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Workshop Report

Regulatory acceptance and use of 3R models for pharmaceuticals and chemicals: Expert opinions on the state of affairs and the way forward

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ABSTRACT

Pharmaceuticals and chemicals are subjected to regulatory safety testing accounting for approximately 25% of laboratory animal use in Europe. This testing meets various objections and has led to the development of a range of 3R models to Replace, Reduce or Refine the animal models. However, these models must overcome many barriers before being accepted for regulatory risk management purposes. This paper describes the barriers and drivers and options to optimize this acceptance process as identified by two expert panels, one on pharmaceuticals and one on chemicals. To untangle the complex acceptance process, the multilevel perspective on technology transitions is applied. This perspective defines influences at the micro-, meso- and macro level which need alignment to induce regulatory acceptance of a 3R model. This paper displays that there are many similar mechanisms within both sectors that prevent 3R models from becoming accepted for regulatory risk assessment and management. Shared barriers include the uncertainty about the value of the new 3R models (micro level), the lack of harmonization of regulatory requirements and acceptance criteria (meso level) and the high levels of risk aversion (macro level). In optimizing the process commitment, communication, cooperation and coordination are identified as critical drivers.

1. Introduction

Test methods used for risk assessment purposes depend heavily on animal models which were developed over the last 50–60 years (Scholtz et al., 2013) and the animal model in this field is often still perceived as the "gold standard". This holds true for both regulators and industry (Scheel and Brekelmans, 2007). Nonetheless, a growing number of models to Replace, Reduce or Refine animal tests (3R models) (Russel and Burch, 1959) has become available. Every so often, these models are scientifically more robust, economically advantageous and ethically preferable in comparison to the existing animal model. Still, regulatory acceptance and use is one of the main challenges 3R models face (Richmond, 2002; Garthoff, 2005; Bottini et al., 2008; Schiffelers et al., 2012). And until now alternative approaches have only rarely been used in regulatory settings (Scholtz et al., 2013).

There is growing international awareness of the slow regulatory acceptance of 3R models. In this context two ad hoc expert panels (see also Section 3) were set up in a combined initiative of TNO (Netherlands Organization of Applied Scientific Research), USBO (Utrecht University School of Governance), the NKCA (Netherlands Knowledge Centre on Alternatives) and the Dutch Ministry of Health to address the following key questions:

- *What are the main factors influencing the regulatory acceptance and use of 3R models for the safety/efficacy testing of pharmaceuticals and the safety testing of chemicals?*
- *How can the involved stakeholder groups contribute to optimizing this process?*

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The experts were invited based on their affiliation with the product sectors pharmaceuticals and/or chemicals and because of their familiarity with the subject of the 3Rs. The distinction between this product sectors was made, based on the assumption that the influences on regulatory acceptance and use of 3R models potentially differ between these sectors. For process optimization purposes, representatives of public and private partners of the development chain from R&D to regulatory approval of pharmaceuticals and chemicals, were invited (for more information on the expert panels see Section 3).

Section 4 of this paper is a reflection of the opinions and ideas that were brought up during the panel discussions. Section 5 consists of an analysis of these findings and of identifiable actions per stakeholder group.

With this report the authors intend to offer a constructive contribution to the international discussion on regulatory acceptance and to stimulate this process where possible.

2. A multilevel perspective on technology transitions

To understand the overall acceptance process of innovations like 3R models, the multilevel perspective on technology transitions was presented to the experts of both panels (Schiffelers et al., 2012). This multidisciplinary approach offers valuable concepts for the analysis of long-term technological transitions (Schot and Rip, 1996; Geels, 2006). For innovations to break through the following three levels need alignment (Schiffelers et al., 2012):

1. The micro level consists of the niche in which innovations such as new test methods are developed and tested. Here drivers and barriers are found relating to the development and validation of 3R models;
2. the meso level entails a mix of existing rules and regulations, expertise, practices and institutions that strongly influence the acceptance of innovations like 3R models;
3. the macro level where broader societal features, like the existing material infrastructure, the political culture and coalitions, broad social values, world views, the macro-economy, demography and the natural environment, can be found (Kemp, 2010).

The transition to newer techniques is almost always the "result of the interplay between many factors and actors" at these three different levels (Schiffelers et al., 2012; Geels, 2006). Alignment can occur if the development of an innovation (micro level) overlaps with a change or request for change in the regulatory regime (meso level) and/or within the broader context of society (macro level), creating a 'window of opportunity' (Kingdon, 1995; Geels, 2002). However, if a new technique faces a mismatch with the existing regulatory regime and/or the developments in society, the innovation has little chance to escape from the niche in which it was developed (Kemp, 2010). This is what is often observed when it comes to regulatory acceptance and use of 3R models.

Every level offers a part of the explanation why innovations like 3R models face difficulties in becoming accepted. Additionally, the technology transition approach unveils the-inter-dependencies between the three levels and thereby acknowledges the importance of combining societal and technical factors when examining and/or stimulating the acceptance of 3R models. Finally, the categorization of drivers and barriers into these three levels is significant because the level also gives information on the possibility to control a certain driver or barrier. Generally speaking the factors at the micro level offer more control possibilities than those at the meso- or the macro level.

3. Methodology

In spring 2012 two expert panels were organized which involved a total of 40 Dutch and Belgian experts[1] from the fields of safety assessment, regulatory testing and 3R models. Both the pharmaceuticals and the chemicals panel included a total of 20 experts. The participants derived from the following three stakeholder groups:[2]

1. Regulatory authorities, legislators & policy makers
2. Industry
3. Academia & research organizations

The panel members have contributed to the discussion 'in a private capacity' making use of their expertise and experience as a professional within their specific stakeholder group. The choice for these three stakeholder groups is based on the assumption that these are the central chain partners for regulatory acceptance and use of 3R models.

Both panels aimed at the clarification of the process of regulatory acceptance and use of 3R models and at the examination of possibilities to enhance this process. These goals were targeted through the following three subsequent steps:

Firstly, an inventory of barriers and drivers was made. For this purpose each participant was asked to write down the three barriers and drivers on regulatory acceptance and use of 3R models which they perceived to be most influential. This resulted in a broad range of factors which were grouped in about 25 clusters of comparable factors. The clusters of factors were checked and discussed in plenary and divided into factors at the micro-, meso- and macro level.

Secondly, a further prioritization was made of the factors in terms of their influence on regulatory acceptance and use; Each participant was asked to score the clusters of factors in terms of their perceived influence in the process of regulatory acceptance and use of 3R models within the their product sector. For this purpose, each participant was asked to divide a total of 5 points between the factors they perceived to be most influential on the process of regulatory acceptance and use. This exercise resulted in an overview of those factors with the highest panel scores. In other words, these drivers and barriers are perceived by the panel to be most influential in that particular product sector (see Table 1).

Thirdly, actions were identified that can be pursued by the stakeholder groups in order to optimize the process of regulatory acceptance. This identification took place through a discussion within and between the stakeholder groups on the following 3 questions:

1. which factors can be influenced by the own stakeholder group?
2. How can these factors be influenced/what are possible actions?
3. What can a particular stakeholder group offer to chain partners and what is needed from chain partners in terms of optimizing the process?

[1] The selection of Dutch and Belgian experts might have led to a certain level of bias since these countries are known to be relatively open to the 3Rs in comparison to certain other countries. However, the fact that most of the experts operate in an international context and the fact that all experts were invited to bring forward the dominant drivers and barriers on the acceptance and use of 3Rs for their sector from an international perspective, reduces in our opinion the risk of bias.

[2] For an overview of experts see acknowledgements. In addition several of the authors of this manuscript (i.e. Blaaubloer, Beken, Hendriksen en Koeter) were involved in the panel discussions as experts. Krul and Schiffelers facilitated the panels.