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A new approach to non-clinical testing and animal protection

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1. Framework

For decades, the assessment of medicinal products for the demonstration of their quality, safety and efficacy relied mostly on pre-clinical studies conducted on animals. However, the Pharma Package, currently in the process of publication, introduces a significant shift in approach on this matter: animal testing is no longer the reference method, becoming instead subsidiary in nature, only permissible where no scientifically satisfactory alternative methods exist.

This change forms part of a broader trend of scientific and technological modernisation, which also encompasses the use of real-world data, computational modelling tools and artificial intelligence, likewise aiming to reduce animal testing and to develop alternative methods that allow its use to be diminished.

The provisions on animal testing appear, in substantially identical wording, in both the proposed Directive and the proposed Regulation that make up the Pharma Package.

2. The 3Rs principle

The European Union's approach to the use of animals for scientific purposes has, for several years, been based on the 3Rs principle: replacement, reduction and refinement.

Grounded in Recital 31 of the proposed Directive and, in identical terms, Recital 46 of the proposed Regulation, these principles are reinforced in the sense that the use of animals must be limited to situations where it is strictly necessary, with studies being designed so as to obtain scientifically adequate results using the smallest possible number of animals.

At the same time, procedures must be planned to minimise pain, suffering, distress and lasting harm, in accordance with the applicable guidelines of the European Medicines Agency ("EMA") and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ("ICH").

Beyond reaffirming the 3Rs principle, both instruments impose concrete legal obligations on marketing authorisation applicants, reinforcing the requirement to use alternative methods whenever these are available and scientifically adequate.

Specifically:

A. The prohibition on animal testing where alternatives exist: It is established that marketing authorisation applicants must not carry out animal tests where scientifically satisfactory non-animal testing methods exist. Where such methods are not available, animal tests must be carried out in accordance with Directive 2010/63/EU, as set out in Article 6(7) of the draft Directive. The same obligation appears in Article 6(5) of the draft Regulation, which requires the applicant to demonstrate that the 3Rs principle has been applied in accordance with Directive 2010/63/EU in respect of any animal study supporting the application, and which prohibits animal testing where scientifically satisfactory non-animal methods exist. This is, therefore, a dual-anchor rule: applicable both under the national, mutual recognition and decentralised procedures (via the Directive) and under the centralised procedure (via the Regulation).

B. The new definition of "non-clinical": The proposed Directive introduces, in Article 4(11), a broad definition of "non-clinical", which is significant in that it does not take animal testing as the central model for pre-clinical assessment. On the contrary, it incorporates animal-based tests merely as one of several possible types of non-clinical study.

For the purposes of the proposal, a "non-clinical" study or test may be carried out in vitro, ex vivo, in silico or in chemico, as well as through non-human in vivo tests relating to the investigation of a medicinal product's safety and efficacy. This category may include, among others, simple and complex assays based on human cells, microphysiological systems, computational modelling and other in silico methods, test methods based on human or non-human biology, and animal-based tests.

This formulation is significant because it changes how the different methods are positioned. Animal testing thus ceases to be the implicit starting point and becomes merely one of several possible options.

3. Data sharing and the prohibition on duplication

The aim of reducing animal use is not confined to promoting alternative methods; it also seeks to avoid the unnecessary repetition of studies that have already been carried out.

Recital 32 of the proposed Directive provides for the establishment of procedures to facilitate joint animal testing, wherever possible, with a view to avoiding unnecessary duplication of tests using live animals covered by Directive 2010/63/EU. Applicants and marketing authorisation holders should make every effort to reuse the results of animal studies and to make them publicly available, and applicants for abridged applications should refer to the relevant studies carried out for the reference medicinal product. Recital 47 of the Regulation reproduces this guidance in identical terms for the centralised procedure.

These provisions appear in the recitals rather than in binding articles. The language used, such as "procedures should be in place" and "make all efforts", is deliberately more programmatic in tone, reflecting the fact that its concrete implementation will depend on implementing acts and technical guidance to be developed by the EMA during the transitional period envisaged for 2026–2028.

This anti-duplication logic is reinforced by Article 14 of the proposal, through the letter of access mechanism, defined in Article 4(15) as the original document signed by the data owner authorising the use of that data by third parties. Once a marketing authorisation has been granted, this mechanism allows the application documentation to serve as the basis for subsequent applications concerning other medicinal products, thereby promoting greater efficiency for operators alongside a reduction in the use of animals in non-clinical studies.

4. Authorisation conditions and validation of alternative methods

The integration of non-animal testing methods is not confined to the initial marketing authorisation ("MA") application stage. The proposal allows for the replacement of animal-based methods to be promoted throughout the medicinal product's life cycle as well.

In this regard, Article 44(1)(j) of the proposed Directive allows an MA to be granted subject to a condition that the holder carry out, where appropriate, product-specific validation studies aimed at replacing animal-based control methods with non-animal-based control methods.

The same mechanism is provided for under the centralised procedure by Article 12(4)(m) of the proposed Regulation, which determines that a favourable opinion of the Committee for Medicinal Products for Human Use ("CHMP") may include details of any obligations recommended to the applicant to carry out such validation studies. In these situations, the obligation does not arise directly from the authorisation itself, but from the CHMP opinion underpinning it, which is subsequently incorporated into the European Commission's decision.

This provision is significant because it allows the replacement of animal testing to accompany the medicinal product after its authorisation, avoiding the entrenchment of particular control methods and reinforcing the gradual transition towards non-animal methods. A joint reading of Article 44(1)(j) of the Directive and Article 12(4)(m) of the Regulation confirms that this mechanism operates in parallel under both authorisation routes, albeit through distinct formal instruments.

5. The EMA's institutional role in the transition towards non-animal methods

In addition to imposing obligations on applicants, the Pharma Package assigns the EMA an explicit mandate to accelerate the regulatory acceptance of new non-animal methodologies ("NAMs"). This is one of the most significant institutional innovations of the package in this area, insofar as it transforms what has until now been chiefly a matter of good governance practice into a legal obligation of the EMA.

In particular, Article 138(1) of the Regulation sets out a specific set of tasks in this area. The EMA must cooperate with other authorities and scientific bodies established under Union law with regard to the development of coherent scientific methodologies, including the replacement, reduction and refinement of animal testing and, where possible, the prioritisation of replacement strategies based on in vitro and in silico approaches. It must also provide regulatory support and facilitate the development, validation and regulatory adoption of new approach methodologies, regularly reporting on good practices and key observations concerning the 3Rs. There is, in addition, a mandate to facilitate the joint conduct of non-clinical studies between applicants and MA holders, as well as the sharing of data resulting from non-clinical studies on live animals.

6. Practical implications for operators

For market operators, these changes carry concrete implications from the initial stage of medicinal product development through to post-authorisation management, given that the selection of non-clinical methods will require more robust justification, with identification and assessment of available alternatives before opting for animal testing.

This requirement has a direct bearing on the preparation of the regulatory dossier, where the applicant will need to actively demonstrate compliance with the 3Rs principle, which will entail documenting the alternatives considered and the reasons why they were not adopted, where applicable.

Furthermore, the possibility of an MA being granted subject to a condition means that the replacement of animal testing may continue to be promoted after the medicinal product's authorisation.

7. Next Steps

Although the legislative process has yet to be concluded, the direction of travel is clear: the European pharmaceutical framework is moving towards a progressive integration of non-animal methods into regulatory assessment, keeping pace with scientific developments and a growing ethical and social demand.

The practical effectiveness of these provisions will depend, above all, on the scientific guidance the EMA develops and on the pace of regulatory acceptance of the new methods, in a context where science frequently advances faster than established validation frameworks.

Thinking about tomorrow? Let's talk today.

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