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Concept paper on the development of a reflection paper on the non-clinical development and evaluation of microbiome-based medicinal products

Draft

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1. Introduction

Microbiome-based medicinal products (MMPs) represent an innovative class of therapeutics originating from microbiomes (human, food-related and/or environmental). They are intended to treat or prevent diseases by modulating the human microbiome, such as immune-mediated disorders, recurrent or treatment-resistant infections, metabolic disorders and selected cancer indications (Kinross et al., 2011; de Vos et al., 2022; Yaqub et al., 2025). Among the key concepts in this field is the term microbiota, which refers to the community of microorganisms inhabiting a specific environment, such as the gut, skin, oral cavity or vaginal cavity. These communities typically include bacteria, archaea, fungi, and protozoa (Berg et al., 2020). Depending on the definition used, viruses and bacteriophages may also be considered part of the microbiota (Hou et al., 2022; Salvadori & Rosso, 2024). In contrast, the term 'microbiome' encompasses not only these microbial communities, but also their collective genetic material (genomes), their derivates, and the interactions they have with each other and with their surrounding environment.

Unlike standard pharmaceuticals, MMPs may consist of live or non-living microorganisms or their derivatives. These products can modulate the human microbiome through diverse mechanisms, which vary depending on the strain of microorganism and the site of administration. This complexity introduces unique challenges for non-clinical evaluation. The European Medicines Agency (EMA) recognizes the growing interest and rapid development in this field and acknowledges the need for regulatory guidance to ensure a harmonized approach to non-clinical development and evaluation.

The objective of this concept paper is to identify aspects specific to MMPs that need to be addressed in a dedicated reflection paper. This reflection paper will outline the current thinking on the non-clinical evaluation of MMPs and support a harmonized approach across the European Union for clinical trials and marketing authorisation applications, as per Directive 2001/83 on medicinal products.

Scope

MMPs are currently regulated under multiple legislative frameworks in the European Union, including Directive 2001/83/EC on medicinal products, and where applicable, the Regulation (EC) No 1394/2007 on advanced therapy medicinal products (ATMPs).

The following table provides an illustrative, non-exhaustive list of product types and examples that fall within the scope of the reflection paper.

Product Type	**Examples**
Live Biotherapeutic Products (LBPs)	Single or mixed live bacteria/yeasts
Whole/Highly Complex Ecosystem-based products	Non-ATMP Substances of Human Origin (SoHO)-derived medicinal products
Non-living MMPs	Inanimate cells

Due to the heterogeneity of MMPs, the following products are intended to be outside the scope of the reflection paper:

- Human Microbiota Transplantation (fecal or other) as a procedure involving administration of Substances of Human Origin (SoHO) preparation, as defined by Regulation (EU) 2024/1938 on standards of quality and safety for substances of human origin intended for human application (SoHO Regulation).

- MMPs containing genetically modified microorganisms as active substances, classified as ATMPs (Regulation (EC) No 1394/2007).
- Products containing microorganisms but not intended to prevent or treat disease, such as food supplements containing probiotic strains, and fermented-food cultures, which fall under nutritional or food categories.
- Microorganisms used in vaccines or other standard immunological products, which are not considered microbiome-based and whose mechanism of action does not involve modulation of the human microbiome.
- Phage therapy and other virome-based approaches due to distinct scientific and regulatory considerations compared to MMPs. However, the potential relevance of phage therapy is acknowledged, and it might be considered in future discussions or addressed in a separate concept or reflection paper.

2. Problem statement

The development and evaluation of MMPs pose unique regulatory and scientific challenges that are insufficiently addressed by existing guidelines, which were primarily designed for standard pharmaceuticals (including biologics) and ATMPs (Rodriguez et al. 2025). There is increasing interest from both healthcare providers and the pharmaceutical industry in the use of MMPs to address medical needs unmet by standard treatments.

Currently, there is no regulatory framework for the non-clinical evaluation of MMPs. Conventional pharmacological and toxicological approaches are often not fully applicable, particularly regarding biodistribution, safety, and the use of standard in vivo pharmacodynamic models to support dose selection and efficacy evaluation. The absence of tailored guidance may lead to increased uncertainty for developers, inconsistencies in regulatory submissions and evaluation, and potential delays in product development.

3. Discussion (on the problem statement)

MMPs differ from other medicinal products in various terms and therefore, specific considerations need to be taken into account for their non-clinical evaluation. The proposed reflection paper will address the following aspects:

- Product diversity: MMPs can vary from fixed product compositions to tailored microbial consortia assembled for specific therapeutic purposes. Distinctions in non-clinical development and evaluation approaches may be needed for each product type.
- Target diversity: MMPs exert their biological effect on host physiology via modulation of the microbiome-host interaction and may target any human-associated microbiome, including but not limited to the gut, skin, oral, respiratory, urogenital, and nasal microbiomes.
- Pharmacological models: Standard animal disease models may lack relevance for MMPs due to species-specific microbiome effects and limited translatability. Alternative models and New Approach Methodologies (NAMs) may be considered.
- Safety considerations: MMPs present unique safety challenges, and conventional toxicity testing approaches may not be appropriate. Careful consideration is required regarding biodistribution (including potential translocation), persistence, degradation or elimination pathways, and the possibility of shedding.

To address these issues, the concept paper proposes development of a reflection paper that defines regulatory science needs, consults widely with stakeholders, and supports an adapted non-clinical evaluation approach for MMPs. This effort aims to facilitate responsible innovation while safeguarding public health, creating a flexible yet robust framework that can adapt to ongoing scientific developments.

4. Recommendation

The Non-Clinical Working Party (NcWP) recommends drafting a reflection paper which outlines current thinking on the non-clinical development and evaluation of MMPs and supports a harmonized approach across the European Union for clinical trials and marketing authorisation. The reflection paper will address the issues identified above and provide recommendations on emerging issues in view of future developments and changing practices in the field of MMPs.

5. Proposed timetable

The concept paper will be published for a two-month public consultation period, to incorporate stakeholder feedback and ensure broad applicability. The NcWP will consider all comments received during the public consultation on the concept paper when preparing the draft reflection paper.

6. Resource requirements for preparation

The development of the reflection paper will involve NcWP, EMA Borderline classification group (BLCG), 3Rs Working Party, Quality Working Party (QWP), Clinical Trials Coordination Group (CTCG) and the temporary Drafting Group appointed by the NcWP.

7. Impact assessment (anticipated)

The proposed reflection paper on the non-clinical development and evaluation of microbiome-based medicinal products will address specific regulatory and scientific aspects of MMPs regarding the non-clinical package necessary for clinical trials and marketing authorisation applications. The reflection paper is expected to:

- Enhance regulatory clarity for developers of MMPs.
- Promote harmonized non-clinical evaluation across the EU.
- Reduce unnecessary use of animals to assess the pharmacology and safety of MMPs.
- Reduce uncertainty and potential delays in product development.
- Encourage innovation by supporting flexible, science-based approaches.
- Improve patient safety by ensuring rigorous evaluation of novel MMPs.

8. Interested parties

The following stakeholders are invited to contribute to the development and consultation process:

- Pharmaceutical industry
- Academia and research institutions
- National competent authorities
- EU Agencies and institutions, such as the European Centre for Disease Prevention and Control (ECDC), the European Directorate for the Quality of Medicines and HealthCare (EDQM), and the European Food Safety Authority (EFSA)
- Patient organizations
- Healthcare professionals

9. References to literature, guidelines, etc.

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