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Concept paper on the development of a reflection paper on the non-clinical requirements for severely debilitating or life-threatening diseases

Agreed by Non-clinical Working Party	April 2026
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Start of public consultation	30 July 2026
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Keywords	Non-clinical safety; severely debilitating or life-threatening diseases; tailored non-clinical programmes; 3Rs; NAMs; Weight of evidence approaches;

1. Introduction

Seriously debilitating or life-threatening conditions are those associated with morbidity that has substantial impact on patients' day-to-day functioning and will progress if left untreated, or those associated with a high likelihood of mortality (1). There is currently no European Medicines Agency (EMA) position on how deviations from the core non-clinical ICH guidelines, M3 (2) or S6 (3), could be used to accelerate the development of therapeutics for severely debilitating or life-threatening diseases outside of the scope of ICH S9 (4). A reflection paper would facilitate development of medicinal products in this area, help harmonise non-clinical development, support marketing authorisation applications and earlier patient access to potentially life altering or saving therapies, particularly in those indications where there is an unmet medical need.

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2. Problem statement

In the oncology setting, ICH S9 has served to facilitate faster clinical development while ensuring patient safety. However, outside of oncology there is an absence of regulatory guidance for the non-clinical development of medicinal products for the treatment of other severely debilitating or life-threatening diseases. Currently, deviations from the requirements of ICH M3(R2)/ICH S6(R1)are discussed on an individual basis which can result in inconsistency in evaluations and lack of harmonisation with regards the necessity of non-clinical studies.

Previous literature has argued that a tailored approach could accelerate access to medicinal products intended to treat severely debilitating or life-threatening diseases without compromising on patient safety (5). More recent experience during the Covid-19 pandemic has provided insight of when a tailored approach can inform on strategies to facilitate rapid non-clinical safety evaluation, suggesting that some of the principles used could be applied to other life-threatening diseases. Such approaches could have significant benefits in terms of reducing the timelines for marketing application and accelerate patient access to vital therapies. Furthermore, it would align with the 3R principles: replacing, reducing and refining use whenever appropriate.

The reflection paper will develop and outline general principles for when flexibility and deviations from the requirements of ICH M3 (R2)/ICH S6 (R1) could be appropriate in the context of a medicinal product being developed to treat a severely debilitating and life-threatening disease. In light of the existing ICH S9 guideline and associated Q&A (6) on non-clinical evaluation of medicinal products for the treatment of advanced cancer, such medicinal products would be considered out of scope of the proposed reflection paper.

3. Discussion (on the problem statement)

The non-clinical toxicology studies that are required for the conduct of clinical trials and marketing authorisation are outlined in ICH M3 (R2) and ICH S6 (R1). Although ICH M3 (R2) mentions the potential for flexibilities in the toxicological evaluation for pharmaceuticals intended for life threatening or serious diseases, there is limited guidance on how this may be implemented. The reflection paper will aim to consolidate the regulatory view, taking into account regulatory experience from scientific advice and marketing authorisation applications, and describe a rationale that could be acceptable for a tailored non-clinical testing program. The reflection paper will place strong emphasis on the 3Rs.

The reflection paper will aim to outline:

- Examples of cases where these considerations could be applicable. Opportunities to apply a stream-lined non-clinical package to the development of products for life-threatening or severely debilitating diseases.
- Circumstances where safety testing in line with ICH M3 (R2)/ICH S6 (R1) could remain appropriate e.g. instance in which chronic toxicity studies may be warranted.
- Considerations with regards to the timing and duration of non-clinical studies for clinical trial and marketing authorisation applications e.g. possibilities for deferring studies.
- How to apply weight of evidence (WoE) approaches, modality-specific considerations e.g. small molecules versus biologics and leverage opportunities where data from similar in-class products or platform(s) exist to inform on the safety assessment
- The role of novel approach methods (NAMs) to complement WoE approaches and to comply with the 3Rs principle.

To ensure harmonisation between regulators and developers, interactions with the EMA or national competent authorities (NCAs) will be necessary during development when a tailored non-clinical package is proposed, for example through scientific advice or other appropriate means.

4. Recommendation

The Non-clinical Working Party (NcWP) of the Committee for Human Medicinal Products (CHMP) recommends drafting a new reflection paper on the non-clinical requirements for severely debilitating or life-threatening diseases.

A reflection paper is considered the most appropriate form of guidance and will take into account the issues outlined in section 3.

5. Proposed timetable

It is planned to release a draft reflection paper for consultation in Q3 2027. The concept paper will be published for a two-month public consultation period. NcWP will take into account all comments received during the public consultation on the concept paper when preparing the draft reflection paper.

6. Resource requirements for preparation

The drafting of the new reflection paper will involve establishment of a Drafting Group consisting of members of the NcWP (including one Rapporteur). It is anticipated that at least one plenary session discussion at the NcWP will be needed. The NcWP together with the 3RsWP will draft the document. The Scientific Advice Working Party (SAWP) and the Emergency Task Force (ETF) will be consulted on the draft reflection paper before its release for public consultation. The draft reflection paper will then be adopted by the CHMP for the public consultation.

7. Impact assessment (anticipated)

Regulatory acceptance of a streamlined approach, using a tailored non-clinical strategy to characterise the safety of a molecule, resulting in increasing harmonisation in the evaluation of applications in indications that are identified as severely debilitating or life-threatening. Such a tailored non-clinical strategy that is sufficient to identify relevant risks, can support earlier patient access to new medicinal products.

From the standpoint of the 3Rs, there is scope to reduce the non-clinical study burden for medicinal products developed for severely debilitating or life-threatening diseases. This would reduce the number of animals used without compromising the requirement for a non-clinical toxicity package that adequately characterises relevant safety risks.

8. Interested parties

Pharmaceutical Industry, contract research organisations, Academia, EU NCAs and patient and health care professional groups. Consultation with other working parties or committees will be initiated, as appropriate.

9. References to literature, guidelines, etc.

1. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on compassionate use of medicinal products, pursuant to Article 83 of Regulation (EC) No 726/2004 https://www.ema.europa.eu/docum ents/regulatory-procedural-guide line/guideline-compassionate-use-medicinal-products-pursuant-article-83-regulation-ec-no-726/2004_en.pdf

2. ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m3r2-non-clinical-safety-studies-conduct-human-clinical-trials-and-marketing-authorisation-pharmaceuticals-step-5_en.pdf

3. ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals https://www.ema.europa.eu/en/documents/scientific-guideline/ich-s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals-step-5_en.pdf

4. ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-s9-non-clinical-evaluation-anticancer-pharmaceuticals-step-5_en.pdf

5. Prescott J.S., Andrews P.A., Baker R.W. *et al*. Evaluation of Therapeutics for Advanced-Stage Heart Failure and Other Severely-Debilitating or Life-Threatening Diseases. *Clinical Pharmacology & Therapeutics*. 102: 219-227 (2017). https://doi:10.1002/cpt.730

6. ICH S9 guideline on nonclinical evaluation for anticancer pharmaceuticals - questions and answers https://www.ema.europa.eu/en/documents/scientific-guideline/ich-s9-guideline-nonclinical-evaluation-anticancer-pharmaceuticals-questions-and-answers-step-5_en.pdf