EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Reinforce and further embed application of the 3Rs principles

Underlying actions

EMA's Regulatory Science Strategy to 2025 – Veterinary Stakeholder Workshop

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Reinforce and further embed application of the 3Rs principles – Key points

1. Apply the highest possible 3Rs standards when implementing the NVR
2. Strengthen cooperation with European and international institutions
3. Motivate increased data-sharing by industry to reduce animal use in safety evaluations
4. Encourage medicines' developers to seek qualification of biomarkers that avoid the need for animal studies
5. Promote in-silico methodology (e.g. modelling) and novel in vitro assays to reduce animal use, particularly in toxicology/epidemiology and batch control
6. Explore whether international recognition of qualification of alternative methods strengthens the use of 3Rs principles

Emphasis on in silico modelling

'I agree that novel approaches such as in-silico modelling will benefit drug development and support early efficacy studies, as well as improving predictive ability. And in particular, the action to:
1.2.5 Promote in-silico methodology (e.g. modelling) to reduce animal use, particularly in toxicology/epidemiology and batch control [...] is well recommended. But it ***stops short of making the connection to humans and does not mention in silico clinical trials***'

Promoting regulatory acceptance/international cooperation/ training

'The deletion of in vivo tests for final product testing is highly supported. To ensure the success of EMA's efforts it is of utmost importance that these ***efforts are synchronised with Ph.Eur., [EURL ECVAM] and OIE to avoid divergent requirements***. The ***training of assessors to overcome the reluctance to accept new methods*** and to ***end the trust in in vivo potency tests***'

Leverage existing data

‘[...] there needs to be a sea change away from the use of traditional animal tests, which are preventing real progress from being made and hindering the full realisation of sophisticated innovations in science and technology’

Proposal from commentator: ‘We strongly encourage the EMA to include the ***conduct of retrospective analyses of the existing animal tests as an action***. This would help fully characterise their reliability, reproducibility and applicability domain, which would in turn encourage a significant move towards full implementation of the 3Rs principles and increased development and focus on the use of NAMs, which is necessary to advance regulatory science and deliver safer and more effective healthcare solutions in the long run’

Limitations of in vivo testing / Develop guidance for regulatory compliance

'***Over the last 20 years, the limitations of the traditional approach to toxicity testing, which is heavily focused on animal tests, have become increasingly evident***. [...] Also, while the strategy mentions the importance of engaging with 'emerging science and technological innovation', ***the development and use of new approach methodologies or NAMs is clearly missing*** from the examples provided. [...] The strategy also asks the question [...] '***are we generating new guidance or providing sufficient levels of advice*** to facilitate the utilisation and translation of these innovations?' To this question, our answer would be 'much more work needs to be done'. One of the main reasons why NAMs are not being used, even once they have been validated or qualified, is the ***fear that they will not be accepted by regulators***. Therefore, one of the proposed actions to support the NAMs core recommendation should be ***to develop clear guidance on how these methods can be used to fulfil testing requirements in lieu of traditional animal tests***'

Critical views

'A common human and vet strategy on the approach for non-animal methods and the implementation in licensing procedures is needed. Lessons learnt from IMI VAC2VAC project: there are different approaches and requirements for validation and introduction of new methods in the testing of medicines. ***The hurdles to replace the use of animals in both quality control and safety testing should be lowered and harmonised on a lower level***'

Critical views

'***The 3R principles*** have been implemented more than thoroughly and have reached the stage that they ***hinder the development of new VMPs***. In most countries they have been implemented strictly and lead to an unbalanced restriction to develop new VMPs for certain indications. ***Most studies in animals are and will be even more conducted outside the EEA, even clinical studies***. This leads to insufficiently tested products placed on the market, with high risks for the animals, humans and the environment. Not talking here about the competitiveness of Europe for R&D which is significantly lost compared to many other markets. This does not mean, that we should not adapt 3R principles, especially replace certain studies. However, ***pre-clinical and clinical studies in the target species should stay completely out of these requirements, as long as they follow the established guidance*** and thus being compulsory'

Incentives/international dimension

'***Pursuing 3Rs standards is a worthy goal but requires a significant amount of resources*** that may be justified for new products, but such re-investment in existing products is likely to be problematic, especially for products [...] that do not have a large market; ***the animal welfare benefits of retaining the products must also be put in the balance***. A major challenge is the amount of data requested; it would be better to focus on consistency and benefit-risk. Therefore, [...] ***forms of incentives are needed to promote a switch to in-vitro tests*** for those products, as they do not always warrant further investment, and would be lost from the market if reinforced standards are applied. ***A key barrier to implementing 3Rs is international acceptance outside the EU***. International recognition of 3Rs approaches is necessary. With the still increasing globalisation of the industry, animal testing will still need to be performed as long as one major region/country will require this, even if other regions have adopted alternative methods. We have seen this example occur with the (removal of) target animal batch safety test for veterinary vaccines'

Specific needs of the veterinary sector

'AnimalhealthEurope actively supports the further development and application of 3Rs standards. However, major barriers exist, such as the ***acceptability of alternative methods, the international dimension and the lack of alternative tests developed for the needs of the veterinary sector***'

Legal aspects

Competent authorities with responsibility for regulation of VMPs are separate to those responsible for implementation of Directive 2010/63/EU

Any questions?

Further information

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