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SCIENCE MEDICINES HEALTH

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Human Medicines Research and Development Support Division

Meeting Report:
First EMA workshop on non-animal approaches in support of medicinal product development – challenges and opportunities for use of micro-physiological systems (EMA/CHMP/SWP/250438/2018)

5 October 2017, European Medicines Agency, London

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Objectives of the workshop

On the 5th of October 2017, the European Medicines Agency organised a workshop on organs-on-chip or micro-physiological systems (MPS). MPS represent a rapidly progressing and promising field for the replacement, reduction and refinement of animal experimental testing (the 3Rs principle), as detailed in Directive 2010/63/EU.

This workshop was targeted at the non-clinical development of medicinal products and aimed at:

- mapping the current state of science in this field
- developing a common understanding of the benefits and limits of these methods
- identifying gaps in non-clinical safety testing and stimulating research using MPS to address them, so encouraging MPS use in regulatory testing
- acting as a forum to encourage dialogue between developers, users and regulators
- facilitating the regulatory acceptance of innovative non-animal methods in appropriate, defined contexts during the approval of medicines.

The programme was set up in order to sequentially obtain the view on MPS of the different stakeholders present, namely pharmaceutical industry, academia, and regulators.

Following the presentations, breakout sessions were organised on two topics:

- criteria for regulatory acceptance of MPS
- how can the regulatory science advance in short and midterm through the application of MPS. Identification of most advanced /promising systems. Road map to move forward towards regulatory application of MPS.

Plenary sessions

According to the **Pharmaceutical Industry**, MPS have the potential to fill a gap in non-clinical safety testing and to reduce the uncertainties pertaining to *in vitro* to *in vivo* translation of safety.

MPS can in fact be considered advanced *in vitro* models with improved physiological resemblance to the *in vivo* organism and are expected to lead in principle, but not automatically, to better prediction of safety and efficacy.

Application of adequate cell or tissue models which are well designed and characterised for a specific context of use, in full recognition of their limitations and taking into account extrapolation of *in vitro* to clinical exposure, can enhance biological and mechanistic understanding.

Emerging data with MPS used in target and lead identification, lead optimisation and preclinical safety testing are encouraging and build confidence that MPS can add value in specified situations. Further application and adoption of MPS will require significant multidisciplinary partnerships, including the development of complementary technologies.

On the **academic research scene**, innovation is fast increasing with a wide range of MPS under development. These include various models for:

- target organs of toxicity (e.g. liver, heart, nervous system)
- barrier systems (e.g. vascular, kidney, gut, retina, blood-brain barrier)

- connecting and combining organ systems (combination of liver with kidney, gut or bone marrow, combination of endothelial cells and cardiac cells, or liver with tumour cells and immune cells from spleen or blood to assess efficacy and safety of immune-modulatory drugs)
- incorporating immune components (e.g. non-parenchymal cells in liver, blood tissue co-culture, tissue infiltration of immune cells)
- stem cell models of disease
- studying distribution, metabolism and pharmacokinetic endpoints.

One of the main challenges for academia is securing reliable sources of cells as well as improving the similarity to human biology.

Progress is highly dependent upon partnership between MPS developers and other involved stakeholders, including regulatory authorities. On the EU networking scene, multiple organisations have joined forces to create public-private partnerships from multiple locations, providing a unique integration of multidisciplinary expertise, technologies and facilities.

This EU network works also in collaboration with world-wide scientific research organisations and represents opportunities for future EU funding.

Finally from the **regulatory point of view**, efforts to facilitate regulatory acceptance of innovative 3R methods and foster this paradigm shift are ongoing.

The EU Guideline on the principles of regulatory acceptance of 3Rs testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012) defines regulatory acceptance of such methods and describes a procedure for submission and evaluation of proposals for their acceptance.

In the US, the FDA Predictive Toxicology Roadmap similarly shows the commitment of regulators to promote the development and evaluation of emerging toxicological methods and new technologies and to incorporate such methods and technologies into regulatory review as applicable. A Cooperative Research and Development Agreement (CRADA) to advance and qualify 'Human Emulation Systems' to meet regulatory evaluation criteria for product testing has been signed by FDA. Partnership between government regulators, industry, stakeholders and academia is also established through the FDA-DARPA-NIH Microphysiological Systems Program and the MPS consortium.

At international level, collaboration between regulators and pharmaceutical industry is exemplified with the development of the guideline ICH S5. Focus is on human risk assessment of reproductive toxicity with the use of integrated testing strategies incorporating 3R testing approaches as much as possible. A first concept of qualification of 3R testing methods, also called alternative test methods, has been defined. Qualification ensures confidence in the proposed 3R or alternative test method for a particular context of use. The principles introduced here could guide the qualification of more complex test platforms such as MPS.

Breakout sessions

Criteria for regulatory acceptance of Organ on Chip. Experience with in vivo/in vitro endpoints comparison. Which context of use?

In order to show that an MPS is fit for purpose, the following aspects should be considered:

- definition of the essential parameters, endpoints/mechanisms to be investigated/measured
- definition of the "gold standard" for each endpoint – i.e. which test system or animal model is to be used as reference. This is an important discussion in the frame of replacement of *in vivo* studies
- translation of endpoints/biomarkers from *in vitro* to *in vivo* (human). The direct extrapolation from human *in vitro* to human *in vivo* is considered an advantage. Conversely, clinical adverse effects should be translated into *in vitro* endpoints.

Qualification thus needs to include the assessment of:

- context of use. This could for example include the description of the circumstances under which the MPS is applicable in the assessment of a human medicinal product and the limitations within which the available data adequately support the use of the test method (e.g. applicability of the test method for a particular class of compounds under development in a certain company). A stepwise prospective approach (start simple, then go into more specifics e.g. disease models) is preferred, taking into account both safety and efficacy testing. Context of use should also involve the identification of niche areas where tests might fill a gap, one example could be the case where no informative animal model/species is available.
- reliability, being the measure of the extent that a test method can be performed reproducibly over time when using the same protocol
- relevance, defined as the extent to which the test method correctly measures or predicts the biological effect of interest. This implies concordance with the optimal test system or animal model to be used as reference ("gold standard").
- qualification should be conducted for each method separately, on a case-by-case and programme-per-programme basis
- qualification implies the availability of defined test methodology including aspects related to *in vitro* to *in vivo* extrapolation (IVIVE).

Challenges:

- weight of evidence is currently on side of incumbent animal models
- MPS models are not cheap to run or develop
- need for collaboration between all stakeholders

Actions identified:

The actions involve the need for collaboration between stakeholders and are related to the following topics:

- development of specific guidance for method developers on qualification
- development of endpoint-specific performance standards including a list of reference compounds per each organ system and endpoint, including positive and negative controls

- need for MPS using healthy versus diseased cells: stepwise approach needs to be agreed, taking into account specific contexts of use
- discussion on applicability of clinical biomarkers to demonstrate relevance of endpoints
- need for clarification of the degree of flexibility that can be applied in order to allow for continuous applicability of qualification criteria as a function of time.

How can the regulatory science advance in short and mid-term through the application of MPS Road map to move forward towards regulatory application of MPS for the most advanced/promising systems

This workshop report reflects the common position of the regulatory authorities within the EMA framework.

Thus far no MPS is considered ready for regulatory acceptance.

The heart-on-chip models may be considered as the most advanced towards regulatory applicability but quality data regarding fit-for-purpose assessment are still needed. The generation of this quality data is only possible when there is an agreement among stakeholders on what is considered an acceptable level of qualification.

Actions identified:

- Endpoints that need to be measured in MPS should ideally be discussed and agreed upfront by the relevant stakeholders, namely regulators, method developers and pharmaceutical industry.
- Regulatory guidance already available is not considered sufficient. More detailed guidance is needed and needs to be developed in concert with all stakeholders.
- Regulators should be consulted to define the test system to be used as reference "gold standard" for each endpoint. Cross-validation with clinical data – when available – should be considered.
- Data sharing is considered key to achieve progress in the field. A wealth of data are being generated that could be used to support the path towards qualification. Data sharing is possible through the EMA process of method qualification under the safe harbour approach (see the Guideline on the principles of regulatory acceptance of 3Rs testing approaches, EMA/CHMP/CVMP/JEG-3Rs/450091/2012). In addition, collaborative efforts could also be mediated through consortium work (e.g. Innovative Medicines Initiative).