The European Partnership for Alternative Approaches to Animal Testing

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Draft EPAA Action Programme 2021-2025

1. Introduction, framework and context

1.1. Setting the Scene

The European Partnership for Alternative Approaches to Animal Testing (EPAA) is a partnership[1] between the European Commission and seven Industry sectors with a shared vision to promote and apply the principles of Replacement, Reduction and Refinement (3Rs) of animal use for meeting regulatory and safety testing requirements.

This is the fourth Action Programme of the EPAA since its foundation in 2005. Over the past 15 years there has been considerable progress in the field of 3R approaches: Ground-breaking advances in genetic engineering, toxicogenomics, biochemical sciences, mechanistic understanding of biology processes etc. that have led to *in-vitro* technologies and models allowing for more toxicological endpoints to be tested without the use of animals, or with fewer animals. Organ-on-a chip, pluripotent stem cells and *in-silico* models are rapidly becoming part of the toolbox of state-of-the-art toxicology.

Major progress in non-animal toxicity/safety testing was achieved by implementing the "adverse outcome pathway" (AOP) and "integrated approaches to testing and assessment" (IATA) concepts, which rely mainly on "toxicity pathways", i.e. the cellular response pathways that can result in adverse health effects when sufficiently perturbed. The AOP and IATA concepts have been accepted at international level by the OECD, ICH (International Council on Technical Requirements for Pharmaceuticals for Human Use) and European regulatory agencies and allowed to develop test guidelines with non-animal toxicity tests for a number of complex endpoints (e.g. skin sensitization, OECD 2017).

The EPAA partners from industry and regulatory agencies have played an important role since 2005 in progressing the IATA and AOP concepts across different sectors and in collaboration with international partners. EPAA has contributed, through research projects, cooperation and dissemination actions, to the translation of scientific and technological advances into regulatory practice within Europe and beyond. Regular updates of the OECD test guidelines, the European Pharmacopeia, the REACH annexes on test methods, reports on the implementation of the testing ban on cosmetics and from EPAA members such as ECHA and EURL-ECVAM of the European Commission illustrate these advances. In addition, the EPAA has been active in

[1] EPAA partners include 5 Directorates-General of the European Commission, 37 companies from the chemical, pharmaceutical, cosmetics, detergents, crop protection, animal health and fragrances sectors and their European Trade Associations.

promoting a wider uptake of alternative methods, by implementing and supporting, inter alia, training actions, assessing the use of NAMs, reducing obstacles to uptake and widening applicability areas between sectors.

However, several scientific and regulatory challenges still remain before product safety can be assessed without animal testing. Therefore, further actions and concerted efforts by the EPAA partners remain necessary.

1.2. Prioritisation of EPAA projects

Projects supported by EPAA are prioritized by the Steering Committee according to:

- their relevance to EU policy objectives, sectorial and horizontal legislation (e.g. Directive 2010/63/EU) and guidance;
- the ability to address unmet scientific challenges and avoid duplication;
- whether they have a tangible impact on moving towards non-animal approaches and/or animal welfare;
- regulatory testing areas where high numbers of animals are used and/or where animal use results in severe suffering;
- evidence of commitment from both Industry and Commission partners;
- availability of resources.

Regular reviews will be carried out in order to adapt to the evolving regulatory environment and outputs from third parties' activities. Projects may be discontinued to keep priorities in line with partners' needs or to avoid duplication.

1.3. Mission and Vision

Through the partnership between the European Commission and various industry sectors, the EPAA seeks to promote and support the objectives of the horizontal Directive 2010/63/EU on the protection of animals used for scientific purposes. This Directive maintains the balance between the protection of humans, animals and the environment, animal welfare and scientific innovation as warranted by regulators and required for the continuity of R&D in Europe.

In the next 5 years, the EPAA will focus on closer co-operation with regulators at global, European and national levels striving to promote international harmonisation of regulatory safety testing requirements. The unique range of partners and stakeholders involved in EPAA, including industry, regulators and animal research and welfare groups enables the partnership to act as a forum for cross-sector dialogue. The so-called EPAA Partners Forum, first established in 2017, is a new Forum to further exploit the immense knowledge and expertise of all partners.

The EPAA can reach out to all stakeholders and help provide a coordinated EU voice. Through the involvement of the European Commission and global companies, the EPAA has the possibility to liaise with the wider international community.

1.4. EU legislative context

The new EU Commission (with President Ursula von der Leyen) took office in December 2019 and presented its Communication on The European Green Deal[2]. Under its chapter 2.1.8. a new "chemicals strategy for sustainability" is announced which will also be relevant for the EPAA.

[2] COM(2019)0640

The EU policy on animal welfare is enshrined in the Treaties and implemented in secondary law. The Directive on the protection of animals used for scientific purposes[3] recognises that animals have intrinsic value in themselves, which must be respected, and sets replacement as the ultimate goal while acknowledging that the use of animals continues to be necessary to protect human and animal health and the environment. Importantly, it defines the principle of the 3Rs as the key to more humane and better science.

2. Identifying challenges

The EPAA partners identified ***six challenges*** to be addressed by EPAA and to be highlighted to other initiatives and institutions in order to accelerate the development and implementation of alternative approaches to animal testing. These fundamental challenges of implementing non-animal testing into regulatory practice in Europe and internationally are:

I. Address science and technology gaps

Despite tremendous scientific and technological progress and significant investments in public and private sectors, there are still significant gaps that need to be addressed to move towards non-animal alternatives for several regulatory endpoints. For example, there is a clear need for even better mechanistic understanding of complex toxicology endpoints and associated biomarkers, more effective approaches for *in vitro* to *in vivo* extrapolation, and more useful exploitation of 'omics techniques.

II. Improve intra and inter sectorial collaboration and coordination

There are opportunities for enhancing precompetitive collaboration among companies and sectors. Coordinated research strategies, incentives and models for sustainable and safe sharing of knowledge and data are currently lacking, in particular between industrial sectors. Improving collaboration across sectors reduces fragmentation in R&D strategies, helps coordination between different research funding agencies and administrations in Europe and between different regions of the world (with often diverging regulatory requirements but common consumer safety goals).

III. Optimise translation from research to regulatory practice

Bridge the gap between the new non-animal methods development and their routine use. Where possible, support regulatory practice processes (e.g. OECD, ICH/VICH) and create mechanisms and resources for early involvement of regulators in development and implementation of alternative approaches. This will contribute to accelerating translation from research to practice.

IV. Facilitate acceptance of additional sources of evidence in the current regulatory framework

Foster dialogue between the scientific and regulatory communities to determine together how evidence generated by non-standard tests can be “interfaced” with the information requirements for safety and risk assessment (e.g. toxicokinetics, read-across). Also, more comprehensive and systematic assessment of uncertainties would accelerate validation and uptake of integrated non-animal approaches. A key component of this is understanding what type of data or assessment is actually required for the safe use of a product under the various regulatory frameworks

[3] Directive 2010/63/EU of 22 September 2010

applicable today (following decades of industrial and technological advancements) or in the future, thus enabling prioritization for validating approaches. This includes in particular consideration of exposure-based assessments, increased international recognition of alternative methods and their validation and translation into regulatory acceptance.

V. Communicate scientific opportunities and challenges

Enable clear, transparent communication between industry, academic scientists, policy makers, regulators and the general public, that reflects scientific reality in the context of policy aspirations. Optimise channels to communicate scientific advice to better inform policy discussions on incentives, funding and other mechanisms aiming to identify R&D priorities and promote the use of alternative new approach methodologies (NAMs) in mainstream research and regulatory practice.

VI. Promote education and knowledge-sharing

Provide a variety of innovative learning opportunities for all key actors to enable knowledge-sharing between scientists, method developers, validation bodies, industrial end-users and regulatory safety assessors. In essence, solution providers need to better understand regulatory information requirements, decision-makers need to better understand how to exploit new approach methodologies for relevant safety assessment in today's environment, and education and training initiatives need to be better at engaging people in collective efforts to solve problems and make progress.

The above six challenges have been used to frame the EPAA Action Programme, actions undertaken by the EPAA must fall within the remit of the partnership itself and its members.

3. Actions to address the above challenges

The following actions may take the form of EPAA projects followed by a publication, including, but not limited to workshops and partners fora, as well as cooperation with other partners and institutions. Working collaboratively via increased use of available digital tools will also help to make progress.

3.1 Address Science and Technology gaps and Optimise translation from Research to Regulatory Practice (Challenges I and III)

- Identify research needs for developing or optimising alternative methods for regulatory testing and liaise with European and possibly national research funding bodies. Where possible, pilot proof of concept initiatives that could move to large scale funded projects.

  This is progressed in particular via the EPAA Annual Partners Forum (as an instrument for identifying industry needs and potential synergies to address them).

- For specific endpoints prioritized by EPAA, bridge the gap between the new non-animal methods' development, their acceptance and routine use in regulatory safety testing (e.g. via knowledge-sharing, development of co-sponsored case studies and training workshops with EU regulators, Member States, etc.).

3.2 Improve intra- and inter sectorial collaboration and coordination (Challenge II)

- Identify opportunities and make recommendations on mechanisms and incentives to enhance knowledge and data sharing within and across sectors in order to avoid or reduce animal testing.

- Facilitate coordination between different research funding agencies and administrations in the EU. Help to ensure critical mass of funding and effort on prioritised objectives.

- Develop joint activities with stakeholders and other collaboration structures, including via a multi-sector approach, on topics of mutual interest, e.g. strengthening read-across approaches and their application.

3.3 Facilitate regulatory acceptance of additional sources of evidence in the current regulatory framework (Challenge IV)

- Facilitate international collaboration and pave the way to implementation and international mutual recognition and application of alternative approaches in regulatory decision-making. Again, the yearly EPAA Partners Forum is a vehicle to address this. This can also be achieved through Expert Workshops or sessions, based on case studies, for comprehensive and systematic assessment of uncertainties that would accelerate validation & uptake of integrated non-animal approaches.

- Promote the application, use and acceptance of Integrated Approaches on Testing and Assessment (IATAs) and New Approach Methodologies (NAMs).

- Facilitate early involvement of regulatory agencies and risk managers in the entire EPAA project cycle from planning to implementation (this can be achieved by having EU, or global regulators on the project team from the outset; particularly the EC partners can help by inviting these regulators).

- Help building confidence in exposure-driven Next Generation Risk Assessment (NGRA) approaches and explore how NGRA can be integrated into regulatory frameworks as a possible alternative to currently used risk considerations based on traditional hazard endpoints.

- Explore and facilitate cross-sector use of additional sources of evidence for regulatory decision making (e.g. toxicokinetics, read-across, etc).

3.4 Communicate scientific opportunities and challenges (Challenge V)

- Communication and dissemination activities come in support of all EPAA project outcomes. They aim at improving understanding amongst policy, decision-makers and stakeholders about the scientific and policy framework, opportunities, limitations, barriers to regulatory acceptance of 3Rs methods and the impact of EPAA actions.

- Facilitate communication between industry, academic scientists, policy makers and regulators that reflects scientific reality within the context of policy aspirations.

- Ensure effective communication in easily understandable terms to the general public (e.g. via press articles, interviews with members) about scientific opportunities and challenges in a balanced and objective manner.

- Foster transparency within the scope of EPAA about scientific benefits, limitations, applicability ranges of the test methods, irrespective of whether they are *in vivo, in vitro, in chemico* or *in silico.*

- Develop incentives and/or mechanisms for promoting the application and regulatory recognition of newly accepted alternative methods and approaches.

- Increase recognition of 3Rs research and good practice and encourage young scientists also from areas not directly related to biosciences to increase knowledge and understanding of 3Rs (for example through the Refinement prize, the Science prize and the Student grants).

- Show EPAA's impact on 3Rs to the partners, the scientific community and the public through further developing and improving communication networks and tools (e.g. website, social media, training videos, etc).

3.5 Promote education and knowledge-sharing (Challenge VI)

- Improve access to information and opportunities to connect regulators and regulated, alternative method developers and those who are responsible for alternatives validation, including training opportunities and tools (e.g. training video tutorials, training sessions). In particular, provide opportunities for authorities and regulators to improve their understanding of practical application of AOPs, IATAs and New Approach Methodologies (NAMs) in regulatory decision-making.