European Partnership for Alternative Approaches to Animal Testing

First Annual Progress Report

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The European Partnership for Alternative Approaches to Animal Testing (EPAA) was launched on November 7, 2005 at a conference entitled *Europe goes alternative.* At the end of this conference the founding partners agreed a set of principles known as the *3Rs Declaration*, which articulated the EPAA's vision and established its terms of reference. Its objective is to accelerate the development, validation and acceptance of alternative approaches for the purposes of regulatory safety assessment.

The participants of the Partnership committed themselves to contribute to an Action Programme that identifies short, medium and long-term activities. The Action Programme would identify barriers to progress and propose appropriate solutions in order to promote the development, validation, regulatory acceptance and practical implementation of alternative approaches.

At the Conference, partners also made the commitment to present for the attention of the Council, European Parliament and other relevant stakeholders a report on the implementation of the action programme will be published

Much has been achieved in the first year of the EPAA, and the foundations are now in place to deliver its ambitious objectives. The cooperation, which now drives the EPAA is unique because of the wide range of interests involved, and because of a common determination to make tangible progress in promoting alternative approaches to animal testing. In conformity with the commitment given during the 2005 *Europe goes alternative* conference, we are delighted to present the EPAA's first annual progress report

Brussels, December 2006

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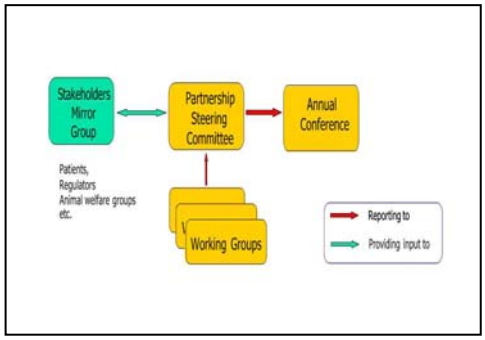
Executive summary

The European Partnership for Alternative Approaches to Animal Testing (EPAA) is a policy initiative launched by Vice President Verheugen and Mr Potočnik of the European Commission, 7 European trade federations and 8 companies, all committed to accelerating, by bringing together resources and know-how, the development, validation and acceptance of alternative approaches for the purposes of regulatory safety assessment. At that occasion, the partners made the commitment to report within one year on progress made.



The EPAA currently involves seven major industry sectors - soaps and detergents, chemicals, cosmetics, pharmaceuticals, bio-industries, crop protection and animal health, and services of the European Commission. The number of company members has increased from 8 to 27 (November 2006).

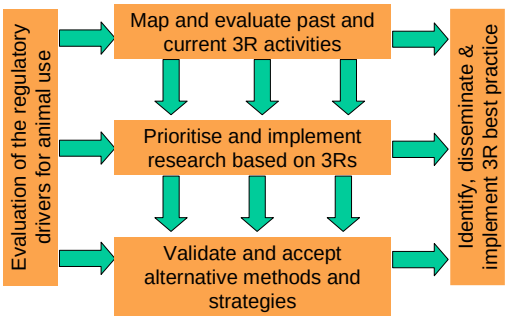
The EPAA works on the basis of a light and manageable structure.

The EPAA Action Programme, adopted in May 2006 constitutes a balanced and coherent initiative towards alternative approaches to animal testing, focusing EPAA's initial short, medium and long-term activities on five major themes

Mapping of past and current 3R activities to share successful approaches and better inform the planning *and* prioritisation of subsequent actions

EPAA's current and future work should be based on knowledge of the various R&D initiatives undertaken by industry and government. EPAA therefore has initiated a review of "in-house" alternative methods and approaches, enabling companies to share the alternative approaches that they use and to identify those with potential for transfer and reapplication within and between sectors, further development or formal validation.

Interlinkage of Working Group Activities



EPAA has also initiated a review of ongoing research projects with the potential to deliver 3Rs benefits, intended to better define future research needs – be it within the EPAA or elsewhere (for example the 7th Framework Programme). In this context, EPAA is also examining the current status of relevant OTS activities and recommendations for (re-) application of OTS elements and further investigations aimed at an overall reduction in animal use. Priorities would be industrial (re-) applicability and international harmonisation

Prioritisation, promotion and implementation of future research based on the application of the 3Rs

EPAA seeks to identify opportunities for a more widespread application of established sector-specific testing strategies for complex endpoints such as reproductive toxicity within safety assessment models in other sectors. For instance, the ACSA[1] approach could also be applicable to the implementation of

[1] Agricultural Chemical Safety Assessment

REACH with a significant reduction of the number of animals used for testing chemicals.

Based on EPAA input, the EU 7th Framework Programme for Research, Technological Development and Demonstration Activities (RTD) included in the first call for proposals a topic (co-ordination action) in support of setting up the respective RTD programme for developing non-animal methods that will allow assessment of repeat systemic dose toxicity without compromising safety assessment. EPAA also defined in detail the boundary conditions for such a multi-annual co-ordination action.

Identification, dissemination and implementation of best practice in the 3Rs

One of the objectives of EPAA is to improve the promotion, dissemination, and implementation of the 3Rs. EPAA therefore completed a mapping and collation of 3Rs organisations within Europe, made available on the EPAA website.

In addition, EPAA has undertaken an analysis to understand what constitutes success in promoting and disseminating information on the 3Rs. This ongoing work will help drive the design of a dissemination strategy for EPAA and result development of guidance and recommendations for use by organisations involved in promoting the 3Rs.

Implementation of the 3Rs in regulation and decision-making

EPAA has undertaken a regulatory review, the first of its kind, to obtain a better understanding of the requirements and implementation mechanisms in the area of regulatory testing involving animals and 3R methods. In its first stage, EPAA focussed on the pharmaceuticals, chemicals, cosmetics and crop protection sectors.

The review identified significant regulatory differences according to sectors, and highlighted various difficulties in implementing alternative methods. This work will constitute a basis for recommendations to be developed in 2007 to reduce animal testing and to overcome difficulties in the implementation of 3Rs in regulatory testing.

EPAA work under this heading also allowed to specify that a significant part of activities/programmes aim at reducing and refining in vivo tests. Full replacement methods are already available for instance for skin corrosion and acute phototoxicity.

Validation and Acceptance

In a pragmatic approach, EPAA identified a number of priorities in work being carried out by ECVAM, for which EPAA partners could provide immediate support on the basis of an agreed list of criteria. The purpose is to pilot a few projects where needs are well defined and which will be most relevant in light of regulatory testing requirements.

In order to increase efficiency in stakeholder collaboration, EPAA intends to create, on the basis of experience with ECVAM, a framework for collaboration to facilitate successful validation.

Given the fact that validated alternative methods are not always necessarily subject to regulatory acceptance, EPAA intends to focus activities also on legal acceptance of validated methods.

European Partnership for Alternative Approaches to Animal Testing

Annual Progress Report

December 2006

Towards a new approach to safety testing

The European Partnership for Alternative Approaches to Animal Testing (EPAA) is a groundbreaking collaboration between the services of the European Commission and a broad range of companies and European industry associations committed to the replacement, reduction and refinement of animal testing (the so-called '3Rs'). Its objective is to accelerate the development, validation and acceptance of alternative approaches for the purposes of regulatory safety assessment.

The EPAA was created in November 2005 with the aim of:

- Stimulating the development, validation and implementation of alternative approaches to animal testing
- Identifying European and international opportunities to address barriers to progress, and ensure mutual acceptance
- Building on past achievements in applying the 3Rs to animal testing
- Supporting development of new, modern approaches to safety assessment
- Fostering dialogue with stakeholders on developments that effectively contribute to animal welfare
- Recognising the importance of intellectual property rights to innovation and the overall competitiveness of European industry

The EPAA currently involves seven major industry sectors - soaps and detergents, chemicals, cosmetics, pharmaceuticals, bio-industries, crop protection and animal health, and services of the European Commission (DGs Enterprise, Environment, Health & Consumer Protection, Research and Joint Research Centre). By sharing knowledge, research and resources, and by taking a genuinely collaborative approach to the 3Rs, the partners intend to make significant progress to the development of alternative approaches in the medium term.

The EPAA was launched on 7 November 2005 at a conference entitled *Europe goes alternative.* At the end of this conference the founding partners agreed a set of principles known as the *3Rs Declaration* (see Appendix 1), which articulated the EPAA's vision and established its terms of reference.

In the months that followed the conference, principles and structures for cooperation and an action programme were discussed by a specially convened working group, and appropriate communication networks and tools were developed for everyone involved in the partnership.

The development of an action programme required extensive consultation among a wide range of experts drawn from industry and European Commission services. Themes for action were determined on the basis of a realistic assessment of needs and potential to make progress, built around five interconnected themes (see page 10).

These discussions were critical in building up the necessary trust and common understanding amongst industry sectors with very different approaches and legal requirements on safety testing. Similarly, a common ground had to be identified between services of the European Commission and industry for making significant advances in a politically sensitive area, where concerns to promote animal welfare have to be balanced against the need to protect public health and the environment.

In its first meeting on 17 May 2006, the EPAA steering committee formally agreed on structures and principles for its operation, and an action programme. Work on the action programme was launched through five working groups, comprising over a 100 experts.

This report reflects the commitment taken during the 2005 Europe Goes Alternative Conference, to inform on a regular basis the European Parliament, Council and other relevant stakeholders on progress in the implementation of the Action Programme. This report also summarises the principles and structures on the basis of which EPAA is functioning.

A. PRINCIPLES AND STRUCTURES OF THE EPAA

The EPAA operates on the basis of the following principles:

- a commitment to the 3Rs Declaration and to active participation in its implementation with a focus on regulatory safety testing
- science based improvement
- a voluntary, consensus based approach
- pragmatic mechanisms and a workable structure
- a wider dialogue with and transparency towards stakeholders and interested parties

The strategy and governance of the partnership is overseen by a representative S**teering Committee**, which is also responsible for the development and implementation of the action programme including the appointment and monitoring of the five expert working groups. Additionally, the steering committee is responsible for communicating the progress of the EPAA to all interested parties, principally through its website (see page 9), the annual progress reports and the annual conference.

Work on the Action Programme is carried out by five **Working Groups**. Each group concentrates on one theme of the EPAA Action Programme. Participation in Working Groups is in principle also open to non-EPAA members.

EPAA members believe that a critical insight into the EPAA work from different stakeholder perspectives is essential to enhance efficiency, output and acceptability of results. Consequently, a **Mirror Group** has been established to reflect the perspective of stakeholders drawn from the animal welfare community, environmental and patients' organisations and academia. This mirror group, chaired by Dagmar Roth Behrendt, Vice President of the European Parliament, met for the first time on 12 October 2006.

Progress on promoting alternative approaches will furthermore be presented to the general public and all interested parties at the occasion of an annual **Conference**.

B. MEMBERSHIP

The EPAA is made up of the services of the European Commission involved in promoting animal welfare and alternative approaches to animal testing, and individual companies and European industry associations committed to the 3Rs Declaration, and willing to actively participate in its implementation.

Industry

Industry is involved through individual companies and industry associations, covering a wide range of sectors which rely on animal testing for the development and safety evaluation of their products.

Originally there were 8 founder companies. As of November 15 2006, the number of member companies had increased to 27:

Astra Zeneca
BASF
Bayer
Beiersdorf
Chanel
Colgate-Palmolive
Dow Europe
Elizabeth Arden
Estée Lauder
Euroderm
Glaxo SmithKline
Henkel
Johnson & Johnson
L'Oreal
LVMH
Merck
Merck Sharp and Dohme
Novo Nordisk
Pfizer
Procter & Gamble
Reckitt Benckiser
Serono
Solvay
StratiCELL
Syngenta
Unilever
Vetoquinol

The EPAA remains committed to utilising the expertise of as many companies as possible, and it is hoped that this list of member companies will continue to grow.

The European industry associations, participating in support of their company members, are:

- The Association for Soaps, Detergents and Maintenance Products (AISE)
- The European Chemical Industry Council (Cefic)
- The European Cosmetic Toiletry and Perfumery Association (Colipa)
- European Crop Protection Association (ECPA)
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- European Association for Bioindustries (EuropaBio)
- International Federation for Animal Health Europe (IFAH-Europe)

European Commission Services

The Commission services involved are:

- Directorate General for Enterprise and Industry (chemicals, medical devices, cosmetics and pharmaceutical)
- Directorate General for Health and Consumer Protection (food and feed, crop protection, the Action Plan on the Protection and Welfare of Animals, Scientific Committee and Risk Assessment).
- Directorate General for Environment (new chemical substances, protection of animals used for experimental and other scientific purposes).
- Directorate General for Research and Development (promotion of R&D on alternative approaches to animal testing)
- Directorate General of the Joint Research Centre, and more particularly ECVAM, the European Centre for the Validation of Alternative Methods and ECB, the European Chemicals Bureau.

C. COMMUNICATION

Committed to provide transparency on its activities, the EPAA has a dedicated website:

www.epaa.eu.com

The website contains background information about the EPAA as well as details about its members, the operation of the steering committee and the mirror group, and the activities of its working groups. Minutes of the meetings of the steering committee and the mirror group are also made available on this website.

The EPAA has also published a brochure setting out its principles, structures and activities. Copies of this brochure are available from the EPAA secretariat, and may also be downloaded from the website.

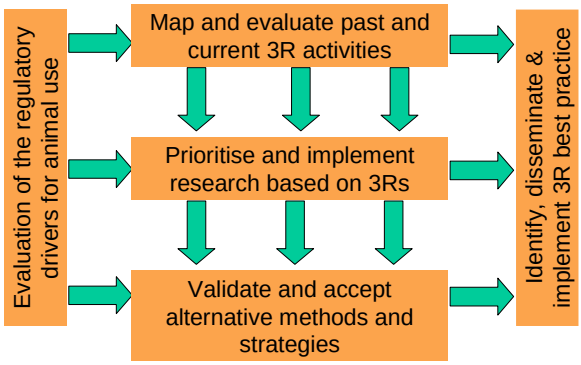
As part of the EPAA's commitment to share ideas and expertise, EPAA representatives gave presentations to the following scientific conferences in 2006:

- BTS/NC3Rs/IVTS Joint Autumn Meeting (organised by the British Toxicology Society), York (UK), 14–15 September 2006;
- INVITOX 2006, 14th International Workshop on In Vitro Toxicology, Ostend (Belgium), 2-5 October 2006;
- IVTIP (In Vitro Testing Industrial Platform) annual conference, Hamburg (Germany), 27 October 2006.

D. ACTION PROGRAMME

The EPAA action programme, adopted in May 2006 and supported by the mirror group in October 2006, identifies a number of concrete activities to take place over an initial period of 5 years. The action programme is a living document, which can be revised in the light of newly identified priorities, input from stakeholders (in particular through the mirror group and the annual conference), and progress from the five working groups.

Interlinkage of Working Group Activities



The action programme describes the EPAA's initial short, medium and long-term activities on five major themes:

- Mapping of past and current 3R activities to better inform the planning and prioritisation of subsequent actions
- Prioritisation, promotion and implementation of future research based on the application of the 3Rs
- Identification, dissemination and implementation of best practice in the use of the 3Rs
- Implementation of the 3Rs in regulation and decision making
- Validation and acceptance based on the 3Rs

All five themes are interdependent and constitute a balanced and coherent initiative towards alternative approaches to animal testing (see diagram).

Five working groups, involving more than 100 experts, have been set up to implement the action programme. These groups draw on the knowledge, expertise and resources of the EPAA member companies to maximise the amount of work being carried out. As a consequence of this approach it is estimated that a multitude of experts across the EPAA member companies are contributing to the goals of the partnership.

For the purposes of this document, the working group reports have focussed on short term activities identified in the action programme. Implementation of other activities will follow at a later stage (for the 5-year visions refer to action programme in Appendix 2).

E PROGRESS OF THE WORKING GROUPS TOWARDS IMPLEMENTATION OF THE ACTION PROGRAMME.

Working group 1
Mapping of past and current 3R activities to share successful approaches and better inform the planning *and* prioritisation of subsequent actions

Alternative approaches to animal testing are developed and applied in industry, within academia and by regulatory authorities. Such approaches and testing strategies are not necessarily fully coordinated due to the various actors and stakeholders involved. Consequently, it is difficult to maintain a full overview of these activities at national, European and international level. Against this background, contributions from previous and current 3R activities need to be identified and consolidated in order to better inform the planning and prioritisation of future activities of the EPAA.

Review of "in-house" use of alternative methods and approaches

The "in-house methods" review will identify industry decision-making processes and criteria for the use of 3 R methods in product development and assessment of regulatory compliance. The aim is to enable companies to share the alternative approaches that they use and to identify those with potential for transfer and reapplication within and between sectors, further development or formal validation. Such approaches may have been developed in-house or they may have been adopted from outside the company and adapted for use.

A questionnaire has been developed and tested within working group 1, prior to being sent to all EPAA member companies and associations in September 2006. A contractor will aid the analysis of the results and help draft a report in cooperation with working group 1 members.

The report will identify methods with potential for subsequent dissemination, transfer, reapplication or validation. A workshop is planned for 2007 to test the outcome and recommendations of the report with a suitable subset of stakeholders, and to agree upon priorities for subsequent action**.** A "living" inventory of in-house use of 3R alternatives and alternative approaches from the pharmaceuticals, animal health, chemicals, cosmetics, cleaning products, biotechnology and plant protection sectors is envisaged.

Ongoing research projects with the potential to deliver 3Rs benefits

The review of ongoing research into alternative methods will identify research projects that should result in 3R benefits relating to the use of animals in the assessment of human, animal and environmental safety and efficacy. This is intended to better inform future research needs – be it within the EPAA or elsewhere (for example the 7th Framework Programme).

Working group 1 has developed and tested a second questionnaire, to be sent to all EPAA member companies and industry associations,

(a) academic and other research institutes involved in relevant Community-sponsored research (with the involvement and assistance of DG R&D) and
(b) interested parties, such as ECOPA[2].

[2] European consensus-platform for alternatives (www.ecopa.eu)

The questionnaire will specifically aim to identify potential 3R benefits and likely industrial applicability of these benefits. As with the first questionnaire, a contractor will assist in the analysis of the results and to help draft a report in cooperation with working group 1 members.

A report evaluating current research efforts, overlap/synergies and areas that appear to be under-represented in current ongoing research within the EU will also be prepared. A web-based inventory containing links to appropriate external websites giving additional details of research programmes is also envisaged. Following analysis of the results from the questionnaire, additional face-to-face discussions, workshops etc. may be considered.

Optimised testing strategies

An additional activity also under consideration within working group 1 is the creation of an inventory of projects evaluating optimised testing strategies (OTS) for regulatory applications across the relevant sectors. The likely product would be a report highlighting the current status of relevant OTS activities and recommendations for (re-)application of OTS elements and further investigations aimed at an overall reduction in animal use. Priorities would be industrial (re-)applicability and international harmonisation. A stepwise approach would be adopted, building on output from the two initial activities underway within working group 1 and also other relevant activities being undertaken by the EPAA. Discussion and interviews with experts from industry and authorities would likewise be required. Other stakeholders could be consulted if needed.

Next steps

Working Group 1 will communicate the results of the various activities to the other working groups. For example, this will permit WG 2 to potentially highlight any gaps in RTD. WG 2 will also monitor the outcome of current pertinent research identified by WG 1. Likewise, WG 3 will potentially disseminate any examples of "best practice" revealed by WG 1. Similarly, any methods with any potential for validation will be shared with WG 5. The output from WG 1 may also have applications outside the EPAA e.g., the output of the research mapping could potentially be used as input (amongst other information) by DG R&D in order to define, with Commission services and Member States, the priority research areas for the calls for tender on alternative approaches to be launched under the 7th Framework Programme. The same information could likewise be usefully employed to help guide industry funded research programmes.

Working group 2
Prioritisation, promotion and implementation of future research based on the application of the 3Rs

The identification of priorities for future research embracing Replacement, Reduction and Refinement (the 3Rs) is a key objective of the EPAA. The focus is on requirements for risk assessments and associated activities that might be implemented within the initial five-year lifespan of the action programme. The work of Working Group 2 is based on the experience and information gathered under working groups 1 and 4. Emphasis will be placed on those opportunities that derive from the close working relationship between 7 industry sectors and the European Commission.

On the basis of wide consultation within and outside the EPAA and with major stakeholders, five activities have been identified, from which the following two research issues were decided to be tackled with high priority.

Opportunities for the more widespread application of established sector-specific testing strategies for complex endpoints, such as reproductive toxicity within safety assessment models in other sectors.

With regard to upcoming EU Chemicals Regulation (REACH), developmental/ reproductive toxicity testing is a key component for the risk assessment of chemicals, and is very resource-intensive in terms of animal numbers, costs and time. However, there are currently no methods in sight that totally replace this kind of safety testing in animals short- to mid-term. Consequently, new testing strategies leading to a reduction and or refinement of animal use immediately should be applied as broadly as possible.

In a workshop held on November 14, 2006, which was attended by more than thirty experts from industry, regulators and the EC, it was concluded that the extended one-generation study as developed by the ACSA project[2] could in principle be applicable to safety testing under REACH as a replacement for the two-generation study (OECD 416). However, it was also agreed that the complex ACSA protocol has to be modified in order to meet the recommendations connected to chemical safety testing. This will deliver animal welfare benefits with regard to both refinement and a reduction in the number of animals used (more than 40 % compared to the two-generation study).

To implement this new test method into the REACH TG, however, the methodology has to be formally validated. The validation would consist of setting up a final test protocol (SOP), experimental work (feasibility study) as well as retrospective validation of the endpoints used. During the workshop, ECVAM agreed to take the lead on the validation and three companies (BASF, Bayer, Syngenta) volunteered to conduct experimental work. In order to achieve this goal as fast as possible, WG 2 together with WG 5 will identify a contact person for all stakeholders involved (ECVAM, EC, regulatory bodies, industry) and set up an expert group to define the modifications of the protocol.

Since major European as well as US American authorities indicated to support this activity, it is believed that within two to three years an OECD guideline could be finalized, which could serve as a basis for a regulatory use of this new methodology.
The final report of this workshop will be presented in February 2007. It will include detailed recommendations regarding modified approaches to safety assessment and ways to define a strategy on how developmental toxicity testing could be performed in the future.

Identify research needs towards hazard characterisation and risk assessment without the use of animals in the area of repeat systemic dose toxicity

The EPAA has as a long-term objective to develop non-animal strategies that will allow assessment of repeat systemic dose toxicity without compromising safety assessment. The short-term goals are to identify relevant research needs to frame a research programme.

Most research initiatives have focused on developing methods and strategies in order to reduce the need for animal tests, however no programme exists yet to develop research to fully replace these tests. It is not anticipated that this action will result in a short-term success, but rather will provide a framework for long-term research that will change

fundamentally the way in which toxicity testing and risk assessment is conducted. It is the possibility of achieving such radical changes in safety assessment paradigms that make this an attractive and important strategic initiative.

To address the challenges indicated above, WG 2 plans to bring together in a Workshop, international scientific experts of the very highest standards who are at the forefront of areas of modern science and technology that have not previously been exploited fully in the context of developing new approaches to toxicity testing and risk assessment. These areas such as molecular medicine, bioinformatics and biomathematical modelling etc, could help to identify completely novel approaches to the issue and to create a conceptual framework for the development of new paradigms for that will allow assessment of repeat systemic dose toxicity without compromising safety assessment, The output of the high-level Workshop will lead to potential research projects and the definition of a multi-annual research programme.

Based on the WG2 discussions, the Commission's Research DG, in the 7th Framework Programme for Research, Technological Development and Demonstration Activities (RTD) reacted rapidly and included in the first call for proposals a topic (co-ordination action) in support of setting up the respective RTD programme in this area.

A brainstorming and planning meeting was organised on 12 December 2006 in order to define in detail the conditions for the Workshop to be held in Q4 2007.

Next steps

Working Group 2 will address and prioritise the gaps for RTD identified by working group 1 and will develop the respective implementation plans for the prioritised actions. A first meeting between working group 1 and working group 2 took place on 6 December 2006, the outcome of which will be presented at the EPAA conference.

WG 2 will evaluate opportunities for optimisation of study designs (e.g. group sizes) in toxicological testing. Furthermore, WG 2 will define recommendations for research on optimization of the inclusion of metabolizing systems into in vitro assays so that they are more capable of serving as definitive tests rather than preliminary screens. These activities however have to be confirmed after mapping of research projects.

Working group 3
Identification, dissemination and implementation of best practice in the 3Rs

Although there is widespread acceptance of the concept of the 3Rs, communication, consistency and implementation of current best practice in their promotion can be further improved. The Partnership intends to develop a plan to promote utilisation of current best practice across the EU. A framework will also be developed for the dissemination of output from any future initiatives undertaken by the Partnership

Mapping the organisations involved in the 3Rs

A large number of organisations have a role in promoting the 3Rs at different levels in Europe, yet it is evident that the promotion, dissemination, and implementation of the 3Rs could be improved. The activities of the different organisations appear to be fragmented, with

different remits, scope, funding and level of impact. It is therefore crucial to identify and assess these activities to establish a dissemination strategy for the EPAA.

The mapping and collation of 3Rs organisations within Europe has been the first activity completed, although it is anticipated that not all players will have been identified and that the number and types of organisations involved will change over time.

The initial mapping confirms the fragmented nature with more than 50 organisations being involved. The organisations have been categorised so that their primary purpose can be identified. Categories include promotion of the 3Rs, validation of test methods, funding research, funding awards and regulatory oversight. In addition, information is being gathered on which organisations have involvement with the 3Rs in regulatory safety testing, as this is the focus of the EPAA.

The EPAA intends to publish on its website a database of organisations involved in the 3Rs with information on their primary purpose and scope. This will be a significant step forward in helping co-ordinate 3R activity across Europe, particularly as such a comprehensive database has not previously been publicly available within the EU.

Identifying best practice

In order to further understand what constitutes success in promoting and disseminating information on the 3Rs, a detailed interview protocol was written. Approximately 15 organisations from each of the categories have been identified for a more in-depth review of their 3Rs programmes (especially those pertaining to regulatory safety testing), funding, resource, dissemination strategies and views on what the barriers to implementation of the 3Rs are. At the time of writing, not all of the in-depth interviews had been completed. However, some general points have been identified for this report, and are given as preliminary conclusions.

- The organisations, which have currently been identified, appear to promote their 3Rs activity mainly to the scientific community. There appears to be a gap in communicating the 3Rs to a wider audience, particularly to the general public, politicians and non- specialists.

- National 3Rs platforms publish scientific work in their national language, and consequently the audience with access to these documents is limited. To encourage dissemination and sharing of best practice across Europe, it would be useful if an ‘umbrella’ or ‘overseeing’ organisation could identify the most significant of these documents and publish them in English.

- Dissemination and implementation strategies and tools vary across the organisations. Many of these strategies and tools should have a wider applicability, and communication tools in particular can play an important role in the promotion of the 3Rs. The tools and strategies identified so far include direct funding of research, annual awards for achievements in the 3Rs, publications, organising workshops, facilitating or being members of initiatives with key stakeholders (e.g. for regulatory safety testing this includes the industry sector and regulatory authorities), websites, newsletters and press releases.

- There is a perception that ECVAM's[3] primary mission is only the development and validation of test methods aimed at replacement. However, ECVAM also works on methods that involve reduction and refinement (as shown by working group 5 on validation & acceptance). It may help the promotion of animal welfare if all aspects of the 3Rs were clearly visible.

- Guidelines should be state of the art. However, some are over 20 years old. A review and update may help promote implementation of the 3Rs more widely, specifically with respect to refinement (e.g. group housing) and reduction (e.g. group sizes). Working group 4 on 3Rs in legislation is looking at these aspects.

- Involvement of regulatory bodies early on in development and validation of 'alternative approaches' is essential. However, the complexity of the regulatory system across seven industry sectors and 25 member states makes this extremely complex and difficult to achieve. Here again, working group 5 on validation & acceptance will provide guidance and recommendations.

Next steps

Once the in-depth interviews have been completed a fuller picture can be gathered. This will help drive the design of a dissemination strategy for EPAA in 2007. Similarly, work on identifying best practice will result in development of guidance and recommendations for use by organisations involved in promoting the 3Rs.

Working group 4
Implementation of the 3Rs in regulation and decision-making

The regulatory review undertaken by the EPAA is the first of its kind carried out to obtain a better understanding of the requirements and implementation mechanisms in the area of regulatory testing involving animals and 3R methods. In its first stage, working group 4 focussed on the pharmaceuticals, chemicals, cosmetics and crop protection sectors.

In five workshops and several informal meetings from May to November 2006, experts from industry, authorities, academia and animal welfare associations have identified hot spots, potential for unnecessary duplication of testing in existing and upcoming legislation as well as problems in the implementation of 3R methods.

Background papers on requirements for regulatory testing, presentations on implementation of regulatory testing requirements in practice, and conclusions and recommendations for specific problem areas are being made available on the EPAA website.

Different legal requirements for different sectors

Current and upcoming community legislation involving regulatory testing differs to a large extent from sector to sector.

- Legislation covers different objectives and uses different mechanisms or procedures to achieve these objectives. Cosmetics legislation for example requires product safety,

[3] European Centre for the Validation of Alternative Methods (www.ecvam.jrc.it)

whilst other pieces of legislation require, among other things, protection of human health and environment (chemicals) or quality, safety and efficacy of products in order to protect public and animal health (pharmaceuticals). Different mechanisms or procedures, such as authorisation procedures for products (pharmaceuticals/crop protection products), industry responsibility and market surveillance schemes (cosmetics) or mixed approaches are aiming at achieving the relevant legal objectives.

- Furthermore, regulatory testing requirements are varied within relevant Community legislation. Testing requirements under REACH mainly depend on the volume of chemical substances to be registered for marketing and in some instances testing can be waived based on exposure considerations. Cosmetics legislation provides for a flexible testing framework and the crop protection directive establishes a strict framework for active substances and plant protection products in which endpoints and test methods are stipulated, regardless of tonnage bands.

- Test methods are mainly established in guidelines, and provide for a harmonised approach at European or international level. Although most of these test methods are anchored in legislation, they do not exclude the application of other methods not included in these guidelines, such as in-house tests. Deviation from such guidelines is possible if justified due to special product characteristics or for specific scientific reasons.

- The Cosmetics Directive is the only Community regulatory framework with the aim of successively phasing out animal testing. It establishes a prohibition to test finished cosmetic products and cosmetic ingredients on animals (testing ban), and a prohibition to market in the European Community, finished cosmetic products and ingredients included in cosmetic products which were tested on animals (marketing ban). REACH will introduce general links regarding the relationship between animal testing and non-animal testing. In all other legislation examined, 3 Rs are applied at the level of implementation, as e.g. through guidance in the pharmaceutical sector. Although pharmaceutical legislation also foresees the use of in vitro tests whenever possible as alternative to animal tests, in practice the 3 Rs are applied at the level of implementation through scientific guidance (as thus the European Pharmacopoeia).

- On top of regulatory differences at EU level, application of test methods and the promotion of alternative approaches is made more complex because of work carried out at different levels, such as ILO, WHO, IMO, OECD, ICH, and VICH..

Combining in vivo and 3R methods

Animal tests are carried out in all industrial sectors examined. However, a lot of activities/programmes aiming at reducing and refining in vivo tests are being put in place by industry, European and national regulatory authorities, as well as through international platforms. Full replacement methods are already available for instance for skin corrosion and acute phototoxicity.

In particular, all complex toxicological endpoints, such as carcinogenicity and reproductive toxicity, entail a significant number of animals per test. An overview on how many animals is used for which toxicological endpoints or other effects are partly given by the statistical

reports on the number of animals used for experimental and other scientific purposes[4]. These reports, however, do not allow an accurate break down of figures for specific sectors and endpoints.

Implementation of testing requirements will usually not lead to unnecessary duplication of testing. However, additional testing may be required for official batch releases of biological products, particularly vaccines, and imports from third countries to ensure safety, efficiency and quality of pharmaceutical products according to EU standards. Furthermore, in some cases, substances can be tested by different manufacturers on the same toxicological endpoint (in the same sector or different sectors). This practice may lead to unnecessary duplication of testing because testing data are not always exchanged among laboratories and companies. Also, in specific EU Member States and non-EU countries, requirements might entail additional animal testing not foreseen in EU law.

Challenges in implementing 3R methods

The regulatory review has identified a number of problems which can hamper the proper implementation of 3 R methods in current and upcoming legislation, and on which further action is necessary.

- There have been some reports of a lack of awareness regarding the availability of alternative methods. It is not clear how widespread this is. However, there have been a number of reasons suggested, including lack of success in promoting and disseminating information on 3 R methods: EPAA has launched activities for identification, dissemination and implementation of best practices in the 3 Rs to improve the current situation (see page 15). These activities mainly include 3 R organisations. However, EPAA will also cover companies and laboratories and explore ways how relevant (alternative) in-house test methods can be made available for other sectors.

- It has been mentioned that the situation with the 3Rs is not always clear. For instance, the notion of "alternative methods" is open for interpretation. As long as the reference method is not specified, an alternative cannot be identified. Furthermore, it is also unclear how 3R methods not included in sector specific legislation can be applied if this legislation refers to specific in-vivo test methods for carrying out regulatory testing. Similarly it remains unclear, how the terms "reasonably and practicably available" are to be interpreted. According to Article 7(2) of the Laboratory Animals Directive 86/609/EEC, "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".

- Lack of and/or slow progress in international harmonisation of regulatory requirements for testing and endpoints.

- Costs could also hinder the implementation of 3 Rs in current legislation. Alternative methods are not always cheaper than animal tests (e.g. need for extensive expert judgement, test material, limited infrastructure or know-how). The evaluation of in vitro

[4] http://ec.europa.eu/environment/chemicals/lab_animals/reports_en.htm

tests can require more resources for expert judgement than the interpretation of a single in vivo test.

- Confidence in traditional test methods, impact of liability issues and the precautionary principle will need careful attention in each specific case.

Next steps

Confidence in traditional test methods, impact of liability issues (e.g. explicit versus implicit testing), intellectual property and the precautionary principle will be evaluated by the work group, in a next step.

A number of specific proposals (horizontal cross over and sector specific) from the workshops have been collected and will be further assessed in dialogue with stakeholders and EU Member States, to improve implementation of 3 Rs in the implementation of safety testing.

As a follow up and in addition to work already carried out, EPAA will start in 2007 to assess current and evolving practice and criteria for reporting of animal use, including recommendations for improving implementation where appropriate. This medium term activity included in the action programme is of particular importance for the partnership, since statistical figures might be used as benchmarks for measuring progress under the EPAA. There are, however, some indications that data on animal testing are generated and collated differently in EU Member States.

In addition to the four sectors already analysed, the EPAA will extend regulatory review to the other sectors, in particular biotechnology, food and feed.

Implementation of all these activities should serve as a basis for recommendations to be developed in 2007 to reduce animal testing and to overcome difficulties in the implementation of 3Rs in regulatory testing.

Working group 5
Validation and Acceptance

The basic concepts of validation and legal acceptance are not used in a uniform manner at national, Community and international level. EU legislation does not provide any definition of "validation" (or criteria for validators) or "regulatory (or legal) acceptance".

Validation

According to OECD Guidance Document 34, validation means the process by which the reliability and relevance of a particular approach, method, process or assessment is established for a defined purpose. Similarly, EN ISO 9000 defines validation as a confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled.

The Commission Communication SEC (91) 1794 final provides ECVAM with a mandate to validate alternative methods. However, validation is also carried out by other national and international bodies. The need for formal validation and type of validation/assessment appropriate for each sector/purpose should be assessed and clarified.

Regulatory acceptance

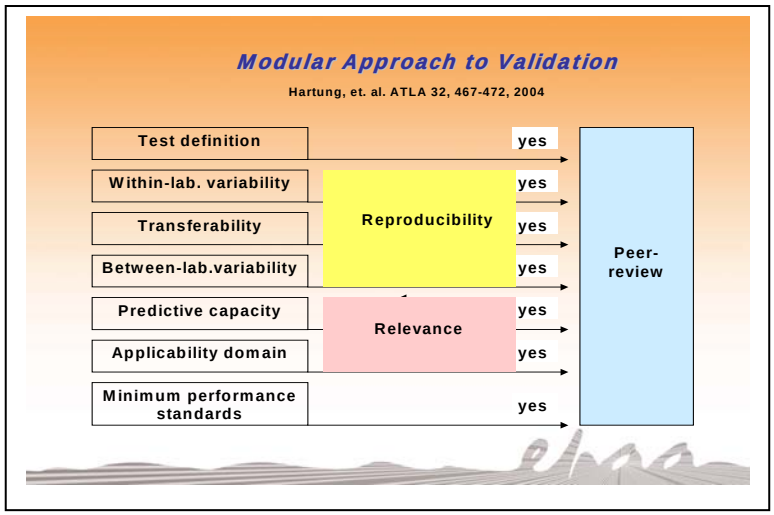
Once an alternative has been validated it has to be accepted by authorities for regulatory purposes, such as marketing authorisation of a product. The regulatory acceptance is not legally defined for all industry sectors.

One can say that alternative methods are legally accepted when they are included in Community legislation or in guidelines adopted by regulatory agencies. Other test methods, such as in-house methods, which are not part of guidance or legislation can also be accepted by national or community authorities in authorisation procedures if acceptance of in-house (or other) methods are not excluded by law (partly the case in the area of toxicological testing under Directive 91/414/EEC). REACH foresees also the use of "suitable" methods, (i.e. sufficiently well developed methods), for example according to the ECVAM criteria for entering into pre-validation.

Understanding the content of the ECVAM validation pipeline with a view to facilitating/ supporting the validation process

A pragmatic approach chosen by working group 5 was to look at the development pipeline of ECVAM dealing with validation at EU level in order to pilot and facilitate the validation of priority methods within the EPAA context (a process which takes typically from 2 to 5 years).

The current alternative methods being considered by ECVAM reflect all 3Rs. Some are replacement tests which, however, often need to be included in a battery of several tests and cannot be used as stand alone. Most of them are refinement and reduction methods, capable of decreasing significantly numbers of *in vivo* tests when used as screens or in a tiered strategy.



The current alternative methods being considered by ECVAM are at very different stages in the validation process. Currently this process encompasses seven modules (see diagram). Amongst the current projects, about 25 are about to enter, or are already within the final validation stage. Amongst these 25, EPAA partners have identified information gaps which need to be addressed to provide the appropriate information to facilitate the validation process.

Prioritisation of the methods requiring immediate support is conducted on the basis of an agreed list of criteria defined and debated in a stakeholders' workshop held in September 2006. The purpose of the prioritisation process is to pilot a few projects where needs are well defined and which will be most relevant in light of regulatory testing requirements.

Other results of the expert consultation include the development of clear profiles of the methods in the ECVAM pipeline, and an inventory of barriers to validation (by ECVAM) with indications of potential ways forward.

Putting in place a framework for collaboration aiming at successful validation (including standard operating procedures (guidance) for both industry and ECVAM and a standard confidentiality agreement) is considered as a major future output of EPAA work on validation.

The above-mentioned documents will be successively published on the EPAA website.

Increasing efficiency in stakeholder collaboration

The EPAA has a great potential to make the process of validation more efficient by enhancing the collaboration between ECVAM and other validation bodies, industry and regulators in order to overcome administrative barriers and to ensure that priority is given to validation of methods which will ultimately be accepted and used.

Having analysed the validation pipeline, EPAA members intend to create a framework for collaboration to facilitate successful validation, which would include inter alia the following elements:

- Setting standard operating procedures for requesting/providing data and substances.
- Looking at possibilities to shorten or rationalise the administrative processes
- Adding a regulatory review module to the validation process
- Involvement of industry at the stage of study design
- Using reference or well-known substances or industry recommended references should be used in the first modules of validation
- Applicability of approaches should be revisited with regulators after 5 years in order to consolidate the relevance of the method.

It is expected that this framework should be ready at the beginning of 2007.

Next steps

Against this background, and in addition to the framework for collaboration mentioned above**,** the EPAA will work on improving the understanding of regulatory requirements vis-à-vis levels of confidence and acceptance of the validation of methods and strategies.

The EPAA will identify criteria and prerequisites for efficient and solid validation as well as legal acceptance of alternative methods and testing strategies in all relevant sectors to speed up availability and applicability of alternative approaches.

It will seek to promote and foster the regulatory acceptance and the use of new testing strategies

One of the future activities will also include preparation of guidance on validation of strategies (involving *in vivo* and/or *in vitro/in silico* methods as well as expert judgement).

On a permanent basis EPAA members will continue to provide support to the validation process in ECVAM.

F. CONCLUSIONS

The European Partnership for Alternative Approaches to Animal Testing (EPAA) is a unique and groundbreaking collaboration between the services of the European Commission and a broad range of companies and European industry associations committed to the replacement, reduction and refinement of animal testing (the so-called '3Rs'). Its objective is to accelerate the development, validation and acceptance of alternative approaches for the purposes of regulatory safety assessment.

A sound, long-term policy promoting alternative approaches to animal use in regulatory safety testing must start with a detailed mapping of existing methods and ongoing research (including in house methods) to identify overlaps and gaps. The inventory, which is being collected by the EPAA, will provide guidance on needs and help to optimise use of resources in industry and for Community-funded projects.

Such a mapping is supporting development of projects, which may apply for funding support by the Commission on a competitive basis, under the conditions and rules of EU framework programmes. It will moreover usefully contribute to good practice sharing and cross-fertilisation amongst sectors.

Promotion of the 3Rs constitutes another fundamental objective of the EPAA. A list of organisations which support and promote the 3Rs and identified best practice in dissemination of information on the 3Rs is being collated. The list of organizations has been published on the EPAA website and will continuously be updated, before finally being made available in the form of a database on the site. Such a database did not exist before at the EU level.

It is also the first time that work has started on a comprehensive inventory of the different legal testing requirements in relation to the 3Rs principles in legislation, implementation and in decision-making. The EPAA workshops to date have shown a number of joint industry and authorities initiatives and areas where progress can be achieved with additional support by European and national regulators. This work will further continue and be extended to other sectors.

EPAA has great potential to make the process of validation more efficient through enhancing the collaboration between ECVAM, industry and regulators by helping to overcome administrative barriers and by ensuring that priority is given to validation of methods that will ultimately be accepted and used. This unprecedented cross-sectoral dialogue builds a common understanding between the different parties' needs and processes.

The majority of actions identified in the work programme have a medium to long-term perspective. At the same time clear milestones, including short-term objectives, have been achieved. For the next stages of the -initiative a set of performance indicators will be developed and internal and external communication about EPAA work will be enhanced.

Annex I

EPAA Steering Committee

co-Chairs :

DG Enterprise and Industry	Georgette Lalis
CEFIC (outgoing) Unilever (incoming)	Colin Humpris Charles Laroche

Members :

European Commission	
DG Enterprise and Industry	Cornelis Brekelmans Siegfried Breier Santos-Ivo, Rui
DG Environment	Sylvain Bintein Susanna Louhimies
DG R&D	Jürgen Büsing Stephane Hogan Andrea Tilche
JRC/ECVAM	Thomas Hartung Maarit Viljanen
DG SANCO	Gigliola Fontanesi Andrea Gavinelli Brita Lepa Maila Puolamaa Cornelis Rhein
European Industry Associations	
AISE	Susanne Zaenker / Charles Laroche
EFPIA	Magda Chlebus
ECPA	Peter Day
EuropaBio	Nathalie Moll (outgoing) Michael Leader (incoming)
Cefic	Colin Humphris (outgoing) (incoming t.b.n.)
Colipa	Bertil Heerink
IFAH-Europe	Rick Clayton
Companies	
L'Oréal	Odile De Silva
Johnson & Johnson	Benjamin Gannon
AstraZeneca	Sally Robinson
Pfizer	Tim Rowan
Procter & Gamble	Véronique Scailteur
Henkel, Phenion	Julia Scheel
Procter & Gamble	Simon Webb
BASF	Hennicke Kamp
Syngenta	Ian Kimber
Bayer	Gernot Klotz
BASF	Karsten Müller

Annex II

EPAA Working Groups

Working Group 1:
Mapping contributions to, and achievements in, the development of alternatives approaches to assessment

Co-chairs:
Simon Webb - Procter & Gamble
Christian Wimmer, DG Research (as of November 2006)

Members of the WG 1**:**
AstraZeneca
Bayer
ECOPA
EUROGROUP for Animals
GlaxoSmithKline
Henkel Phenion
Johnson & Johnson
Pfizer
Unilever

Working Group 2:

Identification of opportunities, including R&D

Co-chairs:
Andrea Tilche (outgoing); Jurgen Buesing (incoming) - DG Research
Hennicke Kamp – BASF

Members of the WG 2**:**
Abott
BASF
Bayer
Covance
DG Research
GlaxoSmithKline
Henkel, Phenion
Intervet
L'Oréal
Lilly
Pfizer
Procter & Gamble
Syngenta
Unilever

Working Group 3:
Encouraging implementation of the current best practice in the utilisation of the 3Rs across Europe

Co-chairs:
Marlies Halder (outgoing)/ Jens Linge (incoming)- DG JRC, ECVAM
Colin Humphris – Cefic (outgoing), Sally Robinson - Astra Zeneca (incoming)

Members of the WG 3:
Covance
EUROGROUP for Animals
Henkel, Phenion
Johnson & Johnson
Lilly
Merial
Novartis
Pfizer

Working Group 4 :
3Rs in the implementation of regulation

Co-chairs:
Siegfried Breier, Siegfried, outgoing, DG Enterprise and Industry
Cornelis Brekelmans, incoming - DG Enterprise and Industry
Gernot Klotz,Bayer
Julia Scheel, Henkel

Members of the WG 4:
Astra Zeneca
BASF
Covance
DG Environment
DG JRC, ECVAM
DG SANCO
EFPIA
EFSA
EMEA
EUROGROUP for Animals
GlaxoSmithKline
Henkel, Phenion
Johnson&Johnson
Pfizer
Syngenta

Working Group 5:
Validation and acceptance

Co-chairs:
Siegfried Breier , outgoing, DG Enterprise and Industry
Cornelis Brekelmans- DG Enterprise and Industry
Laura Gribaldo– DG JRC, ECVAM
Magda Chlebus, EFPIA
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Members of the WG 5 :
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BASF
Bayer
Covance
DG ENTR
DG Environment
DG SANCO
ECOPA
GlaxoSmithKline
Henkel, Phenion
Intervet
Pfizer
Unilever

Annex III

EPAA Mirror Group

Chair:

Dagmar Roth-Behrendt, Vice President of the European Parliament

Members

Prof. Hermann Autrup
Institute of Public Health
University of Arhus

Prof. Jim Bridges
University of Surrey
School of Biomedical and Life Sciences
Chairman of the Scientific Committee on Emerging and Newly Identified Health Risks

Prof. Ove Svendsen
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The Royal Veterinary and Agricultural University
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Prof. Coenraad Hendriksen,
Netherlands Vaccin Institute, Bilthoven
Netherlands Centre Alternatives to Animal Use (NCA)
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Alastair Kent
Director
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Emily McIvor
Animal Welfare Consultant
Brussels/London

Prof. Vera Rogiers
Dept. of Toxicology
Vrije Universiteit Brussel
President of the ECOPA Board
Vice-chair of the Scientific Committee on Consumer Products

Dr. med. Horst Spielmann
Direktor und Professor
Head of Dept. Scientific Services
Head of ZEBET
Bundesinstitut für Risikobewertung
Berlin

Sonja van Tichelen
Director
Eurogroup for Animals
Brussels

Appendix 1

**EUROPEAN PARTNERSHIP FOR
ALTERNATIVE APPROACHES TO ANIMAL TESTING**

3 Rs Declaration[1]

1. – Preamble

The Protocol on Protection and Welfare of Animals annexed to the EC-Treaty aims at ensuring improved protection and respect for the welfare of animals as sentient beings. In formulating and implementing the Community's policies, the Community and the Member States shall pay full regard to the welfare requirements of animals.

All industry sectors, including pharmaceuticals, chemicals, cosmetics, agrochemicals and foods manufacturers, are already obliged to apply available methods to replace, reduce and refine animal use (Three Rs) in safety and efficacy evaluations under the existing animal protection legislation (Directive 86/609/EEC).

The 7th Amendment to the Cosmetics Directive 76/768/EEC, established specific requirements for the cosmetic industry relating to the use of replacement methods for animal-based safety studies by introducing testing and marketing bans.[2]

According to the "Fourth Report on the Statistics on the Number of Animals Used for Experimental and other Scientific Purposes in the Member States of the European Union" the total number of animals used in 2002 was 10.7 million. The European Commission's recent Proposal on the Registration, Evaluation and Authorisation of Chemicals (REACH) has served to highlight stakeholder and general public concerns regarding the continued need for animal testing as a means to protect human and animal health and the environment. At the same time it should be recognised that there is considerable pressure from the public and the regulators to better understand risks to humans and the environment from chemicals and to increase assurance in product safety. In the absence of validated alternative methods, the current legislative paradigm requires animal use.

Likewise, the pharmaceutical industry is largely dependent upon animal studies for predicting human toxicity and efficacy of pharmaceuticals. A role for animal studies prior to human exposure is explicit in the World Medical Association's Ethical Principles for Medical Research Involving Human Subjects ("The Helsinki Declaration").

In fact, most sectors are currently under specific regulatory obligations that today can only be fulfilled with the results of animal studies.

Coupled with a genuine desire of stakeholders to see faster progress towards ultimately replacing animal testing, Community legislation and financing tools represent both challenges and opportunities in the development of alternative approaches. However, further efforts should be made to speed up work toward the replacement of animal testing where possible and reduction and refinement where replacement cannot yet be achieved. In order to achieve

[1] Updated 30 November 2006
[2] 1 Cut-off dates 2009/2013 even in the absence of alternative methods

this necessary change, the Commission is taking leadership in initiating and organising a partnership with Industry on alternative approaches to animal testing based on the 3 Rs principle.

A number of activities are under way to promote the development and validation of Three Rs methods under the EU Research Framework Programmes. Industry has been implementing replacement, reduction, and refinement methods for some time. Some human health effects can already today be assessed using replacement methods, i.e. skin corrosion, skin absorption and acute phototoxicity. Other health effects, such as systemic toxicity, can now be tested using fewer animals and with less severe effects on them.

But despite success achieved to date, it is also recognized that there are still more opportunities to exploit the advantages of increased synergies between the activities carried out at national, European and international level (i.e., through OECD, ICH, VICH and other mechanisms) by all relevant stakeholders.

Advanced technologies (e.g., genomics, proteomics, bioinformatics) and increased knowledge are helping to develop a diverse range of approaches that are less reliant on animals. There is undoubtedly potential to harness such technologies within novel approaches to safety assessment that reduce the reliance on animal use, whilst providing appropriate reassurance of human and animal health and environmental protection. Such potential may also prove to be a market incentive to certain industry sectors. The approach is entirely in keeping with the Lisbon agenda, which calls for the development of new technologies and approaches in order to maintain European competitiveness.

The conference on "Alternative Approaches to Animal Testing – Europe Goes Alternative" on November 7, 2005, in Brussels demonstrates that the European Commission and all other stakeholders keep laboratory animal welfare high on the political agenda. They collectively recognise the need for a new, more coordinated and strengthened approach to laboratory animal welfare and 3 R-approaches to animal testing. Such an approach needs to balance the substantial technical and scientific challenges with the requirements of consumer, patient, occupational, animal and environmental safety.

2. Partnership

A voluntary "European Partnership to Promote Alternative Approaches to Animal Testing " is therefore established to support the development, validation and acceptance of alternative approaches to replace, reduce and refine animal use and apply advanced methodology from biosciences and medicine to develop novel approaches.

The Partnership will allow the European Commission and Industry to collaborate effectively on the basis of an action programme identifying concrete activities and priorities for the promotion of alternative approaches to animal testing. The partnership will facilitate wider dialogue with key stakeholders thereby promoting use of available knowledge, greater transparency and understanding. It will be jointly undertaken by the Commission and industry, and would also seek to establish appropriate links with relevant bodies at national and international levels.

The partnership will be based on pragmatic mechanisms aimed at achieving impact that can be supported by both partners. Participants will contribute to the establishment of the procedures for the management of the partnership, including identification of respective responsibilities and development of performance criteria.

3. Principles

The Partnership should:

- Aim at stimulating the development, validation and implementation of alternative approaches via appropriate resources and financing tools and their regulatory acceptance.
- Identify European and international opportunities to address barriers to progress,foster acceptance and harmonisation of tests by regulators, ensure mutual acceptance and avoid redundancy wherever possible (through OECD, ICH, VICH and other mechanisms).
- Build on past achievements from the different partners in applying the Three Rs to animal use. This will require effective mapping of existing efforts in order to provide a point of departure.
- Support development and use of other modern approaches to gradually change the way safety assessment is carried out.
- Ensure a mechanism for dialogue and communication with other relevant stakeholders on developments that effectively contribute to animal welfare.
- Be mindful of the need to consider innovation, the protection of intellectual property arising from innovation and the implications for the overall competitiveness of European industry.

4. Participation

The participants of the Partnership

- Commit themselves to contribute to an Action Programme to be reviewed and updated every year that identifies short, medium and long term activities and appropriate responsibilities;
- Understand that progress in life sciences provides potential opportunities to further , replace, reduce, refine the use of animals;
- Recognise the importance of the need to maintain a high level of consumer, patient, occupational, animal and environmental safety;
- Acknowledge there is further potential for cooperation and sharing of knowledge between industry sectors;
- Recognise that the regulatory requirements of each industry sector are unique and that this will be reflected in the implementation of any deliverables
- Call on all stakeholders to intensify jointly efforts to make available validated alternatives based on the 3Rs principles: Replacement, Reduction and Refinement;
- Invite interested parties sharing these goals to engage and contribute to the Partnership.

Addendum to the 3 Rs Declaration

Next Steps for the Implementation of the Declaration

The participants of the Partnership on alternative approaches to animal testing based on the 3 Rs principle commit themselves to contribute to an Action Programme that identifies short, medium and long term activities. The Action Programme will be designed from the perspective of identifying barriers to progress and propose appropriate solutions in order to promote the development, validation, regulatory acceptance and practical implementation of alternative approaches. A range of issues will be tackled, including the establishment of priorities, in areas such as:

- Mapping of research activities and current strategies,
- Cooperation in research to strengthen and enlarge current activities between the partners and other relevant stakeholders,
- Development of alternative approaches, including intelligent testing strategies,
- Practical mechanisms to improve the validation process using available knowledge,
- Practical mechanisms to facilitate the regulatory acceptance process of alternative approaches,
- Widening stakeholder dialogue and education,
- Practical mechanisms to foster innovation in the area of alternative approaches.

The action programme will identify and establish appropriate mechanisms and timetables for the implementation of the programme, such as the setting-up of technical working-groups for the different priority areas.

All the necessary steps will be taken to ensure that the action programme will be available during first quarter2006.

An annual report from the Partnership on the implementation of the action programme will be published for the attention of the Council, European Parliament and other relevant stakeholders. The first report on implementation should be published by December 2006.

Appendix 2

Action Programme

Executive Summary

The objective of this action programme is to promote the application of the 3Rs in order to support the development, validation and acceptance of alternative approaches to refine, reduce and replace animal use for safety testing within the sectors participating in the Partnership.

Animal welfare is the subject of significant societal concerns and there is strong support to refine, reduce and replace animal use linked to regulations. The EC Treaty's Protocol on Protection and Welfare of Animals requires that full regard is paid to welfare requirements in formulating and implementing the Communities policies. Whilst there is an imperative to implement the 3Rs to the fullest degree, there is also a parallel responsibility to balance the substantial technical and scientific challenges with the necessary requirements of consumer, patient, occupational, target animal and environmental safety.

Given the diverse Community policies having an impact on animal welfare and use across sectors, there is a need for closer liaison and cooperation in fundamental research, in the formulation and implementation of policy initiatives and in the identification and dissemination of best practices. By effectively pooling Commission and industry experience, expertise and resources, a common coordinated Partnership at EU level and across sectors will be more effective than historically fragmented initiatives in this area.

The main activities in the action programme concentrate upon:

- **Mapping of past and current 3R activities to better inform the planning and prioritisation of subsequent actions:**
- **Prioritisation, promotion and implementation of future research based on the application of the 3Rs**
- **Identification, dissemination and implementation of best practice in the use of the 3Rs:**
- **Implementation of the 3Rs in regulation and decision making**
- **Validation and acceptance based on the 3Rs**

1. Introduction

Under the 3Rs Declaration, the participants of the "European Partnership to Promote Alternative Approaches to Animal Testing" (hereinafter the "Partnership") commit themselves to contribute to an Action Programme to be reviewed and updated every year that identifies short, medium and long term activities and appropriate responsibilities.

The Partnership was established on November 7th 2005 with the adoption of the 3Rs Declaration supporting the research, development, validation and acceptance of alternative approaches to refine, reduce and replace animal use within the participating sectors. It has allowed the European Commission and Industry to collaborate effectively to establish this Action Programme aimed at achieving impact in the development and promotion of alternative approaches that can be supported by both partners.

The Action Programme outlines the partners' initial five year commitment for a structured and comprehensive map of the planned initiatives. It was designed from the perspective of identifying barriers to progress and aims to propose appropriate solutions that will promote the practical implementation of alternative approaches.

2. Objectives

The Partnership between industry and the Commission provides the mechanism via which the partners and other stakeholders collaborate together to promote the development, availability and acceptance of alternative approaches to animal testing in safety assessment. It represents a unique opportunity for the different industrial sectors to cooperate together with the Commission in meeting common established goals and aspires to deliver animal welfare benefits by embracing all 3 Rs. Regulatory developments such as REACH and the 7th Amendment of the Cosmetics Directive will come into effect by the end of this decade and provide additional impetus to the need to develop alternative approaches. The primary objectives that the Partnership wishes to achieve via this action programme are to

- Provide clear, consistent and coordinated direction of efforts to promote the research, development, validation, regulatory acceptance and implementation of alternative approaches
- Provide greater coordination of existing resources and financing tools whilst identifying future resources needs;
- Foster the harmonisation and mutual acceptance of tests and test data by regulators within the EU and beyond;
- Identify European and international opportunities to address barriers to progress via the 3Rs;
- Recognise, build upon and learn from the past achievements of the different partners in applying the 3Rs in order to better inform future activities;
- Ensure a mechanism for dialogue and communication with other relevant stakeholders on developments that effectively contribute to animal welfare;
- Promote innovation as a source of overall competitiveness of European industry and contribution to the Lisbon strategy for growth and employment;
- Identify and disseminate best practice in animal welfare and alternatives across the participating sectors and within the EU.

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3. Approach

The Partnership is based upon the principle of a voluntary, bilateral and cooperative relationship between the Commission and industry. The participants of the Partnership jointly commit themselves to contribute to the establishment, implementation and ownership of the action programme. Collectively they

- Recognise the need for a new, more coordinated, cross-sectoral and strengthened approach to laboratory animal welfare and approaches to animal testing;
- Undertake to focus on all 3Rs in order to maximise the overall impact of the Partnership
- Believe that whilst progress in life sciences provides potential opportunities to further refine, reduce and replace animal use, there is a need to balance the substantial technical and scientific challenges with the necessary requirements of consumer, patient,

- Acknowledge that there is further potential for cooperation and sharing of knowledge between partners and across sectors, even though the regulatory requirements of each sector are necessarily specific
- Promote the need for a coherent research policy that is consistent with regulatory policy based on identified and agreed gaps in knowledge and (regulatory) acceptance;
- Invite interested parties sharing the goals of the Partnership to engage and contribute.

4. Areas of Action

The five main themes represented in the action programme are;

1. **Mapping of past and current 3R activities to better inform the planning and prioritisation of subsequent actions:** Results from previous and current 3R activities need to be identified and consolidated in order to better inform the planning and prioritisation of future activities. The identification of success models and knowledge gaps is a necessary pre-requisite and central foundation to the success of the Partnership.

2. **Prioritisation, promotion and implementation of future research based on the application of the 3Rs:** The identification of priorities for future 3R orientated research is a cornerstone of the Partnership. The focus should be on requirements for risk assessments and activities that might be implemented within the initial 5 year lifespan of the Partnership and based on the experience and information gathered under theme 1. Emphasis will also be placed on those activities that can be addressed most effectively by the Commission and industry in association

3. **Identification, Dissemination and Implementation of best practice in the use of the 3Rs:** Although there is widespread acceptance of the concept of the 3Rs, communication, consistency and implementation of current best practice in their application can be further improved. The Partnership will develop a plan to promote utilisation of current best practice across the EU. A framework will also be developed for the dissemination of output from any future initiatives undertaken by the Partnership.

4. **Implementation of the 3Rs in Regulation and Decision Making**: The Partnership will evaluate the main drivers (e.g., sector specific requirements, safety, liability, evaluation/acceptance of risk by regulators, precaution etc.) for animal use within the context of optimising current and evolving testing requirements. Current reporting practice and criteria of reporting of numbers used in animal testing will also be assessed

5. **Validation and Acceptance based on the 3Rs:** Community legislation, guidelines, administrative practices or international standards give rise to differing validation and acceptance procedures in relation to (alternative) test methods. This is evident across the relevant sectors as well as in comparisons between different geographies. Against this background, there will undoubtedly be opportunities to facilitate and accelerate the validation and acceptance procedures and so impact overall animal use.

The five main actions areas identified above are not intended as stand-alone themes. There are clear linkages between the different action areas that will necessitate a coordinated approach.

5. Activities under the Action Programme on Alternative Approaches

Actions have been identified by Drafting Groups constituted from the Commission services and the industrial sectors represented in the Partnership. The combined experience of the participants in the development, validation and acceptance of alternatives was substantial. The innate synergy of the Partnership (resulting from cooperation between the Commission and industry and across the different sectors) greatly contributed to the process. The challenge was to identify substantive actions that would significantly impact and optimise animal use.

Individual activities have been designated as "short", "medium" or "long" term based upon a timeframe for initiation, reporting and conclusion agreed by the respective drafting groups. Short-term activities are targeted to be initiated within the first year following promulgation of the Action Programme. Medium-term activities are intended for initiation within 2-3 years and long-term within the first 5 years of the Partnership. It should be noted that certain activities initiated in the short-term may be continually updated over the proposed 5 years of the Action Programme. There is however an expectation that such activities will make significant progress within the first year following initiation as they are intended to provide a substantial foundation upon which to base subsequent activities. The Action Programme is also intended as a living document that is likely to be amended and updated by the Steering Committee as the needs for subsequent activities evolve with the delivery of new knowledge, experiences and recommendations from initial activities.

Current agreed activities and timeframes are outlined below:

1 Mapping to share successful approaches and better inform the planning and prioritisation of subsequent actions

- Build on existing knowledge: A review of research projects with the potential to deliver 3Rs benefits and their output.
- An inventory of ongoing projects evaluating optimised testing strategies and constituent elements across all relevant sectors
- Share and implement current approaches: A review/inventory existing (primarily industry in-house) use of 3R alternatives and alternative approaches employed in screening or decision making processes related top safety.

Timeframe: Short-term

2 Prioritisation, promotion and implementation of future research based on the application of the 3Rs – Evaluation of opportunities

- Evaluation of opportunities for the more widespread application of established sector specific testing strategies for complex endpoints such as reproductive toxicity within safety assessment models in other sectors 1).
- To define the path towards hazard characterisation and risk assessment without the use of animals in the area of repeat dose systemic toxicity. A long-term objective is to develop non-animal methods that will allow assessment of repeat dose systemic toxicity without compromising safety assessment. The short-term goal is to identify relevant research needs (e.g. through a high level workshop) that would frame a research program

Timeframe: Short-term

- Evaluation of opportunities for optimisation study design (e.g., group sizes) in toxicological testing.

- Recommendations for research on optimization of the inclusion of metabolizing systems into in vitro assays so that they are more capable of serving as definitive tests rather than preliminary screens (to be confirmed after mapping of research projects).
- A generic action to prioritise research (especially relevant to risk assessment) based on the mapping and gap analysis undertaken under theme 1. Highlight these priorities within the established FP7 prioritisation process.

Timeframe: Medium and long-term

3 Identification, Dissemination and Implementation of best practice in the use of the 3Rs

- Review of key National and European institutions (including education, industry, competent authorities and NGOs) with experience of 3Rs promotion to understand existing activities promoting best practice.
- Assessment of the effectiveness and potential of existing activities and structures to meet the overall dissemination objectives of the Partnership.

Timeframe: Short-term

- Evaluation of the factors that drive or hinder institutional change in education,
- Definition of new structures and/or enhancement of existing structures necessary for the dissemination of Partnership output and enhancements to existing activities to encourage the adoption of best practice across Europe..
- Creation of communication tools for the dissemination of Partnership output and education/training of stakeholders (including education, industry and Member States).

Timeframe: Medium and long-term

4 Implementation of the 3Rs in Regulation and Decision Making

- Identification of "hot spots" 2) for animal use and welfare in current legislation and guidance via an inventory of regulatory requirements leading to animal use and impacting animal welfare.
- Identification of potential "hot spots" for animal use and welfare in upcoming legislation and guidance via mapping of relevant activities.

Timeframe: Short-term

- Identification and evaluation of drivers (e.g., safety, liability, precaution, risk acceptance etc.) for regulatory testing requirements.
- Assessment of current and evolving practice and criteria for reporting of animal use, including recommendations for improving implementation, where appropriate.
- Identification and consideration of appropriate (sector specific) measures to implement 3Rs in legislation and to avoid redundant testing of animals particularly in "hot spots".

Timeframe: Medium and long-term

5 Validation and Acceptance based on the 3Rs

- Coordinate work to prioritise (via agreed criteria) and facilitate the validation of alternative methods/strategies in the current ECVAM pipeline (includes identification and availability of substances and data necessary for defined and prioritised validation studies).

- Promote and foster regulatory acceptance and use of new testing strategies and 3Rs methods (to include the definition of barriers to acceptance and the involvement of regulators in the development and validation process).
- Identification and addressing of barriers to successful and prompt validation (based on a case study approach).
- Timeframe: Short-term
- Preparation of guidance on how to validate strategies (involving in vivo and/or in vitro/in silico methods as well as expert judgement) for safety assessment purposes (based on a case study approach).
- Understand regulators requirements vis-à-vis levels of confidence and acceptance of the validation of methods/strategies (to include when validation is not explicitly required in the regulatory context). Develop recommendations on 'alternative' processes to formal validation and an assessment of their applicability for different sectors.

Timeframe: Medium and long-term

6. Future Steps

The Partnership Steering Committee will be responsible for;

- prioritisation and coordination of the proposed actions across the different themes;
- identification and establishment of appropriate mechanisms and timetables for the implementation of the programme;
- the constitution and composition of technical working groups and
- securing of necessary resources.

An annual report from the Partnership on the implementation and impact of the action programme will be published for the attention of stakeholders. The first report on implementation should be published by December 2006. The Partnership commits to subsequently communicate on the status of action programme on an ongoing basis.

Responsibility for the design and implementation of the action programme lies with the Partnership. The success is also dependent upon the collaboration and contribution of;

- Member States, which have responsibility (via national regulatory agencies) for implementation, interpretation and application of regulations leading to animal use or the use of non-animal alternatives;
- EU Regulatory Agencies, which have responsibility for implementation, interpretation and application of regulations leading to animal use or the use of non-animal alternatives on a pan-European level;
- Academia, which will be invited to advise on and engage in proposed research;
- Stakeholder groups such as NGOs, which play a key role in translating and reflecting societal interests;
- International organisations or platforms, such as OECD, VICH, ICH, co operations with which will facilitate global harmonisation.

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1) For example, the Agricultural Chemical Safety Assessment (ACSA) for reproductive toxicity.

2) "Hotspots" are priority areas for action that entail significant animal use and/or provide an opportunity for an effective impact on animal use through application of the 3Rs.