Food for Thought ... on Globalisation of Alternative Methods

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Globalisation, the fact that national boundaries are loosing importance, is currently perceived in many fields – certainly also in the field of alternatives: We see that the idea of formal validation has spread from Europe to the USA to Japan and more recently to Korea with first developments in China, India, Russia, Brazil, etc. There are a couple of questions to pose: Why globalisation? Why now? What is driving it? Is it good? If so, how can we support and enhance it?

The third article of the "Food for Thought" series appears in print few months after the Japanese World Conference with satellite symposia in China and Korea. Some reflections on this phenomenon shall stimulate discussion.

Hypothesis 1: Science is global, regulation is national: Globalisation in the area of risk assessment can only take place when regulatory toxicology follows the rules of science

Science is global. It knows no boundaries; it does not acknowledge national frontiers. Science is evaluated by the peers involved on the criteria "is it sound?", "is it believable?" and "is it proven?" (in increasing order). An additional aspect, "is it relevant?", is increasingly added to the evaluation, as science is under economical pressures. Science must not be evaluated on the ground of "where does it come from?". Historically, all attempts to limit the free flow of science have, if at all, led only to a delay in scientific development with the respective disadvantages for these societies. However, in safety assessments we see a compartmentalised, national approach, and, in contrast to scientific progress and development, methods are frozen in time (guidelines), allowing them often to persist for several decades as standard tests or guidelines. Approaches are national and traditionally in obvious contradiction of any other scientific approach. The reason given is typically that human and environmental safety is at stake, but wouldn't many other decisions based on the latest science, such as agent discovery, affect our safety as much? And is there a national safety? Certainly not. Why then this unscientific approach by scientists? The first reason is that proprietary issues are handled, and in extrapolation not only the financial interests of a company but the economical perspectives of a country are at stake.

Hypothesis 2: Some drivers of globalisation can be translated to the field of alternatives

Friedman identified ten drivers ("flatteners") of globalisation in his bestseller "The world is flat" (Friedman, 2006). Among them the opening of the East, the new communication technologies, shared knowledge by internet and global markets are the most relevant for our discussion. They have given us additional competence centres, unlimited real-time communication means, a spirit of sharing knowledge and market forces challenging any compartmentalisation. On the downside there is increased travel demand, communication and information overflow and a pace of market changes that can hardly be followed by precautionary assessments and regulation.

The challenges to the field are to maintain the quality while adapting to the change:

– New competence centres: Over the last few years several new centres have emerged. This offers the opportunity of sharing the burden but also the threat of duplication of efforts and competitive compartmentalisation. The 4C of the desirable process are "communication → coordination → collaboration → convergence" (Fig. 1). We are at stage one to two of this, only with the exception of the close collaboration between the USA and Europe, notably ICCVAM/NICEATM (Interagency Coordinating Committee on the Validation of Alternative Methods/National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods), CAAT (Center of Alternatives to Animal Testing at Johns Hopkins University, Baltimore) and IIVS (Institute for *In Vitro* Sciences, Gaithersburg) in various bilateral collaborations with ECVAM (European

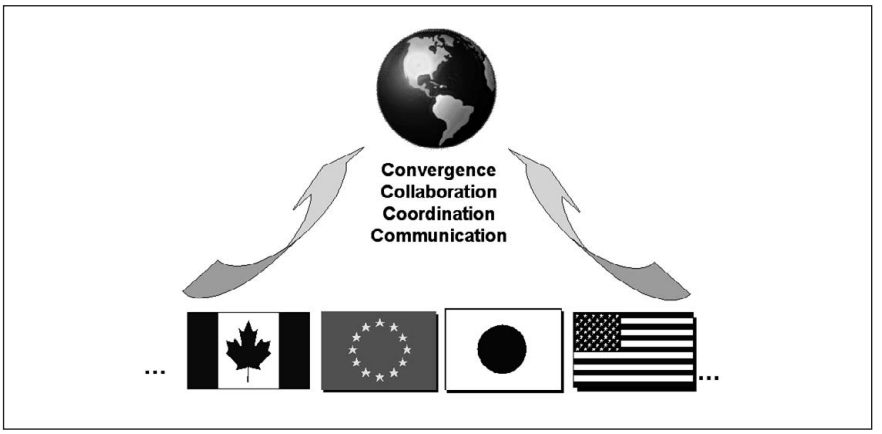

Fig. 1: Toward globalisation

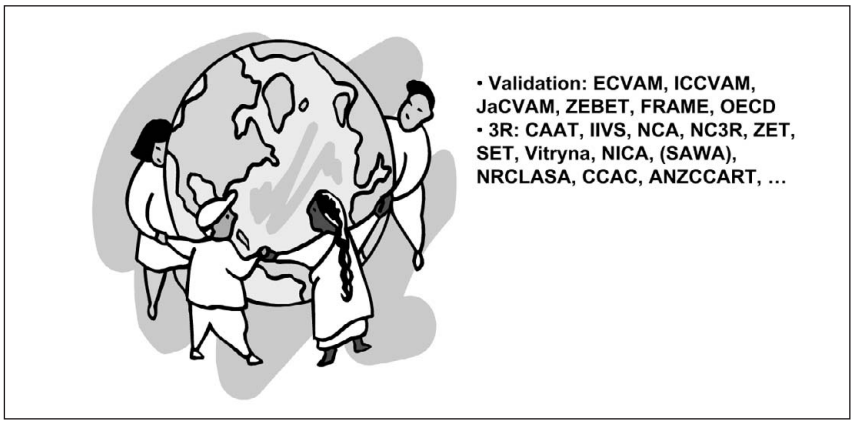

Fig. 2: Laboratory animal welfare and validation centres

Centre for the Validation of Alternative Methods). Over the last 4-5 years activities have been mutually opened up to the benefit of both sides. JaCVAM (Japanese Centre for the Development of Alternative Methods), despite its short history (founded November 2005), is increasingly integrated. But many of the European and other national centres follow their own paths, with the risk of missing developments. It is clear that each centre needs to achieve an individual profile and visibility for their stakeholders, but isolation is costly, reduces impact and makes the centres vulnerable to day-to-day political decisions, as recently seen in Sweden, where one of the most active centres (SAWA – Swedish Animal Welfare Agency) was dissolved on short notice. Certainly, there is always the risk that "collaboration is the same as mutual hindering" (Sloterdijk, 2005). On occasion of its 25th anniversary, CAAT convened the first 3R-Center Meeting, bringing together a dozen of these (Fig. 2). More regular and perhaps also more formalised meetings, for example linked to the series of World Conferences, will be necessary. Thus the challenge is to broaden the number of partners for coordinating efforts and collaborating on the challenges. The hurdle, however, will be convergence, especially when we move from development to validation and acceptance of methods by the international community (see below).

– Communication: More and more players in the field, hundreds of e-mails per day, increasing numbers of scientific networks, associations, conferences and competence centres, make it more and more difficult to maintain an overview of what is happening. The role of key events, like the series of World Conferences, and key journals, like *ATLA, ALTEX, AATEX* and *Toxicology In Vitro*, becomes clear. The fact that the World Conferences have changed now from a three to a two year cycle reflects this need for information exchange.

- Sharing of knowledge: The most important contribution is done here by the databases. Quality control and user-oriented offers are pivotal to serving the scientific "www"-community and authorities, but also non-experts in the animal alternatives field. The ECVAM DataBase service on ALternative Methods (DB-ALM, http://ecvam-dbalm.jrc.ec.europa.eu) was therefore set-up as a database service that provides information that is *ready-for-use* and peer-reviewed and covers various aspects of advanced and alternative techniques. User surveys and analyses of how the offers are taken up, allow tailoring to the need of different user profiles. DB-ALM was launched on the Internet at the end of 2006 on occasion of the 15th anniversary of ECVAM and can refer so far to 917 registered users from 61 countries (Fig. 3) coming from academia (43%), industry (34%) and government (16%) in addition to others (7%). With more and more electronic data retrieval systems of different kinds and contents on alternatives available, it is timely to provide guidance and search strategies to obtain more complete views, e.g. what can I find where and which alternatives are available in a certain field? ECVAM is coordinating and sponsoring the development of such a comprehensive guide, particularly aimed at untrained database users. This will be most relevant for example where ethical committees require researchers to carry out a comprehensive search for alternatives before any animal experiment.

– Market forces: Globalisation is both a driver and an obstacle for alternative methods: Harmonisation of approaches is a prerequisite for common markets and change gives opportunities to update approaches. At the same time, globally acting companies will carry out the traditional animal experiment until the last national market has adapted its regulation. The role of bodies like the OECD (Organisation for Economic Co-operation and Development), ICH (International Conference on Harmonization), the International Cooperation on Harmonization of Technical Re-

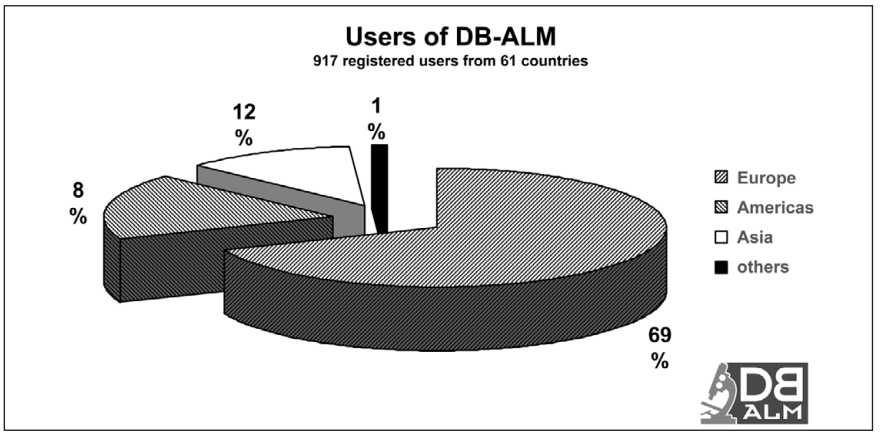

Fig. 3: Users of DB-ALM

quirements for Registration of Veterinary Medicinal Products (VICH) and the International Organization for Standardization (ISO) and most recently (September 2007) the International Collaboratiomon Cosmetic Regulation(ICCR) can thus not be overestimated, since they set standards in the most important economic areas of the world, which are typically followed by the rest. They are based, however, on slow consensus processes, which can hardly cope with the pace of new technologies (e.g. omics, sensors, cellular and computational tests) and products (e.g. nanotechnologies, cell therapies, recombinant products). When our knowledge in the life sciences doubles every seven years, can we really afford processes of standardisation, validation, peer-review and acceptance that span 10 to 16 years? It is noteworthy that it is the global companies that are at this moment most devoted to drive the process of making alternative methods available. This has certainly to do with capacities and capabilities but also with the perceived vested interest.

Hypothesis 3: International harmonisation must not be the pace of the slowest for introducing alternatives

The process of European unification over the last fifty years has shown that even in consensus processes it is not the pace of the slowest which is necessarily followed. Members that push forward combined with a proactive central administration create pressures on the slower members and urge compromises. In our field we see that indeed the push of European legislation or the positive attitude, e.g. of the OECD Secretariat for the chemical Test Guideline Programme, are decisive for progress.

A principal misunderstanding often creates problems in the OECD regulatory acceptance process: The Test Guidelines (TG) of OECD represent a toolbox of standardised tests – they do not represent the complete regulatory acceptance of these tests in all OECD member countries. If Europe for example requires an *in vitro* test for skin irritation in its regulation, making it an OECD TG allows companies outside the EU to carry out the test in any OECD member country for notification in Europe. It does not mean that all member countries now have to request data from the *in vitro* skin irritation test, however, in agreement with the OECD Council decision on Mutual Acceptance of Data (MAD) from 1981 (OECD, 1981), data from OECD Test Guidelines should be accepted for purposes of assessments in all OECD member countries. Still, new methods under development are often blocked or delayed because of the perceived regulatory acceptance of the respective method from a national perspective. OECD member countries should be much more relaxed about the expansion of the toolbox: this is only about how to do it (TG) and not what to do (individual regulation). The fact that such intense discussion takes place about tests that are often not applied in the respective own regulation shows the importance given to global standards and their possible impact back on national regulations.

Hypothesis 4: We need an International Council of Validation Bodies

Sharing of work of validation studies, coordination of efforts and convergence of approaches requires a continuous platform for dialogue that does not depend on the coincidental quality of personal relationships between players and also allows speaking with one voice to global customers such as OECD, ICH, VICH, ICCR and ISO. OECD has made a most important move by requesting validation for any new test method suggested to be developed into a TG, be it alternative or animal-based. The resulting demand of coordinated validation efforts can hardly be met by OECD itself and experiences in the field of endocrine disrupters have shown the difficulties of having an efficient validation and acceptance process that meets the demands for new test methods in OECD member countries. To meet the enhanced need for alternatives, the OECD has initiated a new approach in one of its Validation Management Groups, the VMG-Non-Animal (VMG-NA), which is focused on development of new *in vitro* techniques. In contrast to how the other two VMGs, the VMG-Mammalian and the VMG-Ecotoxicity, have been managed, where most validation work was coordinated by the secretariat, the VMG-NA has, since its inception in 2003, delegated all actual validation work to member countries and mainly serves as an external project coordination entity and discussion forum. The initial reason for this new approach was limited resources of the secretariat and an overwhelming burden of activities generated by the other two VMG's threatening to put a gridlock on the work. The concept developed under the VMG-NA has proven very successful, both in terms of making the best use of limited resources and in delivering validated test methods.

With the adoption of the OECD Guidance Document No. 34 (GD34) on "The Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment" a first, very important step towards developing internationally agreed principles for validation and regulatory acceptance of alternatives was taken (OECD, 2005). The OECD is now in the process of implementing the GD34 principles in all its validation work and the knowledge base is constantly growing. The eight basic criteria in GD34 should always be addressed, but different tests may require slightly different validation set-ups and a degree of case-by-case flexibility should always be maintained. The GD34 is a living document, but it constitutes a framework for how international validation can be performed. However, even though the VMG-NA seems to be delivering new tests for endocrine disrupting chemical testing, there is still a huge challenge for the OECD when these and other types of tests are combined into batteries or testing strategies for risk assessments, since there is no agreement on how this will be done and new guidance needs to be developed within this field.

Experiences gained in validation over the years, for example with regard to standardisation of tests before validation, introduction of a prevalidation step, numbers of substances and laboratories included, are often painful lessons that should not be repeated. In light of the close and trustful collaboration of the different validation bodies of the OECD member countries with each other and OECD, it seems to be more efficient to actively collaborate and provide the valida-

tion services required. OECD is certainly far advanced compared to the other international organisations harmonising testing approaches with regard to formal validation of efforts. Lately, interest in ICH has increased and a dedicated meeting with ICCVAM, JaCVAM and ECVAM was held in May 2007. It appears that closer collaboration is also emerging here.

The creation of an International Council of Validation Bodies (ICVaBo) appears to be a solution to make solid, coordinated offers for validation. It is suggested that one delegate each designated by the different validation bodies forms the board of ICVaBo. This might at the same time represent a starting point to further harmonise the peer-review process. It is an unnecessary loss of energy and resources that, following joint or at least coordinated validation studies, several parallel peer-review processes start. It is most promising to set up a joint peer-review process and that can be employed on a case-by-case basis with only a final endorsement by ICCVAM, ESAC and the respective other national peer-review processes. It is timely to bring together representatives of validation and peer-review bodies to discuss such a joint process.

Hypothesis 5: The positive impact of globalisation on the world-wide introduction of alternatives serves as a role model and increases acceptance of globalisation as a whole

In the sense of neofunctionalism (Haas, 1958), positive visible examples of political processes create trust and buy-in for them in more general terms. In the words of A. R. Zito "When national populations witness the benefits of integration occurring in one policy sector, they will embrace the extension of supranational control into other sectors." (Zito, 2007). Due to its high appeal to many citizens, alternatives to animal experiments qualify especially for such a role. The enormous impact of the OECD principle of Mutual Acceptance of Data (MAD) (OECD, 1981) for saving unnecessary repeated experiments has not been sufficiently leveraged to demonstrate the positive effect of harmonised approaches. This would not only serve to demonstrate to animal welfare activists but also to a more general public the advantages of a globalised approach.

Hypothesis 6: The United Nations Globally Harmonized System (GHS) for classification and labelling of substances represents opportunity and threat for alternative methods

The perspective of world-wide standards for classification and labelling of dangerous substances will help to develop prediction models of alternative methods that are universally applicable. The prediction model is the algorithm translating the result of an *in vitro* test (e.g. cytotoxicity) into the results of the animal test to be replaced (e.g. not, weak or strongly toxic). This will help the adaptation of new alternative methods in other economic areas in the mid-term. However, there are threats to be considered:

– The methods that are currently validated and accepted do not necessarily comply with the new classification thresholds. A re-evaluation of prediction models and the linked performance of the alternative methods might be necessary.
– In some instances the classification shall change from a European plus/minus classification, e.g. skin corrosive or not, to a scheme where weak and strong toxicants are distinguished. This would bear the risk that, for example, the validated and accepted alternative tests for skin corrosion do not give the required distinction for GHS. Fortunately, according to the current state of the play, Europe does not follow this specific change suggested by GHS. However, there are discussions for skin sensitisation to follow this route and introduce the potency information of the Local Lymph Node Assay (LLNA). This would make a qualitative test a quantitative one, which would be much more difficult to replace by an animal-free method. Since it is at least questionable what sensitising potency of a substance means with regard to human risk, this approach is more than questionable. There is some vested interest to make use of "weak sensitisers" below certain threshold dosages. Whether this acute potency, however, has anything to do with chronic consumer safety remains to be shown. If potency information is becoming a regulatory requirement via GHS, this will create a tremendous obstacle for the introduction of replacement methods and the application of the recently validated reduced LLNA (Kimber et al., 2006). This approach, developed by members of the ECVAM sensitisation taskforce, tests only the highest dose of the classically three doses of the LLNA, since it could be shown that practically for all sensitisers the highest dose is positive. For mere hazard assessment this dose is sufficient, cutting animal use in half. In light of the fact that LLNA shall be applied to all 30.000 REACH substances, a considerable saving is achieved (240-300.000 mice).
– Changed classification and labelling schemes reduce the number of reference data available. Where thresholds of classification are changed and old classifications cannot be adapted to the new values, substances can no longer be used as reference standards. Already now, the availability of reference data represents a bottleneck for validation studies.

Hypothesis 7: A globally harmonised glossary of terminology is necessary

Based on the ICCVAM glossary of terms, OECD GD34 has included a glossary. Unfortunately, this part of the document has not received its due attention and consultation was too short to allow an in-depth revision at the time. Therefore, ECVAM has undertaken the effort to draft a more comprehensive glossary. It comprises 136 entries, out of which 123 correspond to autonomous definitions and 13 to cross-references between terms. This glossary is largely drawn on previous terminology efforts, two major sources being the glossary of terms included in the OECD GD34 (1) and the 1997 report of ICCVAM (2), which overlap substantially. 51 entries were added compared to the OECD GD34 glossary.

The glossary was reviewed by ESAC (ECVAM Scientific Advisory Committee) and underwent an inter-service consulta-

tion with DG ENV, DG ENTR, DG SANCO and DG RTD. The document will be published at the end of 2007 (Bouvier d'Yvoire et al., 2007) and is then available via our website (www.ecvam.jrc.it). The document will be submitted to the OECD to further a world-wide accepted standard terminology.

Hypothesis 8: Europe serves as an engine for globalisation of alternative methods

There is no doubt that over the last twenty years Europe has served as a forerunner of alternative methods in legislation and with regard to funding of the development and validation of alternative methods. It is fair to say that at least ten times more public funding was made available than in other economic regions. However, it is less this technological push that makes Europe an engine of globalisation, although this certainly has impact. The more dominant effect, in fact, comes from market forces. With 500 million consumers, Europe represents a key export target for the rest of the world. By requesting standards for cosmetics and chemicals making use of alternative methods, this creates pressures to comply with European standards. Furthermore, testing services, test kits and computer programs represent growing markets, especially in the growing economies of China and India for example. This will be further boosted as soon as these countries achieve OECD accreditation for Good Laboratory Practice compliance, which individual facilities have already received via OECD member countries that carried out accreditation. It is impressive to see the increasing number of contract research laboratories offering their services, e.g. at the US Society of Toxicology meetings. Their offers increasingly include alternative methods also.

Furthermore, the importance given to the subject of alternative methods by the European Commission as e.g. exemplified in the 2006 to 2010 action plan for animal welfare and especially in the dedication of the EU Commission's vice-president Verheugen and in consequence his services in DG Enterprise to this cause, are putting the topic on political agendas world-wide.

Hypothesis 9: Collaboration with the USA is a role model for globalisation of alternative methods

Interactions between ECVAM and governmental bodies in the USA started as early as 1993, shortly after the creation of ECVAM. Since 1995, ECVAM has a bilateral co-operation with the US Interagency Co-ordinating Committee on the Validation of Alternative Methods (ICCVAM). The aim is to have an early exchange of information on the validation of test methods so as to facilitate mutual recognition, acceptance and implementation of scientifically validated testing methods. In addition, this co-operation serves to facilitate the OECD process in providing harmonised protocols to the scientific community and promoting international adoption of validated alternative methods.

Despite the similarity in name, ICCVAM and ECVAM have very different set-ups and roles (Fig. 4). ICCVAM much more resembles ESAC as a regularly meeting advisory and peer-review body. However, it is made up by mainly regulatory agencies, which are exactly the entities not included in ESAC. Although the decisions by ICCVAM do not preclude the acceptance step by the individual agencies, it paves the way to this step, which often represents a major obstacle in the European process. With the formal introduction of an ECVAM Regulatory Advisory Panel (ERAP), some of these limitations shall now be overcome.

The existing collaboration between ECVAM and ICCVAM in the field of alternative testing methods has been strengthened during the last four years and comprises the following activities: ICCVAM has an observer status on ESAC. The Head of ECVAM became member of SACATM, the US Scientific Advisory Committee for Alternative Toxicological Methods. Both ESAC and ICCVAM have agreed on parallel peer-review and arbitration of results for the upcoming peer-reviews (pyrogen tests, haematotoxicity, eye irritation, micronucleus test, skin irritation, etc.). Several studies (acute toxicity, endocrine disrupters, mutagenicity) and six workshops have been and will be jointly carried out. ICCVAM and ECVAM are discussing on creating an International Council of Validation Bodies to coordinate validation studies at the level of OECD. Discussion about formal collaboration with OECD has been initiated. Thus the parallel collaboration with both ICCVAM/NICEATM and OECD (Fig. 5) results in considerable synergy. About 20 visits of ICCVAM members or ICCVAM-nominated experts to ECVAM taskforces, workshops and validation management groups take place per year. The US Food and Drug Agency (FDA) has allotted a specific budget for parts of these travel costs. A sabbatical programme to exchange ECVAM and ICCVAM personnel was agreed upon, but no such exchange has taken place yet. In 2003, the Head of ECVAM also became member of the Scientific Advisory Committee of CAAT, the Centre for Alternatives to Animal Testing of the Johns Hopkins University, Baltimore, which has pioneered the field of alternative methods in the US for

Organisational differences between ICCVAM and ECVAM

	EU	US
R&D	ECVAM + DG RTD	---
Validation	ECVAM	NICEATM
Peer-Review	ESAC	ICCVAM
Regulatory acceptance	diverse	Agencies in ICCVAM

Fig. 4: Organisational differences between ICCVAM and ECVAM

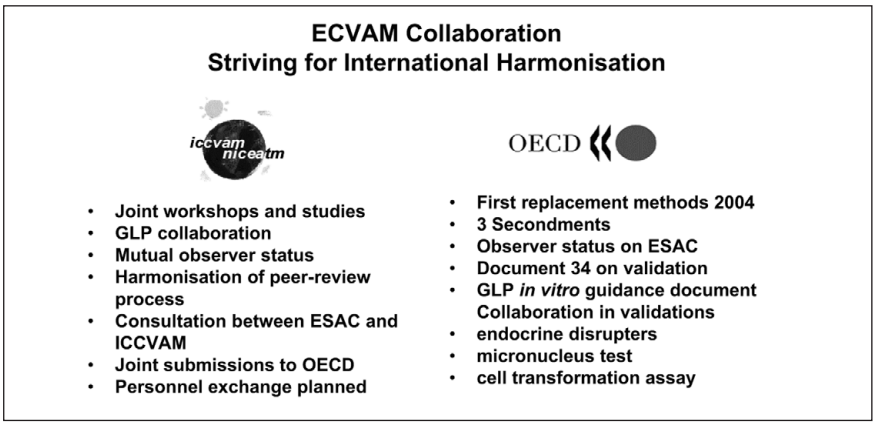

Fig. 5: ECVAM collaboration with ICCVAM/NICEATM and OECD striving for international harmonisation

about 25 years. At the same time, he became a member of the Scientific Advisory Committee of the Institute for In-Vitro Sciences (IIVS), Gaithersburg. Furthermore, a senior American manager from The Procter and Gamble Company was on secondment at ECVAM for two years.

The framework of political collaboration with the USA developed very favourably: The EU-U.S. Guidelines for Regulatory Co-operation and Transparency were finalised in 2002. In November 2002 a *Road Map* containing 5 initial "pilot projects" to implement the Guidelines was agreed, among them:

"Cosmetics: DG ENTR and the U.S. Food and Drug Administration ("FDA") have agreed to co-operate in a pilot project concerning the validation of non-animal testing methods. The co-operation aims at early exchange of information and joint efforts to facilitate the OECD process in this area. The U.S. ICCVAM (Interagency Co-ordinating Committee on the Validation of Alternative Methods) and its European counter-part ECVAM (European Centre for the Validation of Alternative Methods) will collaborate among others on scientific evaluation of proposed methods. Contacts between ECVAM and ICCVAM work well. Intensified co-operation is envisaged."

The collaboration was again reinforced at the April 2007 U.S.-EU Summit.

In conclusion, in recent years the collaboration with the USA has been considerably enlarged and strengthened. Thereby, we succeeded to anticipate discussions on differences in view, which would have been necessary anyway at the stage of international acceptance of results. At the early stage, however, needs and concerns of the partners can still be accommodated in the study design. Often, already communication about concerns was sufficient to clarify and overcome these hurdles.

Hypothesis 10: Education is the means to accelerated globalisation of alternatives

The acceleration of processes making validated alternatives available in Europe makes it difficult for other countries to follow. Testing strategies like the ones developed for REACH (REgistration, Authorization and restriction of CHemicals) require understanding and digestion before they can influence internationally harmonised approaches. These strategies were developed in view of 30.000 existing chemicals to be tested, which is a unique programme world-wide addressing substances on the market for more than 25 years. The comparatively small high production volume chemical programmes outside Europe in contrast result in new test requirements only to a limited extent. Here, there is little need for harmonisation for these "old" chemicals. However, often overlooked, REACH will also be applied to all new chemicals in the future. In order to maintain the mutual acceptance of data, it will be critical to achieve international acceptance of the testing strategies, if their animal and cost saving advantage shall be translated also to new chemicals. Otherwise, the globally acting chemical companies will continue to use as default the current internationally harmonised approach. This is in clear contrast to the spirit of REACH.

Due to the preparation for implementing REACH, a very important process has taken place over the last 18 months that will impact on the use of alternative methods in Europe and possibly beyond: Involving more than 200 experts from regulatory bodies, industry, the European Commission, academia and animal welfare, testing strategies were developed to fulfil the information requirements of REACH for a given chemical. The background is that REACH wants to make use of all sources of information, i.e. existing animal (also from non-GLP, non-guideline studies) and human data, structure-based approaches (read-across, chemical grouping, rule-based systems, (Q)SAR), *in vitro* tests (validated as well as other "suitable" methods) before embarking on animal tests. The development of this guidance was coordinated by ECVAM on behalf of the Commission. The paradigm shift in the use of alternative methods enabled the introduction, already in this consensus process in which all competent authorities of the 25 member states were involved, a number of methods just validated or at the final stages of the validation process. REACH foresees accepting both negative and positive test results from accepted, validated alternative methods, but also allows positive classifications of substances on the basis of "suitable" methods. In the definition of "suitable", the legislation refers to the ECVAM criteria for entering into prevalidation. By establishing a reference laboratory, CORRELATE, and adapting its INVITTOX protocols ECVAM is supporting the definition and use of such methods. REACH also foresees several mechanisms to adapt shortly to technical progress with regard to the availability of further alternative methods. Due to the global market for chemicals, this will impact also on producers outside of Europe and create dynamics for introducing similar approaches in other parts of the world.

Thus education, not only of the European players but also of global stakeholders, is necessary to set the new approaches into practice. This means not only to

promote the test strategies and their components to OECD acceptance but also to share internationally the how and why of the new way chemicals are assessed in Europe. The first step here is the availability of test guidelines and more detailed protocols as well as training. The INVITTOX protocols of the ECVAM DataBase for ALternative Methods (DB-ALM) can become instrumental here. The data sector of INVITTOX will be used within the context of the European chemicals policy REACH to ensure the use of adequately documented and suitable methods for the assessment of adverse effects of chemicals. In addition, novel means such as e-learning need to be explored to enable the transfer of novel methods to new laboratories.

The network of validation bodies will be critical to complement this spread with the evaluation necessary to build trust in new approaches. Since many of the testing strategies are more than a battery of tests and thus more than the sum of the individual components, it will be critical to develop the principles for validation of test strategies in order to convince regulatory bodies world-wide of their feasibility, reliability and relevance. At present, guidance on these specific issues is missing in OECD GD34 and specific guidance will have to be developed.

Hypothesis 11: Globalisation of alternatives is taking place now because of the synchrony of several favourable driving factors

Certainly globalisation is ongoing – it is a general phenomenon. However, globalisation of the world has accelerated over the last two decades. Why does the field of alternatives only join in now?

Thomas L. Friedman (Friedman, 2006) has pointed out that societal changes are not linear but take place incrementally when several favourable factors coincide. The same can be applied to alternative methods:

- The biotech revolution has provided us with the technological means.
- The proof of principle of the first successfully accepted methods demonstrates feasibility.
- Legislative pressures promote the development.
- Global industry seeks international harmonisation of safety standards.
- New technologies in agent discovery require higher through-put not obtainable with traditional methods.
- New products (e.g. human recombinant proteins and antibodies, nanoparticles) require new approaches.
- The limitations of the delayed adaptation of safety testing are increasingly perceived (e.g. high attrition rates, i.e. failure of substances in clinical trials; high false-positive rates of precautionary approaches).
- New geographical regions are becoming involved in the development of alternatives, adding brain power and new thoughts and novel techniques.

The convergence of these driving factors requires a new platform emphasizing more horizontal activities and thus prompting the development of an International Validation Body. For this body to be efficient it needs to combine new techniques and alternative approaches together with the already existing internationally accepted test methods or guidelines. The major international organisation with an expressed strong devotion to alternatives seems to be the OECD. To speed up the international acceptance of alternatives and their validation it is key that international collaboration is broadly enhanced and that the establishment of an International Validation Board is well anchored, both in the alternative society as well as in the established international regulatory community. To cite once again Victor Hugo "Nothing is as strong as an idea whose time has come". This time it appears to be a global idea.

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