Annual Conference 2023 of the European Partnership for Alternative Approaches to Animal Testing (EPAA), Brussels, 15 November 2023

"PROTECTION OF PEOPLE AND OUR ENVIRONMENT THROUGH NAMs"

Introduction:

Giacomo Mattino', the EPAA European Commission Co-Chair, provided the opening remarks along with **Gavin Maxwell**, the EPAA Industry Co-Chair. Giacomo Mattino' noted the record attendance at the 18th Annual Conference, with more than 300 participants joining in person and online.

He thought that it was a very interesting time to be discussing alternatives to animal testing; the European Commission was focused on this topic and wanted to make the most of the accelerated progress in the field. The Commission was fully supportive of this work, but recognised it was a long-term goal that required a stepwise approach; animal testing currently remains important in risk assessment.

He confirmed the continued funding for alternatives by the European Commission; it has already spent more than €1 billion on over 300 projects during the last two decades. There was also the question of translating this into legislation.

He pointed out that the European Parliament elections and a new European Commission were imminent; it was important to make sure the issue of alternatives remained prominent on the agenda; the conference programme, he said, would reflect this.

Gavin Maxwell stressed that, during the event, there would be a greater space for interaction – a 2022 recommendation – and plenty of time for questions.

Keynote speeches:

Keynote speaker 1: **Christos Vasilakos**, for Maria Spyraki MEP

The first keynote speech was delivered by Christos Vasilakos, Senior Policy Advisor in the European Parliament, representing the MEP Maria Spyraki who was unavailable. He stressed that Maria Spyraki's commitment to ending animal testing without undermining scientific progress was long standing, particularly in the field of rare diseases.

He said she hoped that the audience shared the recognition that a lack of funding, and other barriers, were hindering the acceptance of alternative methods for regulatory purposes; urgent action was needed. Wider acceptance of new methodologies – including *in vitro* and *in silico* methods – was required. More money was needed to establish rapid and reliable non-animal safety assessment methods in all relevant fields, not only in cosmetics.

He said that Maria Spyraki recognised that the transition to non-animal testing methods needed to be an essential political priority. While acknowledging the current necessity for some degree of animal testing, a detailed roadmap with concrete milestones was required to ensure a comprehensive approach across all relevant legislation. This will also require resources to address this, and provisions to this end have been made.

Safe cruelty-free cosmetics initiative has captured the concerns of citizens; these have been presented to the European Parliament at plenary. It calls on the European

Commission to strengthen legislation, initiate changes to cosmetic ingredients and propose a modernisation to the chemical legislation to manage additional animal testing requirements.

Concerns remain over the effectiveness of alternative methods in health and pharmaceuticals. There need to be initiatives to encourage more new methods and to reduce the reliance on animal testing. The Commission should also work with the OECD to find ways to reduce animal testing in third countries.

The current strategy is not being implemented effectively. There needs to be a holistic approach to phasing out, one that recognises that there are remaining gaps, particularly in rare disease research. EPAA has a key role to play, which is why the European Parliament values its exchanges with the Partnership. He assured the ongoing support from Ms Spyraki in maintaining and growing EPAA's visibility.

Keynote speaker 2: **Nicolas Dudoignon**

The second keynote speech was delivered by Nicolas Dudoignon, Chief Veterinary Officer, Corporate Responsibility, Sanofi. He noted that the work of EPAA was mainly focused on safety assessment and in his presentation he would provide the perspective of the pharmaceutical industry, particularly on NAMs.

He highlighted that while the goal remained to eliminate the use of animals in research, testing and education, the public still sought treatments and vaccines for unmet needs. Pharma companies seek to deliver these, but at the same time they wish to make it clear that, while committing to the reduction in their use, the use of animals during development remains a sound scientific choice.

He pointed out the various stages in a drug lifecycle where such use is necessary, principally exploratory research, studying drug metabolism, studying season and antibody production as well as potency and safety testing of batches. The research and testing activities are driven by science and by reliance on proven models is essential to address specific scientific questions. The testing method selected depends on the circumstances, but animals remain a small but integral part of a comprehensive approach. Despite the fact that animal models cannot be rejected outright he stressed that the ability must be systemically challenged and core animal protection principles adhered to. He explained that Sanofi has its own internal strategy – the IRTS - to guide the selection of testing criteria, with the ultimate goal of reducing animal use by 50% over 10 years (by 2030). The core tenets of the IRTS were improve the experimental design, network knowledge sharing and collaboration in advocacy. The latter was particularly important, because it would not be possible to fully eliminate animal testing until health authorities accepted non-animal alternatives.

In conclusion, he pointed out that the models and approaches are both complex and complementary. Science should be the driver for the development and uptake of NAMs, and for choosing the most appropriate model to use. Conclusion and commitment are key for encouraging the science and bridging gaps, achieving international regulatory acceptance and for developing a transparent approach.

Coffee break

Session1 - State of the Partnership:

Gavin Maxwell and Christiane Hohensee (member of the EPAA Mirror Group, representative for the EUROGROUP for Animals) then provided an overview of the 'State of the Partnership' for EPAA.

Gavin Maxwell*:*

From the industry side, Gavin Maxwell shared an overview of the EPAA highlights for 2023. He stressed the ultimate goal of EPAA – animal-free, safe and sustainable innovation, and he believed that considerable advances towards that goal had been made during this year. The ambition of EPAA was fully supported by the European Parliament, and the European Commission has said that this ultimate goal was "enshrined in EU legislation", and that there was an EU Replacement Roadmap in process.

From EPAA's perspective, it was aiding this transition by driving research to regulatory use, cross-sector consensus and multistakeholder collaboration. He highlighted two landmarks; EFSA's publication of 'Development of Roadmap for Action on NAMs in Risk Assessment' and the hosting of the 'One Conference' in June 2022 to discuss the recommendations. There was also ECHA's workshop entitled 'Towards an animal-free regulatory system for industrial chemicals', which focused minds on replacement. The next step should be bringing these together as part of the roadmap. The 'EU Replacement Roadmap' workshop in December would be important in this respect.

EPAA's new highlight activities this year included a 'NAM Designathon 2023 – Challenge for human systemic toxicity'; the Partner's Forum on the 'Use of NAMs in Environmental Safety Assessment' (a new topic for EPAA) and the 'NAM User Forum'.

From a dissemination and communication perspective, EPAA had hosted a joint workshop with EDQM on the 'Future of Pyrogenicity testing', participated in the 'World Congress on Alternatives and Animal Use in the Life Sciences 12' and organised a lunch debate - to review progress on the roadmap for phasing out animal testing in chemical safety assessments- in the European Parliament, hosted by Tilly Metz MEP. An exhibition is planned in the Parliament for 2024. There were also a number of media articles.

He pointed the audience to the EPAA Annual Report – available online – and urged people to read through it see if there were areas where they could help disseminate further on activities, or even potentially collaborate.

He concluded by acknowledging the contributions and collaborations made by everyone to the work. He pointed out that EPAA was an open collaboration project and encouraged people to become involved.

Christiane Hohensee*:*

Christiane Hohensee (member of the EPAA Mirror Group, representative for the EUROGROUP for Animals) provided perspective from the Mirror Group, which is made up of members of civil society representatives. It is designed to reflect the views of academia, 3Rs organisations, animal welfare organisations and politicians.

The group meets quarterly and has expanded over the last year with four new members, increasing its size and diversity. The group scrutinises the work of the EPAA and makes its own proposals also.

In closing, she said she was looking forward to the pending 'EU Replacement Roadmap' workshop in December.

EPAA Refinement Prize Ceremony:

Marco Fabbri, from the European Commission's REACH unit, announced the winner of the biannual EPAA Refinement Prize for 2023. This award, worth €6000, goes to the lab technician, animal caretaker or technologist demonstrating outstanding achievements in implementing and raising awareness of refinements in animal testing, with the winner being selected by a committee from industry, the European Commission and the Mirror Group. This year's award went to **Dana Matzek**, of Ludwig-Maximilians Universität in Munich, for a case study on Mobile-R-Pen, a universally applicable floor housing system for rabbits.

Dana Matzek gave a short presentation on Mobil-R-Pen. She pointed out that rabbits – with a total of 350,000 animals - were the third-most widely used species of mammal in testing. She highlighted some of the difficulties associated with caging for rabbits, noting that while floor housing was an alternative to cages, it still presented issues around space usage and areas such as hygiene and animal handling. The compromise – so-called 'flatdecks' – addressed several of the issues, but not all of them.

Mobil-R-Pen – with 'R' standing for 'Refinement' is a step forward, deploying innovative and flexible approaches. It provides an animal- and user-friendly husbandry environment, reducing anxiety and stress among the animals. Its benefits have been scientifically validated. The next step is to look at improvements that can benefit other species. Accepting the prize, Dana Matzek thanked her supporters and collaborators.

Lunch break

Session 2 - Panel discussion 1 and Q&A:

There followed a moderated discussion (chemicals sector) on the **'Impact of CSS on innovation and animal testing**,

Conference moderator: **Jose Tarazona**

Participants:

- Katrin Schutte, DG ENV
- Sylvie Lemoine, Cefic
- Julia Baines, PETA
- Ofelia Bercaru, ECHA
- Merel Ritskes-Hoitinga, Utrecht University
- Georg Streck, DG GROW

Moderator Jose Tarazona began by introducing how the session would unfold.

***Katrin Schutte**, DG ENV*

Katrin Schutte, from DG ENV opened with a short presentation on the CSS; 'the Chemicals Strategy for Sustainability'. This, she explained, was the EU's approach for sustainability for a toxic-free environment. Published in October 2020, it forms part of the EU's ambitions for zero pollution, a key commitment under the European Green Deal. The CSS reflected the reality that global chemicals production - including some that are hazardous to humans and the environment - was likely to double by the end of the decade.

The strategy has five building blocks:

- Boosting innovation
- Strengthening legislation for better protection
- Simplification and coherence
- Knowledge and science
- Global actions.

The revision to the REACH Regulation will address three main issues:

- Unaddressed risks
- Low efficiency of regulatory processes
- Insufficient compliance

There were specific points on registration as part of the REACH revision:

- More information on critical hazard properties
- Requiring registration of certain polymers of concern
- More information on use and exposure
- The 'cocktail' effect (mixture assessment factor)

Annex XI, on adaptation to standard testing procedures, would also be updated.

On Evaluation, all registrations would need to comply with the legal requirements and following improvements are planned for the Evaluation chapter:

- Giving the agency the power to revoke registration numbers
- Improved procedures for filling data gaps, including by group assessment and mandating testing
- Streamlining of substance evaluation procedures (hazard-based).

On reform of authorisations and restrictions, these would reflect the problems with the slow pace of restrictions and an overly burdensome and bureaucratic authorisation processes. The goal was to increase speed and efficiency and to incentivise substitution. The measures under consideration include earlier information on use and exposure earlier in the process, reformation of authorisation and restriction processes; the introduction of an 'essential use' concept and extending the generic risk management approach.

She finished her overview by pointing out that the European Commission was working on a legislative proposal on chemicals data. The idea was to establish a common data platform on chemicals, and ensure that the data within was findable, accessible, interoperable and reusable. Adoption by the European Commission is expected by the end of this year.

***Sylvie Lemoine**, Cefic*

Sylvie Lemoine provided the chemical industry's broader perspective, which was to fully support a gradual transition to animal-free testing. She added that it had to be realistic and be part of the broader industrial transition. There was a quandary; the wider public expect more data on chemicals, but they want this without recourse to animal testing. All stakeholders need to work together to resolve this issue, and they need to approach the challenge with an open mind. The chemical industry therefore supports, and will engage in the roadmap with a strong focus on chemicals.

With or without the REACH revision, Cefic accepted there was a need to modernise chemical legislation; there was a lot that could be done now, under the current REACH. It would be possible to modernise chemical regulation by progressive uptake of existing

NAMs – e.g., making use of them for read across - and to encourage regulatory acceptance and confidence, to improve uses and exposure information add to secure internationally harmonised NAM methodologies and mutual acceptance of data. She wondered also whether – given that Europe has the largest chemical database – is there the potential to leverage this, via AI, to create new NAMs? It could potentially even give Europe a competitive advantage.

***Julia Baines**, PETA*

Julia Baines began with the urgency of the need for a chemicals roadmap. There are going to be greater demands for information, so this is increasingly pressing. At the same time, there are limitations on using animal data; they are not the 'gold standard' they are often positioned as, given the wide variability in data. The chemical roadmap is a route to transitioning to a better way of assessing human and environmental exposure and obtaining better data for making decisions.

For such a roadmap, there was a need to continually review the methods in use. Some will become obsolete, and it's important to remain abreast of the latest advances. There is also a need to work with other agencies and how to ingrate academic advances. Goals are also important – for funding, infrastructure, training – all are valid milestones and worth monitoring.

She also stressed the vital importance of stakeholder input from all sectors; everyone needs to be in this together. It's important that NAMs are not developed in silos – there needs to be communication. On validation; it's important not to think in terms of one-for-one replacements. NAMs don't replace animal studies; they provide different ways of generating evidence.

She felt there was also a third pillar; a social component, and a need to properly manage this transition. There was a need to recognise, and try to meet, public expectations.

***Ofelia Bercaru**, ECHA*

Ofelia Bercaru began by reiterating the ongoing support of ECHA for the replacement of animal testing, above and beyond their legal requirements. She set out three areas where ECHA supports these activities.

The first of these is in making better use of the available data, both for easier read-across and for developing new computational models, which due to wider coverage of chemical space will improve predictability and accuracy. The ability to more accurately predict toxic properties will lead to wider regulatory acceptance of computational methods and can help companies to identify potentially dangerous chemicals at early stage of development. This area is done in close collaboration with OECD to have the data in harmonised formats to facilitate reuse.

The second area of support is the workshop that ECHA hosted, which saw stakeholders discuss their critical needs for replacements, and what could be done in the future to assist the process. This was a first step towards developing a common understanding of what new approach methodologies (NAMs), can achieve in the short and long term.

The third area is ensuring better collaboration between researchers and regulators. This will help researchers focus on those methods that will get faster regulatory approval. To support this, ECHA recently published the key areas of regulatory challenge, as its

contribution to the PARC project. Replacement of animal testing is one of the main elements of this document.

In conclusion, she stressed the importance of all stakeholders working together; only this way will there be real progress in replacing animal testing. It is a multidimensional challenge.

***Merel Ritskes-Hoitinga**, Utrecht University*

Merel Ritskes-Hoitinga provided an academic perspective. She explained that – as a result of scientific and technological progress – the goals of a transition roadmap for phasing out animal testing were feasible. In safety science, she highlighted the use of AI. However, the use of scientific evidence alone is insufficient to accelerate the transition process; it is imperative to also integrate social sciences.

In her view, the multidisciplinary field of transition science identifies the best way to accelerate processes. The SAFE (Safety Assessment through Animal-free Evolution) consortium will use transformative governance approaches to speed up the process of validation and acceptance of non-animal new-approach methods in the EU and US.

***Georg Streck**, DG GROW*

Georg Streck highlighted three main points: The REACH revision, the Commission roadmap for phasing out animal testing for chemical safety assessments and the workshop on the Commission roadmap.

On the REACH revision, he gave some examples of the considerations being made; the Commission was working to see where replacements to animal studies could be made, offering some examples. Adaptations to Annex XI could see new ways of fulfilling information requirements using NAMs.

He pointed to the Commission roadmap for phasing out animal testing for chemical safety assessments. This was the response to the 'Save cruelty-free cosmetics' European Citizens' Initiative. Details about the Commission roadmap considerations are available online in the Communication of the Commission (2023) 5041.

He also provided details of how to participate in the Commission workshop in December 2023.

Panel discussion

Sylvie Lemoine felt there was significant overlap and alignment between the perspectives given. She thought it was time to move from 'thinking' to 'doing'.

Merel Ritskes-Hoitinga wanted to comment on the one-for-one replacement concept; she felt this was being misunderstood and encouraged people to look at the European Commission's e-module 52, freely available on ETPLAS (Education and Training Platform for Laboratory Animal Science). It explains the three types of replacement clearly. She added that the REACH database was suitable for AI use.

Jose Tarazona felt that using all the available data and information for safety assessment is key. He asked the panellists how all this could be brought together to make it easier to use.

Ofelia Bercaru said considerable work had been undertaken by the Commission within the chemicals strategy on a European common data platform. This would mean that the data coming from the various agencies – pesticides, biocides, REACH data and (to an extent) pharmaceutical data – will be available in a harmonised format. This will assist in reuse and development of new models. She pointed out that ECHA is working with other countries – Canada, the US and Australia - to put other data into the EUCLID format.

Georg Streck agreed that stakeholder involvement was extremely important; the coming workshop was an important opportunity for this. On regulatory acceptance and confidence, he felt this was a key point; regulators need the confidence that NAMs really provide what's needed to assess the chemicals and protect human health and the environment. Looking at the use of AI/big data, there needs to be checks on whether the outputs are reliable and trustworthy. For gaining confidence, he agreed it was an issue and was something that would benefit from further brainstorming.

Julia Baines felt that, on the issue of confidence, it was something that could be worked on right now. She hoped that the European Commission – when drafting the roadmap – was working with other regulators on how to build the required confidence. She felt EPAA could have a role here– for example – in developing suitable case studies. In terms of regulatory needs, she felt the focus should shift from endpoints themselves to looking at what protection goals these endpoints were trying to achieve. Katrin Schutte acknowledged this and said it would be a consideration for the roadmap.

Sylvie Lemoine said that – from an industry perspective - this will require considerable expertise. Often SMEs don't have this expertise, and she wondered how to make it work for the industry as a whole.

On the issue of transformative governance, Katrin Schutte said it was a natural bias to look at scientific evidence. However, she accepted what Merel Ritskes-Hoitinga had said concerning about it not being enough in itself to accelerate the shift to NAMs – if it were, it would have happened. She said she wanted to know more about transition science. Merel Ritskes-Hoitinga said animal testing was a relatively new area for transition science. She explained that the process required agreeing the priority areas for promotion with the stakeholders, and together identifying the barriers and the opportunities for acceleration. She had been told that there were 250,000 chemicals where information was lacking; it highlights why NAMs are necessary, because it's not possible to get the information from animal studies; the process needs to be speeded up. It's a work in progress.

Julia Baines believed that transformative governance is about identifying the different aspects required to make a roadmap successful, by defining not just the goal but the milestones on the way. It requires identifying the differing workgroups to make this a reality and to advance on the ultimate goal of phasing out the use of animals.

Sylvie Lemoine highlighted the need for political leadership as well; the Commission is keen to export greater standards to the rest of the world; it could do the same with the replacement of animal testing; she felt it was an element that was missing from the CSS, and we should build on the political momentum. Katrin Schutte said that commitment to non-animal science was already there, but accepted this was not the same as sustained political leadership; the need remains to 'walk the talk'.

Audience questions

Jay Ingram of the Humane Society International wanted Katrin Schutte to expand on the wider use and exposure information in the REACH registration; something he thought was

welcome. At the same time, however, streamlining substance evaluation procedures and that this would be hazard-based. He wondered what was the purpose of generating this data.

Katrin Schutte responded that the hazard focus needs to be there, but the increased use and exposure information should help define the correct risk management measures. It was not a surrogate for information on chemicals.

Vera Rogiers (member of the EPAA Mirror Group) wondered if - as well as building confidence – there should be a safe harbour for results. She sees a reluctance on the part of industry to enter new results if that facility isn't available to them.

Sylvie Lemoine fully agreed on the need for a safe space; there is much to learn from failures as there is from successes. Where this should be is not clear. Vera Rogiers felt there was a need for the European Commission to provide some funding for establishing this facility. Katrin Schutte said that one reason that this hasn't - yet- been explored was a reflection of the wide nature of chemicals falling within the scope of REACH as compared to Cosmetics. This is why Annex XI was being updated. She remained, however, open to suggestions.

Kirk Leech from the European Animal Research Association felt that resistance to change reflected a trust in the available science, and that the full transition to an animal-free approach cannot be met because the alternatives are not there. He added that using social science to explain why physical science has not replaced animal use seems 'back to front'.

Julia Baines said that it seemed naïve to not see resistance to change as a barrier. She gave examples of proven replacement methods that had not been taken up; this, she felt suggested that it was not simply about the science. She argued that social sciences could identify what the true nature of the barrier was; a proactive approach was required. Katrin Schutte, however, pointed out that - with at least one of the replacement methods mentioned - that it was indeed true that the alternative had been available for some time, the adoption had not been straightforward. There had been a number of unforeseen issues that had arisen, but they were part of the learning process.

***Online audience questions**: 'Who is it that lacks confidence in NAMs?'*

Ofelia Bercaru said there needs to be strong consistency between the regulatory framework and the uptake of NAMs. When building the roadmap, it was important that this spanned all pieces of relevant legislation, how the data was collected, how to improve data sharing, avoid unnecessary testing and agree what NAMs should be developed.

Sylvie Lemoine felt that the reason for the lack of confidence was twofold. Part was the lack of 'safe harbour'; the other was that certain NAMs had not been tested in all chemistries, so doubts inevitably remain; industry need the mechanisms to gain confidence. She felt there wasn't a reluctance to change in industry. As far as the regulators are concerned, this mostly lies in the Member States; this could be overcome through an advisory scientific committee, with sufficient trust. Overall, she felt the momentum was there.

Georg Streck echoed this; he felt we need to have more information on the domain of applicability of animal testing and when we can use it for specific chemicals. In terms of confidence in NAMs, all sides needed certainty – not just industry. He thought the advisory committee was an idea worthy of further exploration.

Merel Ritskes-Hoitinga agreed that there was a need to establish confidence in NAMs, but there was also a need to be critical of the existing system. She gave the example that pesticides had been tested in animals but we know next to nothing about their neurodegenerative effects in humans, so the system does not offer the protection it should.

***Online audience questions**: 'How do we ensure confidence in the validation of NAMs?'*

Julia Baines referred to the van der Zalm paper, which sets out the relevant parameters. It was a holistic assessment that was required. By understanding the technical characteristics of the test and what it's trying to achieve and work with regulators to make sure it's fit for purpose. Georg Streck pointed out that this topic will be addressed in a session at the December workshop.

Session wrap-ups

Katrin Schutte thanked the audience; she was struck by the alignment in ideas and the clarity in what was required. She encouraged people to attend the workshop in December to help speed up progress.

Sylvie Lemoine encouraged people to maintain momentum, take action where required, to always keep an open mind and to recognise the power of digital – we may already be behind in that domain.

Julia Baines thanked the Commission for working on a roadmap; it was this kind of attitude that would move things along.

Ofelia Bercaru said she saw a positive attitude from all stakeholders and a willingness for change. Working together will accelerate the process of moving away from animal testing.

Merel Ritskes-Hoitinga made a statement to the effect that ending animal testing would benefit all, and that therefore there should be a goal in the transition roadmap to reduce animal testing by 80% by 2030.

Georg Streck pointed out that – as the last panellist to speak - there was little left to add, and that he agreed with his fellow panellists.

Moderator Jose Tarazona thanked the panel and summarised by saying "The moment is now".

Session closed - Coffee break

Session 2 - Panel discussion 2 and Q&A:

There followed a moderated discussion (pharmaceutical sector) on the 'Impact of pharma strategy on innovation and animal testing,

Conference Moderator: **Jose Tarazona**

Participants:

- Sara Rafael Almeida, DG SANTE
- Kirsty Reid, EFPIA

- Sonja Beken, EMA
- Peter van Meer, Medicines Evaluation Board (MEB)
- Emma Grange, member of the EPAA Mirror Group, Cruelty Free Europe

Jose Tarazona again began by introducing how the session would unfold.

Sara Rafael Almeida, *DG SANTE*

Sara Rafael Almeida presented the provisions of the recent reform of the general pharmaceutical legislation, with a focus on those that particularly affect the 3Rs principle. This revision is part of the Pharmaceutical Strategy for Europe. The political objectives of the reform were sixfold – access to medicines, availability of medicines, affordability of medicines, competitiveness of the industry, ensuring environmental sustainability and combatting antimicrobial resistance – with the goal of creating a single market of medicines in the EU.

On the 3Rs principle, the proposal specifically strengthens this through a number of measures, including using New Approach Methodologies, where possible, in place of animal testing. Significantly, it will also place obligations on marketing authorisation applicants/holders, including to demonstrate compliance with 3Rs, reusing existing animal studies where possible, making the results of any animal studies undertaken publicly available and using alternatives where possible. In addition, the proposal encourages greater cooperation between EU agencies and national competent authoritiesin assessing substances, facilitating data sharing, and carrying out joint non-clinical studies to avoid unnecessary duplication of tests with live animals.

Kirsty Reid, *EFPIA*

Kirsty Reid began by reminding the audience of the pharmaceutical industry's existing public commitment to phasing in new methodologies. She pointed out that since 2010, EFPIA had been publishing case studies on the activities of member companies on this topic. EFPIA is a member of EPAA and also collaborates with the IMI and its successor, the IHI.

She said that EFPIA welcomes the revisions to the pharmaceutical legislation and is happy to see the measures on animal welfare. EFPIA itself is exploring further ideas to advance this and is discussing with the EMA on how to set up a regulatory taskforce. She listed a number of their other activities and initiatives. She reaffirmed EFPIA's commitment to further involvement.

Sonja Beken, *EMA*

Sonja Beken explained that the EMA already has a joint 3Rs working party for the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Veterinary Medicinal Products (CVMP). This working party has an extensive workplan, including updating the current inventory of regulatory testing requirements and identifying opportunities for the 3Rs implementation in the regulatory guidelines. It also looks at ways to promote the regulatory acceptance of NAMs. She felt that work on stakeholder interaction was particularly important and pointed out the need to work together; an annual stakeholder consultation was part of this. She stressed this work was not being undertaken alone; the working group was supported by the EMA secretariat and by a newly established expert community, as a well as several drafting groups.

On the reform of the pharma legislation, EMA welcomed the strong 3Rs wording, but was most interested in the 'how' of implementation. She highlighted the value of multistakeholder discussions in producing consensus.

Peter van Meer, *Medicines Evaluation Board (MEB)*

Peter van Meer wished to address the opportunities from a regulatory perspective. He said that NAMs themselves are not enough; it is important to keep thinking about which animal studies were really needed to bring medicines to patients. He pointed out that there had been a significant shift in drug development strategies in recent years towards a dialogue with developers and academia.

He explained the importance of weight of evidence in certain studies, and the importance of asking the question – for animal testing - "is this test really necessary?" and "do we need this at this moment in time?".

An EPAA consortium investigated this, to see how much a long-term study actually contributed to monoclonal antibodies product safety. Top line findings were that it rarely identified novel safety issues; let alone critical issues. From this, the consortium developed a weight of evidence approach. The revised pharma strategy seems to recognise this, promising smarter, more scientific, efficient and patient-centric approaches.

Emma Grange, *Cruelty Free Europe*

Emma Grange pointed out that, when planning any transition, targets become important. At Cruelty Free Europe (CFE), they have developed a 'RAT' (Replace Animal Tests) list, highlighting 10 regulatory tests still conducted in the EU despite there being validated non-animal options available. Were all 10 tests to be stopped, 1.4 million animals could be spared annually in the EU. CFE believed the barriers to overcoming the use of NAMs in these areas were relatively easy to address; therefore they could act as good initial targets on the roadmap. She then mentioned the routine use of second species testing for pharmaceuticals. Given sufficient resources, CFE believed some tests could be eliminated.

CFE has seen an increase in the availability of non-animal testing methods in pharmaceuticals, but not always with clear guidance on their use. To this end CFE hosted a number of workshops with experts who mapped how they could be used and where the gaps lie. More activities like this are needed to encourage their use in more settings than early stage investigations.

Panel discussion

The moderator posed the question to the panel as to whether there were any lessons for applications in chemicals.

Kirsty Reid pointed out that the pharmaceutical industry by definition produces chemicals, so it falls into both spheres of operation already. However, pharma was in a niche of its own, producing medicines that are biologically active and as such faced much more rigorous testing. However, there are opportunities to align with the chemicals industry on testing approaches.

Sara Rafael Almeida said the issue wasn't new, but the topic currently has fresh momentum, with a revamp in the scope of the 3Rs working group. Efforts would increase

even without changes to the pharmaceutical legislation. Still, this review in the legislation was a great opportunity to reduce animal testing, and one that should be seized.

Sonja Beken agreed that pharmaceuticals were very niche; much of the work was done on a product basis and in specific dossiers, including 3Rs-related activities. In terms of collaboration, the 3Rs working group of EMA is working closely with veterinary colleagues, which allows for discussion and harmonisation activities.

The moderator observed that the pharmaceutical sector seemed to have greater confidence in non-animal methods than the chemical sector; he wondered how that had come about. Kirsty Reid wanted to add to this, pointing out that the pharmaceutical industry was able to propose methodologies that were not yet validated and have them considered on a case-by-case basis. She wanted to know how industry could be sure that their proposals were taken into consideration.

Sonja Beken stressed that context of use was the main consideration; i.e. what use – or combination of uses – will you be using these NAMs? This will define the type of evidence that will be needed.

The moderator wondered how best to approach a dossier with a lot of innovative approaches; Peter van Meer said he didn't really know – he rarely saw them. He thought a 'safe harbour' approach was the best option, as it allowed regulators to see the methods and therefore start to understand them. He felt an approach for scientific advice was a valid one, and that advice is non-binding. Trust building and scientific dialogue were key.

In terms of barriers to implementing NAMs, Kirsty Reid said a large number of these new approaches were already in place and being used. They were reducing number of animals being used, but the alternatives lack the complexity to cover the full impacts on biological systems – but this is evolving. She added that a global acceptance of such methods would make a significant contribution.

Sonja Beken pointed out that the range of modalities deployed by the pharmaceutical industry mean that the regulators had no choice but to think differently. What was important was not to give a testing strategy, but to give the criteria for acceptance of a result.

Audience questions

Vera Rogiers (member of the EPAA Mirror Group) wanted to know why – particularly in pharmaceuticals - there was so little heard about human-derived cell and tissues, etc., in alternative methodologies. Do human-sourced materials cause the industry a problem?

Kirsty Reid thought part of the problem might be a regional aspect the acceptance of such sources, but wasn't sure. Sonja Beken added it was looking into how to define qualification criteria and 'gold standards'.

Audience questions

Pierre Sultana from AnimalhealthEurope (AHE) said that 3Rs was a priority for the global animal health organisation. He said that AHE has set up a standing group on the 3Rs to support this priority. This would help support the work being done in the EMA and the visibility of the accepted NAMs. He wanted to know if there were any thoughts on avoiding a sense of public deception around the wording used when talking about animal testing.

Emma Grange agreed clear communication – and not being misleading – was important. She felt it wasn't well understood by the public what the value of animal testing is. Without that, making the case for NAMs becomes more challenging. She wondered whether this should be part of the roadmap.

Sara Rafael Almeida said it was about what science could enable us to do. The development context of medicine development is a unique one and is oriented towards risk management. She felt that people like the panellists, who are equipped with these insights could be good ambassadors for this communication aspect.

David John from AHE added to his colleague's intervention, stressing that what was important to their sector was determined by the fact that for them, the animal was the patient. So, there would still have to be products tested in animals. Sonja Beken said that this wasn't a safety test per se, but a clinical trial and thus not in the scope of the Regulation; however, she recognised the point being made and the need for further reflection.

Audience questions

Julia Baines of PETA UK felt that a number of existing animal tests were redundant, because they don't meet a regulatory need or are simply not very reliable. She wanted to know what more could be done to eliminate these redundant methods and make sure they're not used.

Kirsty Reid agreed that there are such redundancies; while Sonja Beken pointed out that there were two reflection papers being revised and will soon be published for public consultation; this would provide an opportunity to give feedback on such redundant tests. Peter Van Meer said a good way to tackle this would be for journals to simply not publish studies that relied on such redundant texts.

Audience questions

Merel Ritskes-Hoitinga said the Directive 2010/63 states that "when there are 3Rs available, we have to use them"; is this being lived up to? Kirsty Reid was supportive of the Directive. She believed the fact that the EU having the strictest legislation was an important example and a driving force for the new legislation and what EFPIA members are doing internally.

***Online audience questions**: 'How do we ensure the ongoing competitiveness of the EU industry if animal study results are to be publicly available?'*

Kirsty Reid said there was a time and place to make it available; as a representative of the innovative arm of the industry, she saw the argument in favour of not making it available before it goes to market, but ultimately it should be shared.

***Online audience questions**: 'Is there a problem in informing the public that animal tests have their own issues and are not always the best methods of assessment?'*

Sonja Beken said that scientists are not naive; they know about the shortcomings and limitations of models; it's part of their training. Peter Van Meer fully agreed with this.

Session wrap-ups

Sara Rafael Almeida thanked the audience for the opportunity for presenting the proposal. She hoped that the proposal would not lose its ambition along the way and reiterated the Commission's willingness to engage.

Kirsty Reid said the innovative pharmaceutical industry was currently on a science-based road trip; it hadn't yet reached its destination. She urged people to reach out and collaborate.

Sonja Beken said these discussions with stakeholders were immensely valuable. She pointed out that the revision to the pharmaceutical legislation was not the only process ongoing, but it provided invaluable extra momentum.

Peter Van Meer thought that new legislation was a generational opportunity, and being able to contribute to it was hugely encouraging.

Emma Grange looked forward to an ongoing conversation – challenges remain but all are surmountable; a focus on replacement – and redundancy – would drive us forward.

Session closed

Concluding remarks

In his closing remarks, Giacomo Mattino', the EPAA European Commission Co-Chair, noted that discussion surrounded a common goal which was both clear and important. The reality, however, is that it can only be achieved gradually. There may be disagreements over the speed of the transition, but all who took part in the event agree on the goal. We need transparency and collaboration; but we can also – with chemicals – have the opportunity of a good start via the roadmap.

He felt that we have strengths; the first panel had mentioned science – including AI - that can support the transition, but science alone is not enough. At the same time there are several challenges. Coordination and cooperation – not silo working – is vital for all stakeholders; this includes the Commission and Commission services. There also has to be a place for everyone, including SMEs. Valuing a multistakeholder approach is essential.

We are at a tipping point, if we look at it from a technological development and regulatory viewpoints. We need to be conscious of that and direct our efforts accordingly.

Giacomo Mattino' thanked all those involved in making this conference a success, and the audience for their invaluable contribution. With that, the conference closed.