhMed Annual Meeting in July 2026, chaired by Dr Shinichi Nishiuma. This represents a valuable opportunity to share a global dialogue on the Ethics of Data-driven Research related to the utilisation of real-world data and the development and application of artificial intelligence (AI). Registration via this link.

Webinar time frame: 23 March 2026 CET: 12:00-13:15 JST: 20:00-21:15

Global dialogues with patients and the public! on data-driven research



Reference:

1) Lehmann B, Kurihara C. Summary of the IFAPP Webinar of 6 May 2025: Ethics in Data-driven Research: WMA Declaration of Taipei on Health Databases and Biobanks Part 1: Introduction and future direction. IFAPP TODAY. 2021; No. 55: 8-11. https://ifapp.org/wp-content/uploads/2025/08/IFAPP_TODAY_55_June_2025.pdf

Author: Chieko Kurihara, BA, Specially-appointed Professor, Kanagawa Dental University, Editor-in-chief, Clinical EvaluationこのWebinarは、IFAPPの日本のNMAであるJAPhMed

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IFAPP Pharmaceutical Medicine

Speaker
Prof. Dr Christa Wirthumer-Hoche
Former Head of the Austrian Agency for Medicines and Medical Devices and Chair of the EMA (1) Management Board

Content
The general pharmaceutical legislation adopted on 11 December 2025 represents a major modernisation of EU pharmaceutical law addressing several critical issues such as access, regulatory efficiency, innovation incentives and supply security.

Individual provisions are discussed and their impact on healthcare supply with medicines is outlined. An overview will be presented.

However, this general pharmaceutical legislation alone cannot solve all the challenges in the pharmaceutical sector; supplementary legislation is needed, such as the Critical Medicines Act, European Health Data Space and AI (2) tools. The interaction between these regulations is also examined.

Register in advance for this webinar

After registering, you will receive a confirmation email containing information about joining the webinar.

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CV of Prof. Dr Christa Wirthumer-Hoche

Prof. Dipl. Ing. Dr Christa Wirthumer-Hoche studied biochemistry and graduated at the Technical University, Vienna, in 1981, and wrote her doctoral thesis at the Institute for Medical Physiology, graduating in 1983. She joined the Austrian National Institute for Quality Control of Drugs, afterwards the Austrian Federal Ministry of Health and Women and from 2006 to 2023 the Austrian Medicines and Medical Device Agency, always in a leading role. In October 2013, she was appointed Head of the Austrian Agency for Medicines and Medical Devices.

At a European level, from 1994 to 2023, Prof. Wirthumer-Hoche has been involved in different European committees and working groups and, in 2016, she was the first woman to be elected Chair of the EMA's Management Board and was re-elected for a second term in 2019. Also at international level, within ICH (3) and ICMRA (4) she was an active member.

Since 1 April 2023 Prof. Wirthumer-Hoche has been retired but is still active as a lecturer on the subject "regulatory affairs and cooperation of different stakeholders in Europe in the field of marketing authorisation and life cycle activities of medicinal products", at different universities. During the review of the general Pharma legislation, she was a consultant to the Ministry of Health of Austria. She was and is involved in EC (5) projects that support the establishment of national regulatory authorities in countries with less developed regulatory systems.

Abbreviations

1) EMA: European Medicines Agency
2) AI: Artificial Intelligence
3) ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
4) ICMRA: International coalition of Medicines Regulatory Authorities
5) EC: European Commission

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Free Webinars

- 19 February 2026 - EU In Vitro Diagnostic Regulation (IVDR) implementation. State of play and challenges
  Click here to register.
- 23 March 2026 - Ethics in Data-Driven Research (Part 3): Opinions from patients and the public.
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- 15 April 2026 - New Provisions in the pharma legislation: will they solve the future challenges concerning pharmaceuticals
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