BRIEFING ON NEW EU DIRECTIVE FOR HUMAN MEDICINES

Deliver Europe's Modernisation Deal: Updating Annex II to Future-Proof Medicines Testing

The European Commission initiated the long-awaited reform of the EU's General Pharmaceuticals Legislation in 2023. Two years later, in December 2025, the Parliament, Commission and Council of the EU, reached a political agreement on a new draft Directive for medicines for human use. A key achievement of this reform is the alignment of the new Directive with other major EU regulatory frameworks, embedding explicit provisions to replace animal tests in line with the requirement to use animals as a last resort. In 2022, 498,360 animals were used in tests to satisfy EU requirements for medicinal products for human use, accounting for nearly half of all regulatory animal use in the EU and Norway (see ALURES database).

Under the new Directive animal testing may only be conducted when scientifically necessary and no suitable non-animal testing strategies exist. Such strategies may include *in vitro* cell cultures, complex *in vitro* models such as organs-on-chips, computational models, AI-based models, and combinations thereof. With the development of a roadmap to phase out animal tests for chemical safety assessment, the EU Commission has committed to a systemic transition to an animal-free regulatory system, including for pharmaceuticals. This requires a clear strategy, and PETA has already set the foundation with its Research Modernisation Deal. It sets out six concrete steps for shifting away from experiments on animals, including the immediate removal of animal testing requirements that fail to provide meaningful information, and the global advancement of state-of-the-art, non-animal methods that can replace them.

These specific actions can be implemented in the next phase of finalising the new Directive: updating the standard testing protocols set out in Annex II, a process the Commission has committed to initiating once the main text is adopted. Annex II has not yet been revised and still reflects the wording of Directive 2001/83/EC. The update will occur via a delegated act before the transposition deadline and provides a once-in-a-generation opportunity to future-proof and modernise the regulatory requirements for testing human medicines. This is the moment for the EU to deliver its own "Modernisation Deal" by integrating cutting-edge, human-relevant, non-animal methods at the heart of the new EU pharmaceutical legislation.

To fully capture this potential, the three reforms below should guide the update of Annex II:

1. REMOVE OUTDATED ANIMAL TESTING REQUIREMENTS

The Directive should reflect current scientific capabilities by eliminating automatic requirements for animal tests prior to first-in-human trials. Instead, Annex II should:

- **End the standard requirement to conduct animal tests** before clinical trials in humans, allowing non-animal methods to serve as the primary source of evidence.
- **Enable flexible regulatory pathways** that encourage sharing of data from new testing strategies, even when they deviate from existing international guidelines.
- **Introduce a mechanism that allows regulators to provide feedback on proposals** to replace required animal tests with non-animal testing strategies, and to enforce the requirement to test on animals only as a last resort before developers design new evidence packages; similar to REACH (Registration, Evaluation, Authorisation and Restrictions of Chemicals) testing proposal.

2. ESTABLISH NON-ANIMAL APPROACHES AS THE NEW REGULATORY STANDARD

To align Annex II with scientific progress and EU commitments, the updated text should:

- **Require tiered, step-by-step testing strategies** that prioritise scientifically valid non-animal methods.
- **Replace prescriptive test mandates with information objectives** that focus on the data needed to answer a regulatory question, rather than explicitly specifying the method to be used to generate that data.
- **Introduce incentives that drive the transition** to non-animal testing strategies, such as priority access to Innovation Task Force (ITF) briefing meetings, Scientific Advice (SA) or Voluntary Data Submissions (VDS).

3. IMPROVE THE FRAMEWORK FOR ENVIRONMENTAL RISK ASSESSMENT (ERA)

To modernise environmental safety assessments and manage legacy pharmaceutical substances more effectively, Annex II should:

- **Mandate a step-wise, proportionate data-generation framework** for risk-based prioritisation of legacy APIs, with non-animal methods as a first-line approach to filling information gaps.
- **Implement the decision tree developed in the PREMIER Project** (see Coors *et al.* 2023) to reduce the requirement for testing on fish by approximately 35% without compromising environmental protection.
- **Enable independent data submissions for ERA monographs** to improve transparency and promote non-animal methods and other high-quality scientific evidence.

To facilitate the reform, the **European Medicines Agency must receive a meaningful budget**, particularly for expanding staffing and expertise within the 3Rs Working Party. Adequate resources are essential to manage the expected rise in ITF meetings, SA procedures, and VDS pathways.

Non-clinical assessors will require **protected time for specialised training and for structured engagement with relevant stakeholders** via dedicated forums.

In parallel, **investment in enabling infrastructure**—such as a secure, interoperable data-sharing platform—is crucial to ensure efficient evidence evaluation and to accelerate the integration of modern, non-animal approaches across the regulatory system.

If implemented boldly, these reforms will **enhance patient safety, strengthen environmental protection, uphold Europe's ethical commitments, and cement the EU's global leadership in innovative regulatory science.** The decisions taken now will shape the development of medicines for decades. This is the EU's moment to deliver its Modernisation Deal.

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