

START-UP

Scientific and Technological Issues in
Alternatives Research in
Drug Development and Union Politics

Project Partners

ecopa

Vera Rogiers
Lab.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

Paul De Knop
Building M – fifth floor
Room M523
Pleinlaan 2
B - 1050 Elsene
Tel. +32-2-629.21.40
Fax. +32-2-629.36.50
e-mail: rector@vub.ac.be

Contact details

There is no website for the START-UP project, but additional information can be found on the *ecopa* website: <http://www.ecopa.eu>

Stijn Budts
Secretary of *ecopa*
Lab.Toxicology
Laarbeeklaan 103
B - 1090 Brussels
Tel. +32-2-477.45.85
Fax.+32-2-477.45.82
e-mail: ecopa@vub.ac.be

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 workshops 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 and D.

Started at a kick off meeting in Leverkusen/Germany at Bayer AG, the expert meetings in Madrid (Ministeria de Sanidad), Basle (Novartis Research Center) and Alicante (Pueblo Acantilado, at the biannual eSI meeting) were then followed by Workshops on Refinement (Istituto di Sanita, Rome, I), on Reduction (University of Innsbruck, A) and on Replacement (Budapest, H). 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.

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, metabolomics, 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 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 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 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 of establishments. 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 of 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 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

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.

1. 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.
2. 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.
3. 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 biopharmaceuticals. The use of non-human primates (in a number of indicated cases), humanised models and transgenic animals seems relevant.
4. 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

5. 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.
6. 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,...
7. 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.
8. 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

Workshop proposals

Proposals of the *ecopa* **START-UP** project



