"The EU approach to deadlines regarding alternative methods: the Commission's support activities for 3Rs"

Ladies and Gentlemen,

In the first place, I would like to thank ECOPA for providing me with the opportunity to explain the basis of the European policy with regard to the replacement, reduction and refinement of animal testing.

The promotion of the 3Rs is a key policy issue, and that its impact in increasingly being felt, be this in regulatory reform, or in implementation of regulatory requirements, or in other activities such as validation, acceptance and dissemination. Furthermore, today this impact is not confined anymore to Europe, but is being felt world-wide.

In my presentation, I will shortly make some comments on the following issues:

- Regulatory incentives to the use of the 3Rs
- Research
- International Cooperation
- EPAA.

Regulation

Ever increasing compelling regulatory incentives have become a key driver for the promotion of the 3Rs in Europe.

The concept of the 3Rs was first introduced in European law by Directive 86/609 of 24 November 1986 regarding the protection of animals used for experimental and other scientific purposes. According to its article 7, an experiment shall not be performed if another scientifically satisfactory method of obtaining the result sought, not entailing the use of an animal, is reasonably and practicably available. In a choice between experiments, those which use the minimum number of animals, involve animals with the lowest degree of neurophysiological sensitivity, cause the least pain, suffering, distress or lasting harm and which are most likely to provide satisfactory results must be selected. All experiments shall be designed to avoid distress and unnecessary pain and suffering to the experimental animals.

On 5 November, the Commission adopted a proposal to modify this Directive, reinforcing the provisions on the 3Rs. This regulatory reform will be subject of a specific presentation by my colleague Susanna Louhimies.

On a more general level, the Treaty of Amsterdam[i], signed on 2 October 1997, introduced a Protocol on animal welfare. According to this Protocol, the European Community and its Member States must, as a principle, pay full regard to the welfare requirements of animals when they formulate and implement the Community's policies on agriculture, transport, internal market and research.

The full extent of these Union's commitment to alternative methods became particularly clear in the subsequent discussions regarding modification of the EU Directive on cosmetics products.[ii]

The 7th Amendment of the Cosmetic Products Directive[iii] introduced a ban on animal testing of final cosmetics products, as the safety of final products can be assessed on the basis of an assessment of ingredients. As regards ingredients, the 7th amendment introduced a phase-out of any animal testing with deadlines of 2009 and 2013 dependent upon the complexity of the endpoint.

Today, for 7 safety tests relevant for the 2009 deadlines, 4 alternative methods have been regulatory accepted and one will be accepted in the course of 2009. For the remaining 2 safety tests, on eye irritation and acute toxicity, all efforts are made by the Commission and Industry to ensure that alternative methods will be available in 2009/2010. For the 2013 deadline which concerns more complex endpoints, the development of alternative methods is scientifically difficult and the time allocated may not be enough despite Commission and Industry efforts. In 2011, the Commission will make a overall assessment, and, if needed, make the appropriate proposals.

Legal provisions concerning the 3Rs were introduced also via the new EU regulation on chemicals, the so-called REACH.[iv] According to REACH, chemicals on the European market must be assessed on their safety, and it therefore implies a temporary increase in animal testing. Given the scale of testing involved, REACH also introduced legally binding mechanisms to replace, reduce and refine animal testing. As a basic rule, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort. Detailed rules on data sharing are laid down in the provisions regarding the Substance Information Exchange Forums (SIEF) and relevant guidance on data sharing published by the ECHA.[v]

More recently, the European Parliament and the Council are discussing a proposal for a revision of the Plant Protection Products Directive.[vi] In its

proposal, first of all, the Commission adopts recommendation of the EFSA Plant Protection Products Panel on a replacement and reduction of particular animal testing in Annexes II and III. [vii]

The new regulation will confirm the principle that tests on animals are to be undertaken only where no other alternatives are possible, and that, when no alternatives are available, other appropriate testing strategies shall be used to keep the number of animals used to a minimum.

The new regulation will also establish that studies conducted in the past, although not fully compliant with today's standards and GLP, may be integrated into the assessment, if scientifically valid, thereby removing the need for repeating animal tests, especially for carcinogenicity and reproductive toxicity studies

Like REACH, the regulation will contain stringent provisions on data sharing.[viii]

Adoption of the new regulation is foreseen for the first half of 2009.

Provisions on testing and consequently the promotion of the 3Rs are in many cases introduced through fast-track regulatory procedures, for which the Commission has received a delegation from Parliament and Council. At the occasion of the introduction of test methods for REACH in May this year, the Commission took a commitment on reviewing internal procedures aimed at accepting alternative test methods. In the same context, the Commission undertook to consider, with the OECD, how OECD procedures could be streamlined. A report on this process will be published before the end of this year.

Overall, therefore, we see that the principle of the 3Rs will be considered in a specific way each time regulatory change is introduced for product regulation that involves animal testing. We see a focused approach by the regulator to sharpen and improve provisions on data-sharing. Finally, regulatory processes for implementing legislation through the so-called Comitology, are subject or review to speed up procedures where-ever this is possible.

Research

Also in its Research policy the Commission strongly supports the promotion of the 3Rs, mainly through the RTD Framework Programmes. As explained Commissioner Potocnik during the EPAA Conference on 3 November, we have high expectations for a number of FP6 projects on replacement still going on. FP7 started a significant number of new initiatives ranging from integrated testing strategies to co-ordination and

support actions aimed at making best use of limited amount of money available.

The replacement of animal tests is higher than ever on the political agenda. Large efforts have been made in research over the last 20 years to replace, reduce and refine the use of animals in experimentation through alternative approaches in safety testing. More than 150 million Euro have been spent through European RTD Framework Programmes since the mid-eighties. The 7th European RTD Framework Programme continues to support financially research in this area, mainly through the Theme "Health" and "Environment" Themes.

Replacement remains a key issue in our research policy as demonstrated by the specific programme 'HEALTH' of FP7. A group of some 10 experts is now working on the definition of a work programme to put in place the long-term building research blocks for 'the full replacement of animal tests in safety testing'. But, whilst replacement is a key priority, we remain also focused on reduction and refinement.

Through the FP6 Environment programme, 3R research is being supported to anticipate the expected future massive use of testing for industrial chemicals under the REACH Regulation. Emphasis has been put on mathematical modelling and on the development of Integrated Testing Strategies.

In FP7 research continues to focus on safety testing and risk assessment for human health and the environment. The development of screening methods for "REACH-chemicals" will be supported through a coordinated call under the FP7 Environment Theme together with the US-EPA.

The Commission is also diversifying the way research is being implemented. For instance, we launched the Joint Technology Initiative on Innovative Medicines – IMI – a public-private partnership between the pharmaceuticals industry represented by EFPIA and the European Commission. It promotes the inclusion of the 3Rs principle in numerous topics of the work programme and did so specifically in its first call. This will continue in future IMI calls prepared jointly by the EFPIA and the Commission.

Last year, the Commission was approached by COLIPA, the European association of manufacturers of cosmetics, suggesting a new, joint effort by industry and Commission to intensify research on "repeated dose systemic toxicity". This joint research initiative is currently under negotiation between the Commission and COLIPA It is planned to launch a call for proposals next year under the the FP 7 HEALTH programme. As announced Commissioner Potocnik, we will pay more attention to

coordination of research activities to avoid duplication. Furthermore, we will ensure a better monitoring, evaluation and dissemination of results.

But we are also improving our internal knowledge base, in particular through the Institute for Health and Consumer Protection of the Joint Research Centre in Ispra. Most of the toxicological 'endpoints' require an integrated testing approach, combining laboratory and computer simulation methods and the use of test batteries. By building competences in this area, the Ispra Institute will be well placed to scientifically assess and potentially validate suitable new technologies which may have great potential to even further reduce the use of animals for toxicity testing.

Finally, in the near future and in close collaboration with DG ENV and DG ENTR, the JRC will launch a dedicated website called TSAR2. This will present information on the status of alternative methods - starting from the submission to ECVAM - for validation by the regulatory process.

International cooperation

The promotion of the 3Rs in regulatory testing is only effective if initiatives to promote the 3Rs have a global dimension. It makes little impact on animal testing if animal testing is banned in one region, but remains obligatory in another region.

Therefore, in parallel with action in Europe, the European Commission has put the issue of the 3Rs on the agenda of its regulatory dialogue wit its main trading partners: today, the 3Rs are a standing point on the agenda of the regulatory dialogue with the United States, Japan, Canada and Australia.

Work is carried out in different fora and subject of monitoring in our bi- or multilaterals talks.

For instance, in the area of pharmaceutical products, work is going on in the EDQM in relation to a proposal to avoid duplication of testing for batch release. The ICH is currently considering a proposal to reduce and eventually replace acute toxicity testing for pharmaceuticals as a follow up by a collaborative research project coordinated by the UK Centre for 3Rs and which resulted in a recommendation to waive the actue toxicity testing the development of pharmaceutical products.

Particular relevant in this context are however action undertaken in the cosmetics area, where regulatory drivers are the strongest, and where, once again, action for cosmetics becomes a precursor for other areas.

In September 2007, the European Commission and regulators from the US, Canada, Japan and Australia, launched, with industry, the ICCR, the International Cooperation on Cosmetic Regulation. One of the ICCR’s

priorities is animal testing. In its meeting of September 2007, the ICCR invited ICCVAM, ECVAM, JaCVAM and Canada to propose options to ensure a collaborative approach on validation and peer review.

As a follow-up, in their second meeting, in July 2008, the ICCR created the International Cooperation on Alternative Test Methods (ICATM) working group to enhance cooperation in replacing, reducing, and refining animal testing. The ICATM framework will address three critical areas of cooperation: (1) validation studies, (2) independent peer review of the scientific validity of test methods, and (3) development of formal test method recommendations on alternative testing methods.

Although the ICATM was launched at the instigation of authorities in charge of cosmetics, its impact will go beyond the mere sector of cosmetics.

The European Partnership for Alternative Approaches to Animal Testing.

Finally, I would like to say a few words about the European Partnership for Alternative Approaches to the Animal Testing, the EPAA.

The EPAA is a voluntary, consensus based partnership launched in 2005 between the European Commission and industry from seven large sectors, represented today by some 37 companies and their respective European trade associations. EPAA is cooperation between "regulators" and "the regulated", all convinced that the success of promoting the 3Rs lies in a holistic approach towards implementing regulatory requirements by joining resources and efforts.

EPAA activities range from research up to validation and acceptance, placing strong emphasis also on dissemination: dissemination and information will be the EPAA lead theme for 2009, as announced by Vice President Gunter Verheugen during the EPAA 2008 Conference.

More and more the EPAA succeeds in launching projects that allow sectors participating to benefit from experience and practices gained elsewhere, and to promote a cross fertilisation. Concrete examples of this fresh integrated approach are projects such as

Acute toxity: Following a project carried out in the pharmaceutical sector, now subject of a follow-up by ICH as I mentioned before, EPAA has initiated a project in order to verify retrospectively the regulatory relevance of acute toxicity testing in the sectors of cosmetics, agrochemicals, chemicals,…. .A proposal and call for participation to EPAA members received good feedback. Current discussions should lead to the organisation of a dedicated workshop with additional experts in 2009.

EPAA intends to examine the implications for classification and alternative approaches development, with a focus on skin and eye effects. A proposal for a project on "Evidence Based Classification: GHS Classification & Labelling for Skin and Eye irritation: Making use of Weight of Evidence, Expert Judgment and Bridging Principles to avoid Animal Testing" Was sent out in May 2008. The experience from different sectors regarding these toxicological effects will be taken into account. Work on this project has started in the meantime.

More in the area of research, mention should be made of the EPAA databases on research, one providing a non-exhaustive inventory of alternative tests and approaches employed by companies in screening or decision-making processes related to product safety evaluation and the other providing a non-exhaustive list of ongoing research projects that are intended to result in 3Rs benefits in the assessment of human, animal and environmental safety. In November 2008, the EPAA had a Workshop on in vitro Metabolism, based on the information contained in the EPAA databases. Also in November, EPAA organised a workshop on approaches to validate and ultimately accept for regulation Intelligent Testing Strategies.

In April 2008, EPAA organised a workshop on "New Perspectives on Safety" bringing together eminent scientists from different disciplines to advise on the research needed to enable future hazard identification without the use of animal testing. This workshop identified areas of complementary science which have the capacity to revolutionise the science of safety assessment. Participants agreed there is a case for reconsidering the science base for regulatory testing in the field of repeat dose systemic toxicity. EPAA is now in the process of following up the various recommendations made.

Another EPAA project consists in the verification whether the alternative test developed for agrochemicals by the ILSI/HESI project on agricultural chemical safety assessment (ACSA) could also be applied to other sectors such as industrial chemicals.

An EPAA workshop organised in 2006 concluded that the extended one-generation study could, in principle, be applicable to safety testing under REACH. However, it was also agreed that the complex ACSA protocol would have to be modified in order to meet the current requirements for industrial chemical safety testing. Currently, EPAA companies are involved in feasibility studies based on these modified protocol.

Eventually, the project should lead to an OECD guideline for an extended one-generation study. Implementation would lead to a more than 40% reduction in the number of animals used compared to the two-generation study currently required.

Other EPAA projects bear on pragmatic issues, such as standard operating procedures for cooperation between ECVAM and industry for the delivery of data with a view to validation of alternative methods, mechanisms to accelerated regulatory acceptance, procedures to facilitate validation.

Given the emphasis on dissemination for 2009, several EPAA projects take a particular relevance such as the "single portal". In various sectors, the implementation of regulatory testing requirements is subject to bilateral company/regulatory authority dialogue and scientific advice. It was considered useful to look at how experience gained in this process can be reapplied within sectors or across sectors and how reporting of 3Rs issues, follow up and reapplication between sectors could be enhanced. A project, the "one-stop shop", was launched in 2008. Results and follow-up to a questionnaire sent out for scoping and interest are currently being evaluated.

Overall, EPAA has been instrumental in the implementation of 3R culture at the level of industry, regulators, academia, etc, not only in Europe, but at the global level. It has increased 3R's awareness, and is considered unique in the world.

Ladies and Gentlemen,

Once again I would like to thank you for all you do for the welfare of animals and for having given me the pleasure and honour to explain our commitment and policy on the 3Rs. I will conclude by wishing you an interesting and fruitful conference. We look forward to working with ECOPA.

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[i] Treaty of Amsterdam amending the Treaty on European Union, the Treaties establishing the European Communities and related acts; Official Journal C 340, 10 November 1997

[ii] Council Directive 76/768 of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products

[iii] Directive 2003/15/EC of the European Parliament and of the Council of 27 February 2003 amending Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products (Text with EEA relevance) ; Official Journal L 066 , 11/03/2003 P. 0026 – 0035

[iv] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC,OJ L 396 of 30.12.2006

v Chemicals must be registered and data required for registration vary on the basis of tonnages produced. In order to reduce animal testing to a minimum, data relevant for registration must be shared. Thus, if a relevant study involving tests on vertebrate animals is available within the SIEF, a participant of that SIEF must request that study. Similarly, if a relevant study not involving tests on vertebrate animals is available within the SIEF, a SIEF participant may request that study. In both cases, costs will be shared in a fair, transparent and non discriminatory way. Penalties are foreseen in case owners of a study refuse to provide either proof of the cost of that study or the study itself.

[vi] If a relevant study involving tests is not available within the SIEF, only one study shall be conducted per information requirement within each SIEF by one of its participants, acting on behalf of the others. Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market

[vii] Introduction of the tiered approach; for short-term toxicity, the 1-Year dog study will be deleted; for genotoxicity, the rodent dominant lethal assay will be deleted; as regards the multi-generation studies, the F1-extended one generation study is to be considered as alternative approach to multi-generation study as soon as developed and validated

[viii] For instance, industry must employ every effort to share tests and studies involving vertebrate animals and inform competent authorities, if there is no agreement for test sharing, national courts will determine costs to be shared.