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Committee for Medicinal Products for Human Use (CHMP)
Committee for Veterinary Medicinal Products (CVMP)

Concept paper on the revision of the Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)

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Agreed by the Non-Clinical Working Party	June 2023
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Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support .

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1. Introduction

The Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012) was adopted almost 7 years ago. This guideline aims to encourage stakeholders and authorities to initiate, support and accept development and use of 3Rs testing approaches with the aim to replace, reduce and refine in vivo animal studies for human and veterinary medicinal products.

At the time of its implementation, this guideline provided not only a definition of what is understood by regulatory acceptance of 3R testing approaches, but also provided guidance on the scientific and technical criteria for regulatory acceptance of 3Rs testing approaches. Pathways for regulatory acceptance of 3Rs testing approaches, as well as procedures for submission and evaluation of a proposal for regulatory acceptance of 3Rs testing approaches were described.

Since its implementation, scientific, technological and regulatory knowledge on 3R testing approaches, as for example in the field of microphysiological systems (MPS[1]), including organ-on-chip models (OoC), has significantly evolved. Consequently, there is a need for more specific guidance to define the regulatory acceptance criteria for specific models, such as MPS, including OoC models, for specific contexts of use (COU) to be applied in the pharmaceutical area. This specific guidance will be included as annexed information to the revised guideline and is intended to assist in the development and potential regulatory use of these New Approach Methodologies (NAMs). This approach will enable the necessary flexibility for future updating as a function of the scientific, technological progress in the field.

In addition, there is a need for defining the most important 3Rs-related terms to act as the basis for the drafting of EMA documents in the field of NAMs and to fully inform all involved stakeholders. This will be expanded upon in a new dedicated section in the guideline.

2. Problem statement

The revision of the guideline for the principles of regulatory acceptance of 3Rs testing approaches will focus on the provision of a section on 3Rs terminology that is currently lacking in the document, as well as annexed guidance for regulatory acceptance of MPS, including OoC models, for specific COUs to be applied in the pharmaceutical area.

Currently a large variety of definitions exist for a wide range of 3Rs-related terms. To facilitate drafting of EMA documents in the field, and to fully inform and align all relevant stakeholders, a clear definition of 3Rs-related terms should be established. Specifically, to enable description of regulatory requirements for qualification of NAMs, terms should be clearly defined. This revision aims to provide EMA's definition of critical 3Rs-related terminology.

A second aim of the revision is to provide, as annexed information, more specific guidance on regulatory acceptance criteria for developers of MPS in specific COUs.

[1] Microphysiological systems (MPS) are microfluidic devices capable of emulating human (or any other animal species') biology in vitro at the smallest biologically acceptable scale, defined by purpose. The application of fluid flow (dynamic) for the physiological nutrition of the tissues and the creation of microenvironmental biomolecular gradients and relevant mechanical cues (e.g., shear stress) is a major aspect of these systems, differentiating them from conventional (static) cell and tissue cultures. An MPS-based organ model or Organ-on-Chip (OoC) is a fit-for-purpose microfluidic device, containing living engineered organ substructures in a controlled microenvironment, that recapitulates one or more aspects of the organ's dynamics, functionality and (patho)physiological response in vivo under real-time monitoring. Organoid-on-chip, spheroid-on-chip and tissue chip are subsets of the term organ-on-chip specifying that the organ model is an organoid, a spheroid or a tissue, respectively. (Marx et al, 2020)

MPS models may offer unique insights into drug safety assessment and could be more predictive of *in vivo* biology than the *in vitro* and *in vivo* models currently used in drug discovery and development. These models could potentially increase the reliability of the prediction of both efficacy and safety of new medicinal products and hence not only improve translational success of drug candidates into the clinic, but also impact the 3Rs in non-clinical safety testing. (Baran et al., 2022)

Incorporation of these new technologies into drug development is deemed challenging with one of the most critical hurdles being the establishment of robust qualification packages built around specific COUs. In addition, it should be noted that the extent of qualification requirements may vary depending upon both the COU and how the data obtained will be used for decision making.

In order to encourage and facilitate the further development and regulatory acceptance of MPS models, the availability of COU-specific qualification criteria is considered critical.

Consequently, the scope of both annexes will be limited to the aspects related to COU-based qualification for safety testing (safety pharmacology and/or toxicity testing) of human medicinal products. Aspects pertaining to standardisation (technical and biological) of MPS, including OoC, will not be addressed.

3. Discussion (on the problem statement)

A stepwise process is proposed by the 3RsWP to support the revision of the guideline on the principles of regulatory acceptance of 3Rs testing approaches, including the drafting of the annexes that will define regulatory acceptance criteria for MPS and an additional section of the guideline on 3Rs terminology:

1. Endorsement of the Concept Paper by the Non-clinical Working Party (NcWP), CHMP, and CVMP.
2. Set up of a drafting group for the revision of the guideline. Members are to be drawn from the Non-clinical and New Approach Methodologies European Specialised Expert Community (NC NAMs ESEC), which comprises all members of the 3RsWP, the NcWP and the veterinary Safety Working Party (SWP-V), as well as additional experts whose membership has been endorsed by both CHMP and CVMP.
3. Organisation of multistakeholder workshop(s) focused on generating the necessary input for the drafting of the annexes to define regulatory acceptance criteria for MPS, including OoC models, for specific COUs to be applied in the pharmaceutical area, encompassing targeted discussions on performance criteria, selection of reference compounds (and underlying data requirements), detailed description of COUs, gold standards, exposure modelling (quantitative in vitro in vivo extrapolation, QIVIVE) etc. It will need to be discussed/decided whether both COUs will be tackled in 1 workshop with 2 breakout sessions or whether separate workshops would be needed per COU.
4. Start-up of 1 or 2 drafting subgroups for the annexes to define regulatory acceptance criteria for MPS, including OoC models, for specific COU to be applied in the pharmaceutical area.

The 3RsWP will oversee and support the drafting groups by:

- Establishing of a general roadmap for qualification of NAMs (using the process followed here as a blueprint and finetuning based on accumulated experience).
- Organising a preparatory meeting to establish the sequence of events, the detailed scope of the annexes, the expertise needs per annex and the agenda for multistakeholder COU-based workshop(s).

4. Recommendation

The Joint CHMP and CVMP 3RsWP recommends the revision of the Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches, to include a new section on 3Rs-related terminology and two annexes on regulatory acceptance criteria for MPS, including OoC technologies for specific COUs to be applied in the pharmaceutical area.

Considering the state of the art of MPS, including OoC technologies, the current large-scale initiatives related to performance assessment of MPS (e.g. IQ MPS Affiliate - https://www.iqmps.org/; EUROoCs - https://euroocs.eu/), the main causes of safety-related drug attrition, and the current regulatory guidances (e.g. Q&A ICH S7B/E14), it is deemed most appropriate to aim in a first instance for the development of two annexes pertaining to:

- Liver-on-chip COU of predicting drug-induced liver injury (cf. Ewart et al. 2022)
- Heart-on-chip COU of safety pharmacology testing (cf. ICH S7B/E14 Q&A)

Consideration will be given in the annexes to the internationally harmonised qualification criteria established in the context of ICH S5(R3).

The drafting of these annexes will be based on scientific review and stakeholder consultation during targeted workshops.

5. Proposed timetable

First revision of the Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches to include a new section on 3R's-related terminology:

It is anticipated that the draft revised guideline including the new section on 3Rs-related terminology will be published 6 months after the end of the public consultation of this concept paper. The draft revised guideline including this new section on 3Rs-related terminology will be released for a 3-month consultation.

Second revision of the Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches to include annexes on regulatory acceptance criteria for MPS, including OoC models for a specific COU to be applied in the pharmaceutical area:

It is anticipated that a draft annex on regulatory acceptance criteria for MPS, including OoC models for a first COU will be available 18 months after the end of the public consultation of this concept paper. The selection of either the liver-on-chip or heart-on-chip will be driven by the outcome of the scientific review and stakeholder consultation during the targeted workshops. The draft revised guideline including this annex on the regulatory acceptance criteria for MPS, including OoC models for the first COU will be released for a 3-month consultation.

A draft annex on regulatory acceptance criteria for MPS, including OoC models for a second COU will build on the learnings achieved with the first one and a timetable on the availability of this second draft annex will be identified accordingly.

In the future, additional annexes on regulatory acceptance criteria for additional models for other COUs will be developed as needed.

6. Resource requirements for preparation

The revision of the Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches and the preparation of annexes on regulatory acceptance criteria for MPS, including OoC models, will involve specific expertise and consultation needs:

- Interested members of NcWP & 3RsWP: COU-specific knowledge (e.g. cardiovascular safety pharmacology, liver toxicity), qualification-knowledge (e.g. related to ICH S5(R3), ICH S7/E14 Q&A), MPS/OoC knowledge
- NC NAMs ESEC: COU-specific knowledge (e.g. cardiovascular safety pharmacology, liver toxicity), qualification-knowledge (e.g. related to ICH S5(R3), ICH S7/E14 Q&A), MPS/OoC knowledge
- EU Reference Laboratory for alternatives to animal testing (EURL-ECVAM): input focused on 3Rs terminology and qualification within a particular COU
- Methodology Working Party (MWP): e.g. QIVIVE extrapolation modelling

7. Impact assessment (anticipated)

The revision of the Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches and the annexes on regulatory acceptance criteria for MPS, including OoC models are anticipated to provide harmonised agreements on 3Rs-related terminology and on regulatory acceptance criteria for MPS, including OoC models for specific COU for use by end-users (e.g. pharmaceutical industry) and other interested parties (e.g. Contract Research Organisations, method developers, etc.) to support the development and qualification of 3Rs testing approaches, including MPS and OoC models, and to foster uptake of these methods in regulatory submissions.

8. Interested parties

NcWP, NC & NAM ESEC, EURL-ECVAM, MWP

Considering the importance of global harmonisation of qualification criteria for MPS/OoC for a specific COU, FDA will be liaised with.

9. References to literature, guidelines, etc.

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