Position paper by Prescrire about Biotech act regulation proposal

Proposal for a regulation establishing a framework of measures for strengthening Union's biotechnology and biomanufacturing sectors particularly in the area of health (COM(2025) 1022 final – 2025/0406(COD))

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General comment

With this proposed Biotech Act regulation, the European Commission aims to strengthen the competitiveness of the health biotechnology sector in the European Union. However, following the analysis carried out by Prescrire, it appears that a number of proposals risk undermining the protection of human health. This appears to be in contradiction with Article 168 of the Treaty on the Functioning of the European Union, which stipulates that "*A high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities*. "

This position paper focuses on three points:

1) The revision of the clinical trial regulation
2) The extension of the supplementary protection certificate (SPC)
3) Regulatory sandboxes

Article 58 (*pages 121 to 160*) of the proposal is amending the clinical trial regulation 536/2014. These amendments place considerable emphasis on measures designed to streamline the process for clinical trial sponsors, whilst showing a worrying neglect for the protection of clinical trial participants and the production of high-quality clinical data.

The Article 27 (*p94*) proposal to extend the supplementary protection certificate (SPC) for certain biotechnology-derived medicines by one year will result in considerable additional costs for Member States' healthcare systems, due to the delay in bringing less expensive biosimilar medicines to market. This could undermine solidarity-based healthcare systems and penalise the biosimilar industry, which is crucial for public health and the biotechnology sector. Consequently, Prescrire opposes Article 27.

Regulatory sandboxes undermine the current framework of bringing health products on the market and raise numerous concerns from a public health perspective. Prescrire therefore opposes Articles 39 and 40 (*p102-105*).

Clinical trials

Few positive proposals

We note two positive measures in this Biotech act proposal:

- The introduction of an ethical review of part 1 of the assessment report (scientific aspects) in the authorisation procedure of multinational clinical trials carried out by the ethics committee of the reporting Member state *(art 58(5) p128 concerning paragraph 2 of replaced article 6 of regulation 536/2014).*
- The establishment of a regulatory framework under legislation on clinical trials for health products which combine a medicine with a medical device or an in vitro medical device *(art 58(13) concerning the proposed new article 14c p137-138*). This could improve the assessment of the later.

Stronger focus on comparative clinical trials to demonstrate clinical progress for patient instead of overuse clinical trials against placebo

All too often, sponsors choose to conduct placebo-controlled clinical trials to test a new experimental drug, even though a standard of care is already available. This is unethical for subjects in the control arm, as they cannot benefit from the best existing therapeutic option, as stated in Article 33 of the 2024 version of the Declaration of Helsinki. Furthermore, this prevents the clinical trial from demonstrating that the experimental drug represents a potential advance for future patients, compared with the standard of care. The Biotech act should specify the exceptional situations in which the use of a placebo could be authorised when a proven treatment already exists.

A clinical trial for a previously authorised medicine doesn't always mean that there are less risks for participants

The regulation proposal distinguishes "minimal intervention trials" from "low intervention trial" (*articles 58(1a) and 58(1b) p 121*). This kind of trials apply to investigational medicinal products previously authorised as medicines and respectively used in a clinical trial within the same indication as the previous authorisation ("minimal") or off-label ("low").

New authorised cancer drugs are for example often firstly authorised in a very limited patient population. At this stage often important uncertainties in the efficacy and the safety profile of the drug remain due to a lack of evidence, and especially when a conditional marketing authorisation is granted. Therefore, data from other clinical trials are needed to reduce uncertainties ("minimal intervention trial"). After a first authorisation in a specific indication, companies try to increase the number of indications of the drugs and carry out new clinical trials to achieve it ("low intervention trial"). At this stage however, not all adverse effects of a drug are well known and other adverse effects may appear in other patient populations. Therefore, in those situations, the level of risk to participants in minimal and low intervention trials may be similar to that in common trials. We therefore recommend to exclude low and minimal intervention trials for products covered by a conditional marketing authorisation or a marketing authorisation granted under exceptional circumstances, because these types of marketing authorisation are usually associated with high uncertainties about adverse events.

To guarantee a similar level of protection to clinical trial participants in all clinical trials and to avoid a quality decrease of available clinical data we recommend to delete some proposals:

- The potential lowering of requirements for the application dossier of low and minimal intervention clinical trials (*Recital 138 p62 and art 58(23)(b), art 58(23)(c) p145*).
- The potential lowering of reporting requirements of adverse events for minimal and low intervention clinical trials (*Recital 138 p62 and art 58(31) p150*).
- The introduction of a regulatory sandbox framework that provides for adjustments and exemptions to allow clinical trials that cannot be conducted under the standard procedure (*Art 58(24) concerning the proposed new chapter IVb p147-149*).

Speed up of clinical trials authorisation processes and oversight power reduction of member states concerned for multinational trials: a risk for the safety of clinical trial participants and for quality of data

The time taken for the clinical trial authorisation process accounts for only a small part of the total time to conduct clinical trials. Whilst the authorisation process takes only a few months (between two and five months under current legislation), the duration of a clinical trial takes usually several years. These few months are crucial in assessing whether the clinical trial will adequately protect the rights, safety, dignity and well-being of participants, and whether the data collected will be reliable and robust. This process should also ensure that participants' interests take precedence over all other interests, and this requires sufficient time.

The Biotech act proposal includes important reductions in clinical trial authorisation procedural time limits which can lead to a lack of time to carry out a thorough assessment (*Recitals 122-129 p58-60 and art 58(4-6) p125-131 ,art 58(11) p 133-135 ,art58(16-21) p140-144*). The removal of the possible additional 50 days for the assessment report of part I (scientific aspects of the clinical trial) for an initial application dossier or a substantial modification in order to consult specialists for investigational medicines produced with biotechnological processes or "advanced therapy investigational medicinal products" is especially concerning (*art 58(5) p126-129 and art 58(17) p140-141 amending art 6§7 p10 and art 18§5 p20 of regulation 536/2014*). In the current clinical trial legislation, the approval decision falls to the reporting Member state if the Member state concerned fails to notify the sponsor of his decision in due time. There is a tacit approval for a substantial modification of part II (ethical aspects of the clinical trial) when a member state concerned doesn't notify the sponsor of its decision in due time. The reduction of procedural time could therefore lead member states concerned to do a minimal assessment to comply with deadlines. Participants' interests and the quality of data produced by clinical trials could suffer as a result. Taking all these factors into account, we oppose any measures aimed at speeding up the clinical trials authorisation procedures putting at risk participants safety protection and leading to a data quality decline, particularly if additional resources are not made available to regulatory authorities and ethic committees. The procedural time limits set out in Regulation 536/2014 should be retained.

	Clinical trial Regulation 536/2014	Biotech act proposal
Time limit for initial authorisation	**From 75 days to 106 days** (**+ 50 days** to consult specialists for "*advanced therapy investigational medicinal products*" or investigational medicines produced with biotechnological processes)	**From 47 days to 75 days**
Time limit for substantial modification	**From 64 days to 96 days** (**+ 50 days** to consult specialists for "*advanced therapy investigational medicinal products*" or investigational medicines produced with biotechnological processes)	**From 33 days to 47 days**

The Biotech act regulation proposal introduces the possibility of parallel substantial modifications in clinical trials (*art 58(15) p139*). This means that the sponsor could submit multiple requests for substantial modifications, which would be assessed simultaneously within a limited timeframe, resulting in an increased workload for regulatory authorities and ethic committees. After the start of a clinical trial, any modification in the conduct, design, methodology, investigational or auxiliary medicinal product can impair the data reliability and robustness. Substantial modifications should therefore be exceptional. Parallel substantial modifications aren't advisable because they could increase the number of such drawbacks.

Under this Biotech act regulation proposal, the decision on whether to classify a clinical trial as 'minimal intervention' or 'low intervention', if requested by the sponsor, would be taken at an early stage during the application dossier validation phase, under the single responsibility of the reporting Member state within 7 days after the dossier submission by the sponsor (*art 58(4) p125-126 according the proposed new article 5b*). Under current legislation, this decision to classify a clinical trial as 'low intervention' is made during the assessment of aspects covered by part I (scientific aspects) (*art 6 §1 of regulation 536/2014 p8*). This kind of decision requires scientific expertise, and the current procedures should therefore be maintained.

This Biotech act regulation proposal aims to give a stronger leading role to the reporting Member State in multinational clinical trials but this leads to reducing Member states concerned responsibilities who should in the contrary stay to be involved in all aspects of a clinical trial conducted in his country. Furthermore, the double-check carry out by Member states concerned is useful for the assessment of clinical trial authorisation and shouldn't be weaken. Prescrire is therefore opposing:

- the removal of the Member state concerned review for other considerations than ethical aspects during the assessment of Part I for minimal intervention trial (*art 58(5) p129 concerning proposed new paragraph 5a of replaced article 6 of regulation 536/2014*);

- the possibility for a Member state concerned to rely on the ethical review of the ethic committee of the reporting Member state for the assessment of part II (*art 58(6) p130 concerning paragraph 2 of replaced article 7 of regulation 536/2014*);
- the removal of item c) of article 8§2 in regulation 536/2014 "**considerations as regards subject safety and data reliability and robustness submitted".** This removes the possibility for a Member state concerned to oppose the reporting Member state conclusion on the ground of the considerations mentioned above (*art 58(7) p131 and same amendment in art58(13) p137-138 concerning proposed new article 14c, art 58(18) p142 ,art 58(22) p144*).

Inclusion of vulnerable participants in clinical trials

Article 58(28) (*p150*) does not provide sufficient protection for incapacitated subjects and does not adequately reflect Article 20 of the 2024 version of the Declaration of Helsinki. Point e) shouldn't be deleted but amended as follows: "the clinical trial is essential with respect to incapacitated subjects and data of comparable validity cannot be obtained in clinical trials on persons able to give informed consent, or by other research methods**, or when excluding them would perpetuate or exacerbate their marginalisation";**

In order not to undermine the protection of minors participating in clinical trials we oppose article 58(29) (*p150*) which is contradictory to Article 19 and 20 of the 2024 version of the Declaration of Helsinki. From this point of view, we consider ethically appropriate to conduct a clinical trial involving participants who are minors only if the trial is intended to investigate treatments for a medical condition that occurs exclusively in minors, or if the trial is essential in relation to minors in order to validate data obtained from clinical trials involving individuals capable of giving informed consent or through other research methods.

We welcome the amendment (*art58(30) p150*) which states that women who become pregnant or begin breastfeeding while participating in a clinical trial shall not be automatically excluded from participation, but this amendment isn't enough regarding person protection in clinical trials. Indeed, such possibility must be included right from the start in the clinical trial protocol and the woman must be informed of this possibility before inclusion. When a woman becomes pregnant or begins breastfeeding while participating in a clinical trial the benefit-risk of the experimental drug changes for the woman and must from then on include the embryo, the foetus or the child after birth as appropriate. It is therefore essential to seek the woman's written informed consent once again.

Artificial intelligence in clinical trials *(art 58(24) page 149 on proposed new article 27e)*

Given that the AI tools currently available have certain limitations and may, in some cases, be a source of errors, participants should be provided with specific information about these limitations and the associated risks.

Extension of the supplementary protection certificate (SPC): a burden on EU healthcare systems, undermining their sustainability

Prescrire opposes the one-year extension of the supplementary protection certificate, as proposed in Recital 57 (*p43*) and Article 27 (*p94*), given the unacceptable financial burden for EU solidarity-based

health systems and possible access problems for patients. This proposal is solely in the interest of biopharmaceutical industry with strong negative impacts on health systems, patients and the European society.

After difficult discussions, recently the Council, the European Parliament and the Commission just adopted a deal on regulatory protection rules and intellectual property provisions in the pharmaceutical package. To us, open again these discussions would clearly show that all is solely about industry interests without any regard for patients and the general interest. Extending the duration of the supplementary protection certificate would increase the pressure on healthcare systems and jeopardize their sustainability and probably restrict patient access. Furthermore, this would delay the arrival of biosimilars, which are significantly less expensive, and would further penalize the biosimilars industry, which is nonetheless crucial to the biotechnology sector and public health.

Regulatory sandboxes for health biotechnology products *(Recitals 79 and 80 page 49 + articles 39 and 40 pages 102-105)*

Regulatory sandboxes raise numerous concerns from a public health perspective. It should be underlined, whatever the new health technology product, EU legislation has to align with article 168(1) of the Treaty on functioning of the European Union calling on EU policies and activities to ensure a high level of human health protection. Regulatory sandboxes undermine the current framework of bringing health products on the market. It paves the way for increased deregulation of authorisation procedures of health products by putting the Commission and competent authorities in conflicting roles. Consequently, Prescrire opposes the use of regulatory sandboxes in healthcare. However, if legislators wish to retain such legislative tool in the future Biotech Act, we would like to highlight certain points requiring attention.

Article 39 insists on various consultations regarding the design and the implementation of regulatory sandboxes. For transparency reasons, the exchange of information should be made publicly available through the Commission website.

Article 40 §7 points out that the developer remains liable under applicable national legislation for any harm inflicted on third parties as a result of the testing taking place in the sandbox. The sandbox regime is described as a controlled regulatory environment for the testing and development of health biotechnology products. As this pathway seems different from clinical trials, in the interest of patients, healthcare professionals and any third party who might be harmed, it should be clarified which national legislation should apply for compensation of victims. It is paramount that this regulation ensures that all participants provide their explicit informed consent to participate in this regulatory pathway and are fully informed about the sandboxes including the exceptions with the normal regulatory framework.

For transparency and accountability reasons, the Commission shall (and not may) publish a report on the lessons learned from the regulatory sandbox (article 40§11).

We want to highlight the importance of maintaining the requirement for solid efficacy evidence before a health product is approved for marketing as the cornerstone of pharmaceutical and health

biotechnology products regulations. The requirement for pre-market efficacy and safety evidence is an important health protection measure, as it prevents harmful exposures.

Conclusion

On some parts, the scope of the proposed Biotech act goes largely beyond the biotechnology sector in particular the many far-reaching amendments relating to clinical trials Regulation No 536/2014. The weakening of this regulation based on the proposed Biotech act will have an important negative impact on all medicines and not only on biotechnology products. The protection of public health, patients and clinical trial participant is of paramount importance and needs to be clearly secured in the European legislation and policies. Prescrire's proposals put forward above are guided by this approach, and we sincerely hope that the co-legislators will take it into account.

About Prescrire

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