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Introduction: Journal of Regulatory Affairs, September-October 2026

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Welcome to the Journal of Regulatory Affairs, featuring articles on the proposed plausible mechanism framework, essential drug delivery output (EDDO) control strategies for drug/biologic combination products, the new lab-developed test compliance landscape for diagnostics, the use of real-world evidence in medical device submissions to the US Food and Drug Administration (FDA), and pediatric frameworks in the US and EU.

We thank the authors for sharing their real-world knowledge and expertise with their global regulatory peers. Their commitment, both in time and effort, to writing the articles and seeing them through to final publication is greatly appreciated. We acknowledge their contributions to the existing regulatory literature and hope others will also consider contributing in this way.

Innovative therapies and drug delivery combinations

In **The proposed plausible mechanism framework: Potential promises and challenges** (p. 5), **Marilyn Gafford, Ronald Hall,** and **William C. Putnam** examine the FDA's guidance on requirements for the expeditious development and approval of individualized therapies targeting specific conditions with known biological causes from an industry perspective. The agency outlined its novel plausible mechanism pathway in December 2025 and followed up in February 2026 with a draft guidance for industry expanding on the initial outline.

The approach centers on the adaptive use of existing regulatory frameworks rather than the creation of a new clinical development paradigm. This strategy provides flexibility and could expedite innovation, but limited precedent and evolving expectations have introduced some uncertainty. Early and ongoing engagement with the FDA is essential to clarify assumptions, align evidence-generation strategies, and reduce downstream regulatory risk. The ability to leverage previously validated tools and existing scientific knowledge may be pivotal in supporting efficient development of future products, particularly as technologies continue to advance. However, unresolved gaps and the risk of unknown long-term patient outcomes following early approval warrant continued caution.

Drug delivery combination products are crucial in delivering medications to patients through safe, effective, reliable administration of the intended dose. In **Optimizing EDDO control strategies for drug/biologic combination products** (p. 15), **Rumi Young and colleagues** examine the development of control strategies for drug/biologic-led combination products for new drug applications (NDAs) and biologics license applications (BLAs). Young, with co-authors **Ashley Boam, Anna Karina Busch, Susan Clemmons, Willy Liou,** and **Shruti Mistry,** address the recent draft guidance on EDDOs, focusing on risk-based control strategies, effective submission strategies, and when to engage with the FDA. They highlight

regulatory expectations for EDDO upstream controls, discuss implementation challenges, and offer insights on practical approaches for robust submissions, including integrating prior knowledge, risk assessments, submission strategies, and global trends.

Diagnostics, devices, and pediatric frameworks

In **Diagnostics in limbo: Evaluating the new lab-developed test compliance landscape** (p. 27), **Daniel Simpson** discusses the current landscape of laboratory-developed tests (LDTs) following a federal court's decision to vacate the FDA's final rule that represented the agency's latest attempt to regulate this category of in vitro diagnostic (IVD) products. The ruling seemed to open the LDT space for IVD developers and manufacturers to introduce their technologies early without the need for FDA premarket clearance or approval. However, potential compliance pitfalls remain, especially for outside entities supplying research-use only materials to Clinical Laboratory Improvement Amendments-certified laboratories for conversion into LDTs for clinical use. This article is a resource for IVD developers and manufacturers developing compliance strategies and considering the LDT approach for their diagnostic technologies.

In **Real-world evidence in FDA medical device submissions: Considerations for regulatory decision making** (p.37), **Anuja Yardi** examines the evolving role of RWE across the device lifecycle and analyzes emerging patterns from FDA examples of use. She addresses practical applications, common challenges, fit-for-purpose evaluation, and factors associated with successful use in regulatory decision making and submissions of medical devices. A structured approach grounded in relevance, reliability, traceability, and scientific validity can help regulatory professionals leverage RWE effectively while maintaining confidence in regulatory decision making and supporting continued innovation in evidence generation.

In **Comparing EU and US pediatric frameworks at a time of reform** (p. 52), **Samantha Gastine, Nadia Boehringer,** and **Anne-Valérie Faucher** examine how the EU and the US have developed distinct but complementary regulatory frameworks to address the use of off-label medicines in children. The article compares key differences in scope, timing, and incentives, and discusses how recent regulatory reforms in the EU are reshaping pediatric development strategies and influencing access to medicines. However, despite these advances, important differences remain in how each system structures obligations, timelines, and incentives, which directly impact development strategies. In this context, pediatric development can no longer be seen as a secondary component of drug development. It requires early anticipation, continuous adaptation, and strong global coordination to ensure both regulatory compliance and meaningful impact for pediatric patients.

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