SEVENTH FRAMEWORK PROGRAMME
THEME 1 – HEALTH

SCIENTIFIC AND TECHNOLOGICAL ISSUES IN 3RS ALTERNATIVES RESEARCH IN THE PROCESS OF DRUG DEVELOPMENT AND UNION POLITICS

START-UP

support action n° 201187

~300‘000 €

ecopa

Vrije Universiteit Brussel

Executive Board and organizer of Expert Meetings:

V. Rogiers (Coordinator)
B. Garthoff (Alicante, E)
J. Castell (Madrid, CH)
P. Maier (Basle, CH)

Organizer of Workshops:

National Consensus Platforms:

Refinement:

IPAMA	A. Stammati
FINCOPA	H. Thati
POLCOPA	M.Stepnick

Reduction

ZET	W. Pfaller
ZonMw	J. De Boer

Replacement:

SET	G. Sponer
HUCOPA	L. Balogh

2008 - 2009

3Rs in the process of drug R + D?

Includes research in academia and industry

Disease pathways and drug interactions are investigated in „Life Sciences“.

Includes drug development

Affects competitiveness of industry in Europe, authorities, reputation of drug compagnies (no 3R related information available up to that time).

High numbers of animals are affected (~4-7 x 10^6 / year)

~30-60% drug R+D; public concern: dogs, pigs, NHP;
only ~10% of the animals for chemical regulatory toxicity testing.

Improvements can be implemented immediately

A great number of 3R method exists allready, no restriction for their use, no validation necessesary, input of the researchers is of importance.

Facts of high concern

M.D. Lindner, Pharmacology and Therapeutics 115 (2007) 148-175
R. Mc Arthur , F. Borsini, Pharmacology, Biochemistry and Behaviour 84 (2006) 436-452
and many others

- Continuing decline in clinical succes rates!
- Lack of efficacy is the biggest reason for failure in clinic!
- Bias on preclinical assessment of potential efficacy?
- Lack of predictive validity of animal models?
- Replication studies, to what extent?

Potential of 3R-methods for improvements in the drug development process

- the role and value of animal disease models

  (including biological drugs, nanobiotechnology)

  → REFINEMENT, REDUCTION

- Identifying 3R-alternative methods which can be implemented during drug R + D
  - basic research
  - mechanistic studies
  - pharmaco-toxicological studies

  → REPLACEMENT, REDUCTION

Concept and Objectives

Identifying (expert meetings)

existing gaps, scientific and technological bottlenecks, ethical concerns and issues related to union politics.

Prioritisation (workshops)

new alternative strategies and tiered approaches in the different stages of the overall drug development process.

Developing (recommendations)

a consensus report between all parties involved

Proposing (229 pages report)

a Road Map for the Commission

Programme: Facts and Figures

Definition of bottlenecks in 3Rs in pharmaceutical discovery and development (2 Expert Meetings)

Madrid (Ministeria de Sanidad, E)

Basle (Novartis Research Center, CH)

3 Workshops on each of the 3 Rs (in collaboration with NCP)

Bottlenecks in REFINEMENT (Istituto di Sanita, Rome, I)

Bottlenecks in REDUCTION (University of Innsbruck, A)

Bottlenecks in REPLACEMENT (Budapest, H)

New Methods and Techniques

(Expert Meeting with young scientists, Alicante, E)

223 participants

109 industrial experts from 42 compagnies

65 academia

29 Regulatory authorities

10 Animal welfare

ANIMAL DISEASE MODELS: The principles

Why used:

- complex, multistep disease
- no representative, single step defined
- several therapeutic concepts possible at different progression stages of a disease

Disadvantages known:

- Relevance for men can often not be proven
  (indirect proof: positive controls)
- Redundancy, compensation within the organism
- time consuming, expensive, unclear safety profile

In principle two type of models:

1) The disease is induced in healthy animals
(e.g. arthritis, asthma, stroke etc.)

2) The disease will be expressed in transgenic or ko animals (rodents)
by genes which are involved in the disease in man (e.g. Alzheimer, Diabetes, Obeisity etc.)

ANIMAL DISEASE MODELS: Facts

- Disease animal models are not standardized

  (dynamic, stages quite complex, often not known, positive controls: drugs in clinical use, but often not available)

- Protocols are optimized to the specific needs and symptoms of the disease
- Often for internal use only
- Mainly symptomatically but when possible mechanistically based

Expert Meeting 2: Focused on animal models representing:

Psychiatric Diseases
Degenerative Brain Diseases
Inflammatory Diseases
Oncology
Infectious Diseases
Respiratory Diseases
Metabolic Diseases

ANIMAL DISEASE MODELS: Questions to the experts

- Serious doubts on the use of animal models as a whole?
- Animal models are not representative for the way a disease progresses in human?
- High attrition due to species differences?
- Changes in research strategy are going on?
- Changes in the use of animal disease models foreseen?

Together with further development and implementation of the 3Rs?

- in the preclinical phase of drug development
- in specific disease areas and animal models
- with respect to the type of drug candidates

ANIMAL DISEASE MODELS: Recommendations

1. Development of human pathways/mechanism based animal disease models (translational animal models, less symptomatic models).

2. Optimisation (quality standards) and harmonisation of study protocols (based on clinical applications) for individual disease models.

3. Maximising the number of non invasive and early or surrogate endpoints (read-outs) within a model (lower burden, more relevant for human diseases, less analgesics, no pain related pathophysiological disturbance of read outs).

4. Development and use of more complex *in vitro systems* (human cells, functional organ specific tissues, co-cultures, slices, ex vivo) in which predictive clinical effects can be investigated e.g. human stem cells derived.

ANIMAL DISEASE MODELS: Recommendations

5. Exchange of non-publishable protocols and data

   (type of compound) derived from animal disease models among pharmaceutical industry and publication of negative data.

6. Reduction or replacement of animal efficacy studies and long-term carcinogenicity studies

   (carried out at later stages of drug development) by intelligent combination of information derived from studies performed during the drug research phase.

7. Development and use of human population pharmaco-kinetic models

   instead of nonexisting (or not reliable) animal disease models.

REFINEMENT: Recommendations

1. Refinement methods for the most painful experiments
   e.g. for cancer research, inflammation experiments.
2. Use of non-invasive imaging methods
   repetitive measurements possible and recognition of disease-related parameters at an early stage (non-painful stage = humane endpoints).
3. Promote welfare of experimental animals
   rather than just focus on the minimisation of suffering.
4. Positive training techniques should be enforced

REFINEMENT: Recommendations

5. Appropriate objective measures of welfare states has to be used and validated

   before during and after the experimental procedures (including breaders, CROs etc).

6. Dissemination and promotion of refinement techniques in EU countries.

7. Implementation of the most advanced practices

   experimental techniques and animal housing, in all the research sites of the pharmaceutical industry in different countries, as well as CROs and academic research partners.

8. Implementation of 3Rs in the spirit of the new European directive

   also in research sites outside the European Union. awareness of the importance of animal welfare should be emphasised.

REDUCTION: Recommendations

1. Priority for test development/optimisation to those *in vitro methods* that can be applied in the later stages of drug development to eliminate toxic substances

2. Application of non-invasive diagnostic methodology, alone or in combination
   should become common practice, in particular in those cases where invasive animal disease models are still in use (asthma, colitis, Parkinson etc).

3. Data sharing between research institutes/companies/academia
   should be substantiated by the creation of a pan-European neutral body, guaranteeing confidentiality.

→ see IMI, „honest broker“

REDUCTION: Recommendations

4. Vaccines production and quality approach

monitoring of all critical stages (consistency approach) should become the rule rather than traditional animal testing of batches.

→ epaa initiative 2011

5. Development of biologics *in vivo* safety testing

should only be performed when human relevant species have been identified. Human-based *in vitro screening* (pharmacology and safety) should be applied wherever feasible and appropriate.

6. Transgenic animals

should be produced only for relevant purposes and in a limited number of well-controlled specialised facilities of high-quality standard.

REPLACEMENT: The world without animals

Trypanosoma brucei *Drosophila melanogaster*

Driving forces:

- low reproducibility of in vivo experiments
  (scientific validity, the limitations of the „animal model“ are often overlooked, or even unknown, publications?
- relevance for human?
  (animals as models for human diseases, species specific differences in metabolism, structures and functions)
- concern about animal welfare (education, information)
- moral justification and ethical issues (political issue)

REPLACEMENT: Recommendations

1. Efficacy of potential drug candidates only when a relevant model exists.
   (authorities should accept such justification)

2. New safety testing strategies
   (based on knowledge gained, new technological developments and existing and emerging alternatives; science should be the driving force)

3. Better integration of safety pharmacology, pharmacokinetic and toxicity studies.

4. Development of a battery of sensitive and specific safety biomarkers with clinical relevance.
   (should be included in new safety testing strategies)

REPLACEMENT: Recommendations

5. Improvements in safety testing

   application of more specific screenings of well identified toxicity pathways.

6. Use of more human-based cells / tissues

   better integration at all stages of *in vitro, in silico, ex vivo* with *in vivo* results.

7. Data sharing; availability of negative results

   suitability of a disease model protocol, but: comparable data quality and standardisation

REPLACEMENT: Recommendations

8. **Consideration of micro dose clinical trials.**
   under well-controlled conditions before finalising safety studies in animals, at least for early PK studies.

9. **Easier use of alternatives for defining the potency of vaccines and sera.**
   from a regulatory point of view; see also → epaa Consistency Approach, EPAA 2011.

10. **Global harmonisation of requirements by regulatory bodies.**
    In particular, adequate testing of biopharmaceuticals. Europe could take the lead in these discussions.

3. Meeting: Young Scientists

New Methods and Techniques

- New approaches:
  - Pharmaceuticals (Hepa RG)
  - Dermato-Cosmetics (mi RNA and gene silencing)
  - Nanoparticles (Toxicity testing)
  - Biotech products (Toxicity testing)
- Immunotoxicology
  (pharmaceuticals and dermato-cosmetics)
- 3R Alternatives in Research and Developments
  (imaging biomarkers, laser capture microdissection, COMICS, high content imaging)

New Methods and Techniques: Recommendations

1. **Cell systems:**
   work further on HepaRG cells, most likely with appropriate stabilisers (epigenetic modifiers such as histone deacetylase inhibitors). Define the applicability domain.

2. **In vitro Disease Models:**
   new *in vitro* models for cancer/skin diseases research e.g. skin cancer, psoriasis as well as flow chamber systems (blood-based) should be further encouraged.

3. **Methods:**

   imaging techniques *in vitro / in vivo,* should be further improved and implemented in as well *in vivo* as in *in vitro* studies.

   e.g. SPECT (Single Positron, Emission Computed Tomography) or Micro PET (Positron Emission Tomography) scanning, high-content cell based imaging; alone or preferentially several techniques combined

New Methods and Techniques: Recommendations

4. Formulation / Biopharma:

new approaches to drug delivery such as the use of nanoparticles (including their toxicity testing orally, in skin and lung) have to be followed. Nanoformulated drugs such as target respectively organ directed have to be anticipated.

5. Toxicology:

already existing immunotox-/sensitising models and techniques (LTT, LLNA, resp. LCSA) should further be delineated with special emphasis on endpoints such as MAP (Mitogen Activated Protein) -kinases, (discriminatory potential for sensitising and irritative compounds).

6. Regulatory:

Communication on new models across sectors, involving the responsible regulatory agencies and competent authorities in the EU, should further be enhanced.

Full agreement! ….and implementation?

1. Agreements over all sectors and all 3Rs !
   - bottlenecks well known and identified
   - recommendation concrete and related to the daily work
   - accepted in 2008-2009 !
2. Several issues are already taken up!
   - in EU projects
   - by the EPAA initiative
   - by IMI
   - National projects
3. 3Rs and the Drug Research and Development process
   - START_UP delivered numerous very specific recommendations
   - Recommendation were proposed and discussed by experts working in an industrial environment (drug researchers).
   - It was a consensus report !
   - Paved the way for 3Rs in drug R+D

Proposed Roadmap