START-UP

SEVENTH FRAMEWORK PROGRAMME

PROJECT

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Contact
Manon Vivier, support of secretariat of ***ecopa***
Dept. of Toxicology,
Laarbeeklaan 103, B - 1090 Brussels
Tel. +32-2-477 45 07 • Fax.+32-2-477 45 82
e-mail: ***ecopa***@vub.ac.be
http://www.***ecopa***.eu; there is no specific website for the START-UP project but information can be found on the ***ecopa*** website

PARTNERS

ecopa
Prof. Vera Rogiers, chair of ***ecopa*** until end of 2009
Dept. of Toxicology
Laarbeeklaan 103, B - 1090 Brussels
Tel. +32-2-477 45 16 • Fax.+32-2-477 45 82
e-mail: vrogiers@vub.ac.be

VUB
Prof. Tamara Vanhaecke (Rector Prof. Paul De Knop)
Dept. of Toxicology,
Laarbeeklaan 103, B - 1090 Brussels
Tel. +32-2-477 45 18 • Fax.+32-2-477 45 82
e-mail: tamara.vanhaecke@vub.ac.be

Scientific and **T**echnological issues in 3Rs **A**lternatives **R**esearch in **T**he process of drug development and **U**nion **P**olitics

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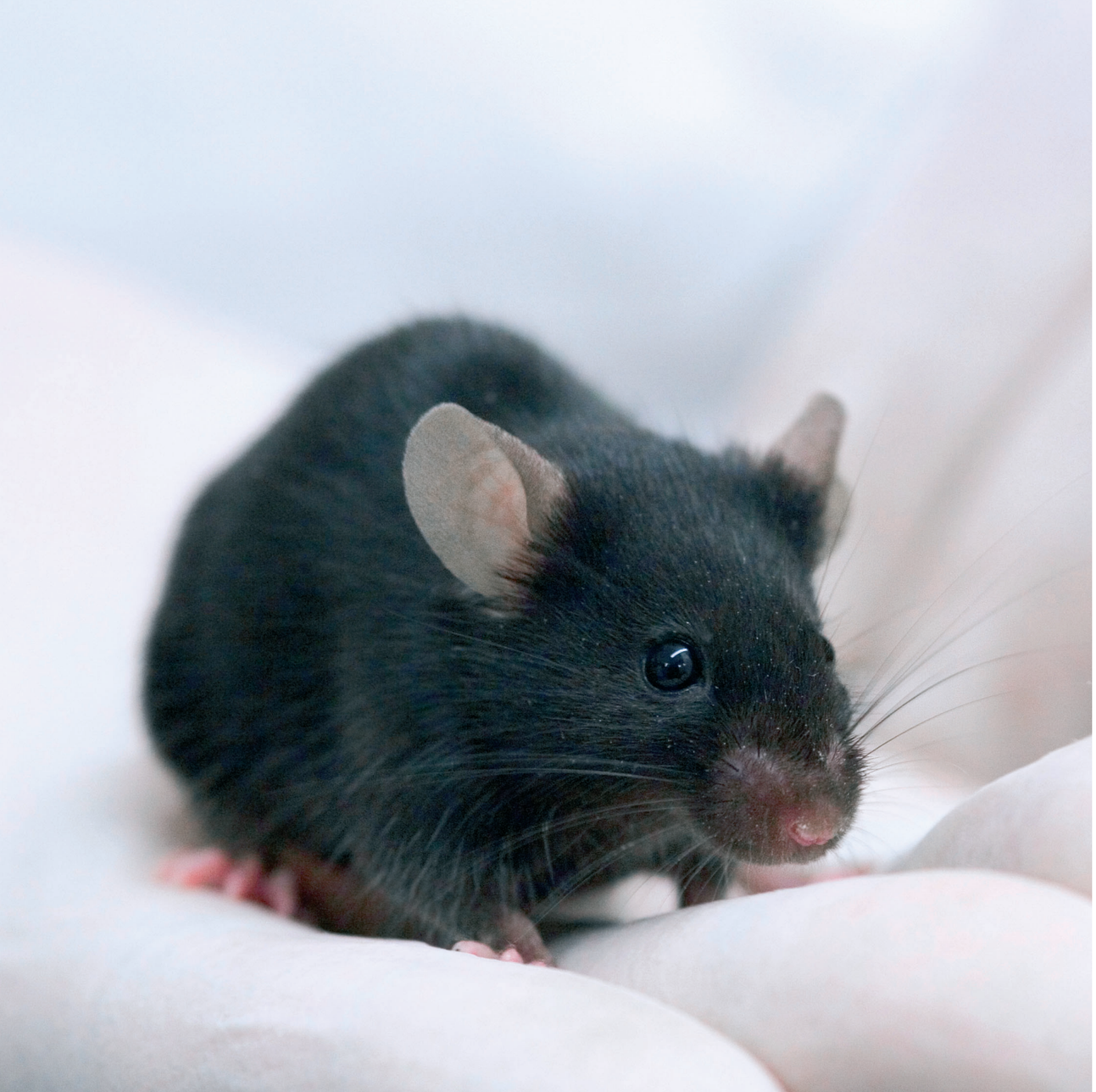


INTRODUCTION

START-UP (Scientific and Technological issues in 3Rs Alternatives Research in The process of drug development and Union Politics) is a support action (n° 201187) within FP7-HEALTH-2007-1.3-2 about the "Bottlenecks in reduction, refinement and replacement of animal testing in pharmaceutical discovery and development". It is coordinated by ***ecopa*** (European Consensus Platform on 3R Alternatives to Animal Experimentation) with the VUB (Vrije Universiteit Brussel) as the second partner, being responsible for the scientific/administrative secretariat of the project. In particular, it is the Department of Toxicology providing the necessary support for ***ecopa***, an international not-for-profit organisation.

The development of 3R-alternatives and their implementation in the safety assessment of the different product types present on the EU market is one of the major objectives of ***ecopa***. This international not-for-profit organisation officially exists since December 2002 and has coordinated before the FP6 CONAM (Consensus Networking on Alternative Methods within Europe) project. ***ecopa*** exists through so-called NCPs (National Consensus Platforms), which are in fact scientific organisations all over Europe, consisting of representatives of the four major parties involved in the use of alternative methods versus experimental animals. These include animal welfare, industry, academia and regulatory bodies. Actually, 16 NCPs exist (14 full members, 2 associate members) being Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Norway, Spain, Sweden, Switzerland, The Netherlands, Ireland and Poland.

Several of these NCPs have worked in this project intensively and constructively together, not only with eminent pharmaceutical experts in the meetings and workshops, but also with representatives of EPAA (European Partnership for Alternative Approaches to Animal Testing), OECD (Organisation for Economic Co-operation and Development), the European Pharmacopoeia and ECVAM (European Centre for Validation of Alternative Methods), with young scientists from all over Europe, with national and EU regulatory bodies, Commission representatives and many others.

CONTENT

INTRODUCTION 3

CONTENTS 4

MEETINGS 5

Expert Meetings 5
Workshop Reduction 5
Workshop Replacement 5

CONCEPT AND PROJECT OBJECTIVES 7

OVERALL EXECUTIVE SUMMARY 9

Overall Recommendations 16

ROAD MAPS 18

CD-ROM 21

MEETINGS

EXPERT MEETINGS

WORKSHOP REFINEMENT

26 - 27 February 2009,
Istituto Superiore di Sanità, Rome, IT

Scientific committee
Bernward Garthoff*, treasurer ***ecopa***, Bayer, DE
Vera Rogiers*, chair ***ecopa***, VUB, BE
José Castell*, vice-chair ***ecopa***, Hospital Universitario La Fe, ES (Expert meetings 1 & 3, Madrid & Alicante)
Peter Maier*, Board Member ***ecopa***, Forschung 3R, CH (Expert meeting 2, Basle)

Scientific committee
Franca Fassio, member of NCP IPAM, Merck Serono, IT
Bernward Garthoff*, treasurer ***ecopa***, Bayer, DE
Peter Maier*, Board Member of ***ecopa***, Forschung 3R, CH
Vera Rogiers*, chair of ***ecopa***, VUB, BE
Annalaura Stammati, member of NCP IPAM, ISS, IT
Maciej Stepnik, member of NCP Polcopa, Nofer Institute of Occupational Medicine, PL
Hanna Tähti, member of NCP Fincopa, University of Tampere, FI
Augusto Vitale, member of NCP IPAM, ISS, IT

WORKSHOP REDUCTION

3 - 4 July 2009,
Hotel Grauer Bär, Innsbruck, AT

Scientific committee
Janna de Boer, member of ZonMW, NL
Bernward Garthoff*, treasurer ***ecopa***, Bayer, DE
Gerhard Gstraunthaler, member of NCP ZET, Innsbruck Medical University, AT
Peter Maier*, Board Member of ***ecopa***, Forschung 3R, CH
Walter Pfaller*, Board Member of ***ecopa***, Innsbruck Medical University, AT
Vera Rogiers*, chair of ***ecopa***, VUB, BE

WORKSHOP REPLACEMENT

2 - 3 October 2009,
Airport Hotel, Budapest, HU

Scientific committee
Gisbert Sponer, member of SET, Bioassay GmbH, DE
Lajos Balogh, member of Hucopa, OSSKI, HU
Bernward Garthoff*, treasurer ***ecopa***, Bayer, DE
Vera Rogiers*, chair ***ecopa***, VUB, BE

* the ***ecopa*** board mentioned was in place until end of 2009, thus as long as the START-UP project was running

CONCEPT AND PROJECT OBJECTIVES

The START-UP project must be seen in the context of the actual situation in the EU (and other parts of the world) with respect to the use of 3R-alternative methods to refine, reduce and replace experimental animals in the development process of several product types and their use as “safety and efficacy guarantee” for human health. In this project focus therefore does not lie on alternative methods as such, but on their potential application in the Pharmaceutical Industry in order to improve the final outcome.

Indeed, the process of lead identification, lead optimisation and bringing a drug candidate to the stage of a pharmaceutical finally being approved for clinical use is a time-consuming process. Identifying “wrong” drug candidates therefore at an early stage during the drug development process and avoiding efforts in optimising under-performing candidates in terms of safety and efficacy are essential for the competitiveness of the European industry. Bringing in alternative methods at the right moment and at the right place could therefore be of tremendous benefit not only in terms of animal numbers, but also in terms of a more successful drug development outcome. Only a limited number of 3R-alternative methods have been officially validated and can be used for regulatory purposes. However, a much greater number of alternative methods exists today that can be applied successfully in basic research, in mechanistic studies, in pharmaco-toxicological studies, etc, all of importance for the Pharmaceutical Industry and at the same time for the experimental animals involved. Basically, no restriction exists in this field as long as the 3R-methodologies used are scientifically sound and relevant and have elucidating and discriminative power at a particular stage of the drug development process.

Therefore, a project such as START-UP was necessary, namely a coordinated initiative covering as much as possible all parties involved, being the scientific world, the Pharmaceutical Industry and the different stakeholders in order to achieve a major collaborative activity to get a good and realistic overview of the current use of experimental animals in the whole drug development process and to assess the possibility to implement new alternative strategies and tiered approaches in the different stages of the overall drug development process. The challenge consisted of identifying existing gaps, scientific and technological bottlenecks, ethical concerns and issues related to Union Politics. This exercise has been carried out successfully.

This study not only provides information on classical drugs, the so-called new chemical entities (NCEs), but also on new biological entities (NBEs). The latter generation of biological drugs (antibodies, proteins…), nanotechnology and nanobiotechnology molecules is a growing field and creates new challenges as safety clearance of all these new types of substances seems to be more complex and sophisticated than is the case for the classical chemical substances.

Consequently in a number of cases using animals for hazard determination is not even relevant. On the contrary, up-to-date fingerprint techniques may offer possibilities to better target the problems and mechanisms involved, so that only relevant molecules on a limited number of animals of the relevant species need some testing in order to guarantee safety and efficacy.

The direct objectives of this project consisted of:

- gathering all relevant information, mentioned above, by organising two Expert Meetings with pharma- and biotech-experts and 3R-specialists (note that an additional third Expert Meeting was organised)
- prioritisation of this information within the three domains of Refinement, Reduction and Replacement
- organisation of three high-level Workshops, one on each of the 3Rs
- developing a Consensus Report between all parties involved on the outcome of the Expert Meetings and Workshops
- proposing Road Maps for the Commission

All these objectives have been met within the given limited timeframe of 2 years.

OVERALL RESULTS

The results are presented as an Overall Executive Summary, followed by the Recommendations and Road Maps showing the way forward and full length detailed reports of the 3 Expert Meetings and 3 Workshops. Also, the detailed report is available on cd-rom and largely distributed among the different stakeholders.

Overall Executive Summary

The basis of the START-UP project was the general intention to cover all the issues of 3Rs-bottlenecks in pharmaceutical research and development, as represented by the abbreviation, i.e. Scientific and Technological issues in 3Rs Alternatives Research in The process of drug development and Union Politics.

In order to have as much coverage as possible, the area was intensively analysed in expert meetings, predominantly of industry, but also of academia, and regulatory authorities. Later on, in the 2nd year of the project, these closed expert meetings were extended to three open work-shops, one on each of the 3Rs. All in all, out of a total of 223 participants, there were 109 industrial experts (out of 42 companies) representing pharmaceutical industry or associated institutions, thereby reflecting in particular all aspects of “pharmaceutical life” in R&D.

Started at a kick off meeting in Leverkusen at Bayer AG, the expert meeting 1 in Madrid (Ministeria de Sanidad, ES), the second in Basle (Novartis Research Center, CH) and the third Alicante (Pueblo Acantilado, ES, at the biannual eSI meeting) were then followed by Workshops on Refinement (Istituto di Sanita, Rome, IT), on Reduction (University of Innsbruck, AT) and on Replace-ment (Budapest, HU). These were collaborations of ***ecopa***’s National Consensus Platforms (NCPs) of Italy, Finland and Poland, respectively, Austria and the Netherlands, respectively, Hungary and Germany. Academia was represented by 65 participants, regulatory authorities by 29, and animal welfare by 10. Also locally interested scientists actively participated.

The results were presented and found entrance into the discussions; the format varied, intentionally, from brain storming sessions and working group style to formal scientific presentation workshops

or plenum style forums to enable free and interactive communication. All presentations and discussions are detailed in report form and are accompanied by an executive summary and a list of specific recommendations. The major outcome is present here as an overall executive summary, followed by the most prominent recommendations and a road map.

It is hoped that some of the topics discussed, might be subject to future projects within coming EU Framework Programmes.

Collation of 3R-topics in pharmaceutical research

- Animal experiments are still needed and realistic progress is actually expected by intelligent combination of refinement, reduction and replacement methodologies / strategies. This is in particular relevant in animal disease models. *In vivo* and *in vitro* research and testing should go together and not be seen as two opposites.
- It was emphasised that an alternative method not necessarily needs to be formally validated, the fact that a test works is for the Pharmaceutical Industry of more importance.
- Data obtained from *in vitro* tests, carried out before *in vivo* experiments start, can efficiently filter compounds of interest. These pre-tests should be of a higher degree of sophistication and complexity than is the case now e.g. use of 3D-cultures, co-cultures, stem-cell derived models, organ-specific and differentiated cell cultures; more human cells use and more attention for the parameters measured e.g. it is unlikely that only one biomarker will cover the complexity of the living organism, therefore a set of specific biomarkers of clinical relevance increases the translational nature of the *in vitro* model used; these should be developed at least for key organs and new and potent tools should be involved (e.g. transcriptomics, metabonomics, biostatistics).
- When animals are involved, they should be of a relevant species for the question posed, otherwise experimentation should be deleted. The same is true for exposure to unrealistic high dosages/exposure scenarios.

- Important fields for further development are teratogenicity and embryotoxicity as these tests are necessary for every newly developed drug coming on the market; for exploration of new opportunities for pharmacodynamics, and for better integration into single test programmes for pharmacokinetics, carcinogenesis, safety pharmacology and toxicology.
- In test development more focus should be on “risk assessment” than on “hazard assessment”.

Concepts of cell system improvements

- These were high on the agenda. Stabilisation (e.g. by epigenetic modifications, miRNA interaction) of existing cell systems, and to use these for long-term testing has potential for toxicity and efficacy testing. In addition, the fact that the heterogeneity of human population is not taken up by current *in vitro* tests deserves efforts to develop models capable of mimicking human variability.

Concepts of data sharing and reporting of “negative” results

- These aspects are important in gaining more basic information and reducing replication of experiments. They are of special importance in certain diseases.
- Essential for sharing data are data quality control, protocol standardisation and in particular protection of intellectual property. It was proposed to overcome this hurdle by establishing a “neutral” pan-European party entity.

Aspects of lab animal husbandry, of best practice for lab animal keeping

- Emphasis was given to positive aspects such as better training of personnel and in particular of competent authorities; positive welfare of experimental animals e.g. via group housing, creation of possibilities for natural behaviour, environmental enrichment, consideration of positive reinforcement training in the case higher animals are involved.
- Proposals for central breeding of controlled and certified quality were particularly brought forward for primates and transgenic animals.
- Emphasis was also given to the importance of the microbiological quality of the animals, leading to better experiments and indirectly leading to less animal use.

Furthering of model development, especially of non-invasive *in vivo* methodology

- This point came up in all meetings and workshops and supports the further transfer of non-invasive diagnostic methodologies (e.g. magnetic resonance imaging, micro CT) from human medicine to laboratory animals allowing not only diagnosis but also long-term monitoring of treatment. In particular, the combination of different non-invasive imaging techniques was seen as a possibility for refinement and reduction and at the same time for gaining better knowledge.
- In particular, in animal disease models this methodology is seen as a key improvement.

Bottlenecks in biologics development

- Use of humanised models, knock-out animals and transgenic animals could help to make more appropriate use of animals as high target specificity is involved. Also transgenic cells/enzymes/ *in vitro* models have relevance.
- More parameters should be combined in one animal study (e.g. safety pharmacology, pharmacokinetics, local toxicity, immunogenicity).
- Standardisation of animal strains, microbiological high quality of animals, use of well-defined environmental conditions and techniques are crucial reduction parameters in this field.

Special case of vaccines quality control

- As in the EU, authorities request that all vaccines lately must be tested, high numbers of animals are consumed. Moving from this traditional quality control concept towards the monitoring of all crucial steps during production could save these animals. This so-called consistency approach was largely supported.
- In vaccines quality control, refinement strategies should be developed and implemented.
- Implementation of existing 3R-methods should be encouraged by improving and global harmonising of the regulatory procedures. Also providing incentives to development and production is considered to be important.
- More attention should go to the neglected area of veterinary vaccines.

Specific disease animal models with high burden to experimental animals

- As animal pain models are not very predictive, well-controlled studies in man using micro dosing were proposed in order to be able to score pain in a realistic way.
- Cancer models are a special target for further improvement, also since by the development of biologics for this topic, the area is more covered. In oncology, genetically engineered models and primary tumour models were said to be productive. A refinement alternative could be the study of surrogate tissues from normal animals which usually exhibit the fully functioning pathways that are targeted. Also the importance of measuring *in vitro* specific biomarkers that can also be detected in the clinical situation came up.

Analysis of Union Politics, country / Member States politics

- Over expectations with respect to alternative methods should be avoided.
- Ethical issues and political restrictions were discussed with respect to human stem cell use. Heterogeneous opinions within the different Member States should be better harmonised.
- Member States should establish National Animal Welfare and Ethics Committees with well-trained personnel to give advice to the competent authorities and permanent ethical review bodies. Networking of these committees should play a role in the exchange and communication of best practices.
- Importance was given to a trans-sector, cross sector-cutting information stream by regulators and industrial partners.

Refined analysis of general EU research strategies

- The general research strategies applied today at the EU level are a burden to potential applicants and the administration of EU Framework Programmes are seen as a hindrance to appropriate research in alternative methods. Less bureaucracy, better integration of research teams, eventual leadership by the pharmaceutical industry, limitation of number of projects per team and need for new names of young scientists and a fresh outlook were all mentioned as possible improvements.

Global harmonisation

- The importance of global harmonisation as the basis for further implementation of alternative methods came up in all meetings and workshops.
- A unified animal legislation and, in this context, specific actions addressed towards the political world were seen as important.
- Communication on new models across sectors, involving regulatory agencies and competent authorities should be enhanced.
- Dissemination and promotion of refinement/reduction techniques in drug development was seen as an important step forward.
- Global harmonisation is highly important and should be pursued even if it is difficult and slow. Worldwide harmonisation should be brought in the execution of pharmaceutical registration and general concepts, also existing Animal Welfare in the different Member States should be better harmonised and the revised Directive 86/609 could help in this process.

In summary, the EU 7th RTD Framework Programme project START-UP has delivered a whole landscape of ideas and potential avenues for further research and development projects within the future EU Framework Programme in regard to 3Rs bottlenecks and EU industry competitiveness; these should be considered when drawing up new project calls in this area in the future. It has been demonstrated that only detailed discussions with experienced experts can lay groundwork for adequate analysis.

Also, these approaches, as laid out in more detail in the individual recommendations, have to be discussed with the experts involved, the Scientific Officers of the EU Commission, the European Parliament representatives as well as the Industry and the interested public. With the pool of experts brought together under START-UP, the furthering of the Road Maps attached, can be achieved.

Further workshops organised by the project partners involved, should spread the message, in order to come up with solutions for some bottlenecks where solutions are not easy to come by.

The Project Coordinator
and the Organisers Team

OVERALL RECOMMENDATIONS

In the detailed report, a list of specific recommendations is given for each Expert Meeting and the 3R-Workshops, making a total of 36 recommendations for further follow-up by the parties concerned and in particular by the Commission.
Here the eight most important recommendations are summarised.

- Reduction and refinement are particularly possible in the field of animal disease models. It is recommended to maximize the number of non-invasive and early or surrogate endpoints within one model. Progress in non-invasive test development is seen in the further development of non-invasive imaging / diagnostic techniques transferred from human medicine to laboratory animals, and their intelligent combination.

- Efforts should be focused on the development of batteries of sensitive and specific safety biomarkers with clinical relevance to be measured during the preclinical *in vitro* testing phase.

- The difference in bottlenecks during the development of biopharmaceuticals versus small molecules pharmaceuticals should be better recognised and dealt with. In particular, the relevance of the animal model came up in the case of biopharmacuticals. The use of non-human primates (in a number of indicated cases), humanised models and transgenic animals seems relevant.

- A lot of animals could be spared without loss of quality in the quality control of vaccines in Europe. Therefore it is highly recommended to study the possibility for drastic change
  - by a better control of the implementation of already existing refinement and reduction alternatives by all producers and regulatory bodies
  - by providing the necessary incentives to apply these alternatives
  - by stimulating the development of new alternatives in this field
  - by applying the so-called Consistency Approach confirming production consistency.
  - by paying special attention to veterinary products.

- It is recommended to develop the possibilities of “data sharing” by creating the necessary working tool, namely the establishment of a “neutral” non biased body that could guarantee confidentiality and as such could take away the fear of losing competitiveness. In this way, also quality control of data and standards of protocols could be assured. Furthermore, it was felt that also the follow-up of “negative” results of high standard could contribute to the reduction process.

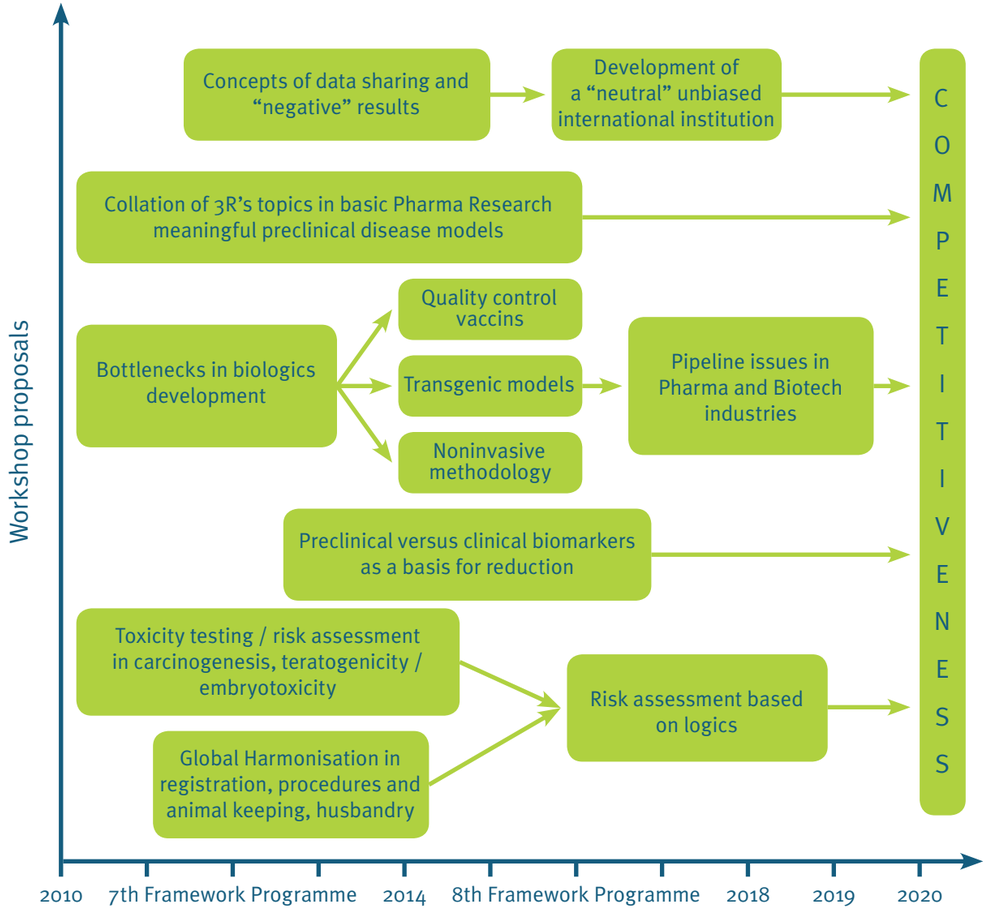
- Animal reduction in drug development is possible by reducing the number of potential interesting molecules that undergo *in vivo* testing by better pre-screening for unwanted effects and deceiving efficacy.
  Therefore, more sophisticated *in vitro* models based on human cells and tissues should be developed and applied in pre-screening: 3D-models, co-cultures, epigenetically stabilised cell lines, stem-cell derived specific cell types,...

- Promotion of positive welfare of experimental animals, besides minimalisation of suffering, is seen as a refinement priority and should include active improvement of the degree of animal welfare in- and outside experimental procedures, backed up by ethological studies on laboratory animals.

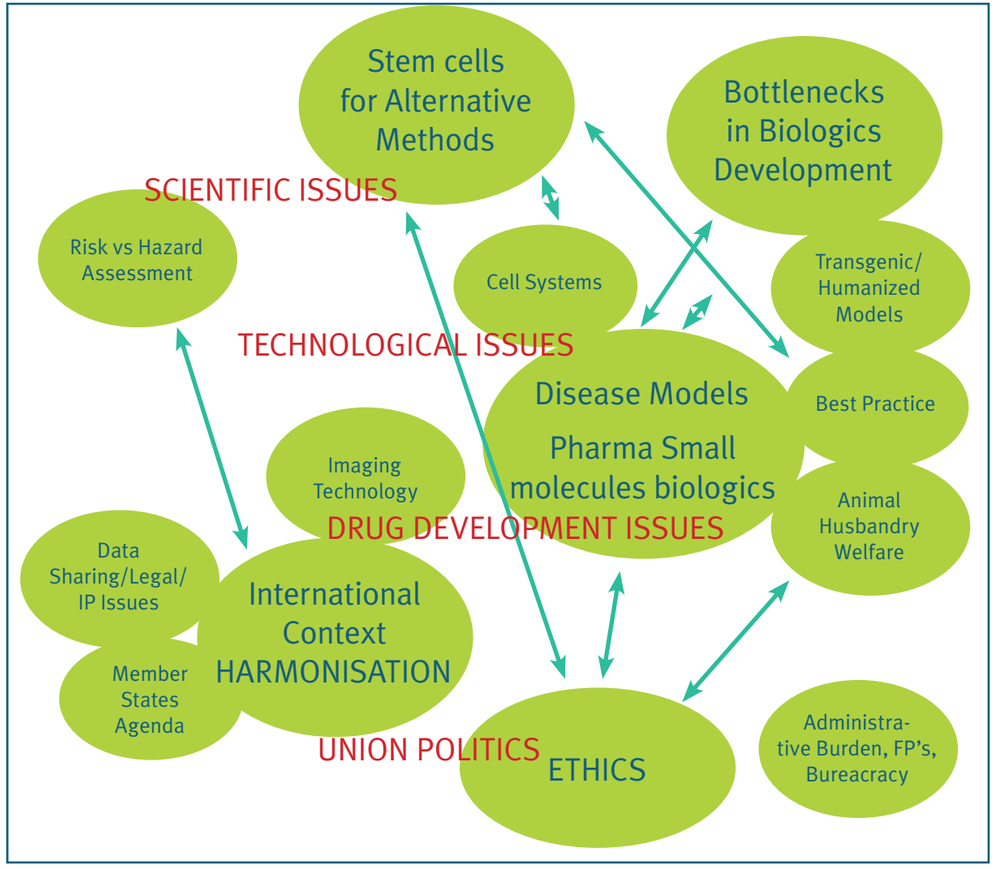
- Global harmonisation is seen as one of the highest priorities for further success in the implementation of the 3Rs. It is thought that all different players internationally involved in drug development, human health, alternative methods development and animal welfare should be brought together to agree on the different procedures to be followed in registration toxicity and efficacy testing, and risk assessment, in the development of biologics and quality control of vaccines, and in the different stages of animal use during drug development, in particular in the case of animal disease models.

ROAD MAPS

Proposals of the *ecopa* Start-up project



Clustering of issues identified in the *ecopa* Start-up project



LIST OF PARTICIPANTS*

- Ahr Hans Jürgen, Bayer, DE
- Alajuuma Paivi, Santen, FI
- Alleva Enrico, ISS, IT
- Amcoff Patrick, OECD, FR
- Amendt Christiane, Merck-Serono, IT
- Azqueta Oscoz Amaya, University of Oslo, FI
- Baffert Fabienne, Novartis, CH
- Ballard Yardy Theresa, Hoffmann - La Roche, CH
- Balogh Lajos, Hucopa, HU
- Banks Christopher, Lab Research Ltd, HU
- Barter Zoe, Simcyp, UK
- Battram Cliff, Novartis, CH
- Beckmann Nicolau, Novartis, CH
- Beken Sonja, Federal Agency for Medicines and Health Products, BE
- Bellocci Mirella, University di Modena e Reggio Emilia, IT
- Beres Erzsebet, Lab Research Ltd, HU
- Bertorelli Rosalia, Schering-Plough, IT
- Bodnar Gabor, Chinoin, HU
- Boehn Susanne, BASF, DE
- Bonafe Roberta, Farmaindustria, ES
- Branchi Igor, ISS, IT
- Bremer Susanne, ECVAM, IT
- Bremm Klaus-Dieter, Bayer, DE
- Buchheit Karl-Heinz, EDQM, FR
- Buckland Gemma, Dr Hadwen Trust, UK
- Budts Stijn, ***ecopa***, BE
- Burek Christof, University of Wurzburg, DE
- Burgemeister Renate, Carl Zeiss MicroImaging GmbH, DE
- Buta Christiane, SET, DE
- Castell José, University Valencia, ES
- Cavéliers Vicky, Vrije Universiteit Brussel, BE
- Chapsal Jean-Michel, Sanofipasteur, FR
- Clinckers Ralph, Vrije Universiteit Brussel, BE
- Coenen Joachim, Merck-Serono, IT
- Coers Pierre, Solvay, BE
- Commandeur Suzan, Leiden University Medical Center, NL
- Conrath Katja, Galapagos, BE
- Costa Patrizia, Fondazione Parco Biomedico, IT
- Cotgreave Ian, AstraZeneca, SE
- Cozens Robert, Novartis, CH
- Crommelin Daan, TI Pharma, NL
- dal Negro Gianni, GlaxoSmithKline, UK
- Dalloul Ahmad, Gedeon Richter, HU
- Dastych Jaroslaw, Polish Academy of Sciences, PL
- Davidson Elizabeth, MHRA, UK
- Dawson Janet, Novartis, CH
- De boer Janna, ZonMW, NL
- De Silva Odile, L'Oreal, FR
- Descamps Johan, GlaxoSmithKline, BE
- Doktorova Tatyana, Vrije Universiteit Brussel, BE
- Dumont Julie, INSERM, FR
- Egresi Andrea, Wessling, HU
- Elekes Ottilia, Gedeon Richter, HU
- Farnaud Sebastian, Dr Hadwen Trust, UK
- Fassio Franca, Merck-Serono, IT
- Fendt Markus, Novartis, CH
- Feyen Jean, Galapagos, BE
- Fingerle Jurgen, Hoffmann - La Roche, CH
- Fraczek Joanna, Vrije Universiteit Brussel, BE
- Frank Jurgen, Life Science Laboratory, AT
- Frankart Aurélie, University of Namur, BE
- Fruhauf Wolf, Ministry of Science and Research, AT
- Garberg Per, BioVitrum AB, SE
- Garthoff Bernward, Bayer, DE
- Gomez Enrique, Carlos Haya Hospital, ES
- Gross Steffen, Paul-Ehrlich Institut, DE
- Gstraunthaler Gerhard, Innsbruck Medical University, AT
- Guillouzo André, INSERM, FR
- Gyertyan Istvan, Hungarian National Scientific Ethical Committee, HU
- Habelt Konrad, Ministry of Health, AT
- Hajdo Eva, Gedeon Richter, HU
- Halasz Attila, Gedeon Richter, HU
- Hammond Tim, AstraZeneca, UK
- Hargitai Judit, Lab Research Ltd, HU
- Haslinger Alois, Ministry of Science and Research, AT
- Heemskerk Johan W. M., Maastricht University, NL
- Hegedius Eszter, Népszabadság Állatvédelem, HU
- Heinonen Tuula, University of Tampere, FI
- Helma Christoph, in silico toxicology, DE
- Hendriksen Coenraad, Netherlands Vaccine Institute, NL
- Hercsuth Eva, Hucopa, HU
- Hirka Gabor, Aurigon, HU
- Hoeveler Arnd, EU Commission, DG Research, BE
- Hollriegl Werner, Baxter, DE
- Horvath Katalin, Aurigon, HU
- Iyer Jay, TI Pharma, IT
- Janoki Gergo, Radiopharmacylab, HU
- Jennings Paul, Innsbruck Medical University, AT
- Jensen Michael, Novartis, CH
- Jones David, EMEA, UK
- Josse Rozenn, Université Rennes, FR
- Juhasz Gabor, OAI Eger, HU
- Karo Adrien, Beagle-Club, BE
- Kireche Mustapha, Clinique Dermatologique CHU, FR
- Kiricisi Peter, EGIS, USA
- Koeper Lydia-Mareen, Bayer, DE
- Kohalmi Krisztina, KKKI, HU
- Kohila Tarja, Helsinki University, FI
- Kolar Roman, Tierschutz Akademie, DE
- Konya Attila, TEVA, HU
- Kramer Nynke, Eawag, CH
- Kubaszky Raluca, Lab Research Ltd, HU
- Kubinyi Gyorgy, OSSKI, HU
- Lahoutte Tony, UZ Brussel, BE
- Lane Sarah, Novartis, CH
- Laskewitz Anke, University medical center Groningen, NL
- Lazar Anna, Civil Rásió/Állatvédelem, HU
- Ledermann Birgit, Novartis, CH
- Lemper Marie, Vrije Universiteit Brussel, BE
- Leyshon Alison, Lab Research Ltd, HU
- Liebsch Manfred, ZEBET, DE
- Lima Beatriz, EMEA, PT
- Lingenhoehl Kurt, Novartis, CH
- Losonci Olga, Chinoin, HU
- Luperi Lucia, Farmaindustria, ES
- Macri Simone, ISS, IT
- Maier Peter, Forschung 3R, CH
- Marty Jurg, Hoffmann - La Roche, CH

* Names and affiliations are provided as available during the START-UP Project

- Marubini Mario, Merck-Serono, IT
- Mayorga Cristobalina, Fundacion IMABIS, ES
- Mayr Oswald, Montavit, AT
- McArthur Robert, McArthur and Associates, AU
- Mildner Michael, Medical University of Vienna, AT
- Milosevic Nada, University of Giessen, DE
- Mittlbock Martina, Vienn Medical University, AT
- Monostory Katalin, KKKI, HU
- Monshouwer Mario, Johnson & Johnson, BE
- Morvan Frederic, Novartis, CH
- Muller Patrick, Novartis, CH
- Muller-Beckmann Bernd, Hoffmann - La Roche, CH
- Musi Barbara, Gambro R&D, SE
- Muzzio Valeria, Merck-Serono, IT
- Nagy Krisztina, Lab Research Ltd, HU
- Newman Joe, AstraZeneca, USA
- Nicklas Werner, DKFZ, DE
- Nobiling Rainer, University of Heidelberg, DE
- Norring Marianna, Julia von Wendt'Foundation, FI
- Novak Istvan, Aurigon, USA
- Oberto Germano, Farmaindustria, ES
- Olejniczak Klaus, EMEA, PT
- Ottesen Jan Lund, Novo Nordisk, NO
- Pallardy Marc, INSERM, FR
- Palminger-Hallen Ira, Swedish Product Agency, SE
- Palos Laszlo, Hucopa, HU
- Paparella Martin, Umweltbudesamt, DE
- Pasanen Markku, University Kuopio, FI
- Patzelt Alexa, Charité - Universitätsmedizin Berlin, DE
- Pelkonen Kai, Ministry of Agriculture and Forestry, FI
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