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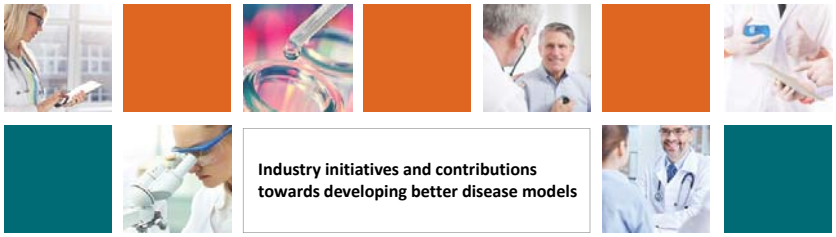
INFRAFRONTIER/IMPC Stakeholder meeting – advancing personalised medicine with animal models

Author: Kirsty Reid * **Date:** 16/11/2017 * **Version:** 1



Industry initiatives and contributions towards developing better disease models

Directive 2010/63 applies at every step from research planning to follow up

Scientific justification Application of 3Rs Choice of species Severity Reuse	Application Ethical review/ benefits and risks Authorisation by competent authorities Non technical summary	Sourcing of animals Authorized establishment Trained personnel Identification Inspections	Animal Welfare Bodies Named veterinarian Housing and Care Anesthesia Reuse	Reporting numbers and severity Euthanasia Retrospective review Sharing tissues Setting free/rehoming

DIRECTIVE 2010/63 – DIRECTIVE 2010/63

Objectives of the Directive

- Harmonise legislation to ensure a "level playing field" for all those impacted (MS, user community) and for the competitiveness of EU research and industry;
- To ensure appropriate standards of welfare in line with Article 13 of TFEU through effective application of the Three Rs in the use, care and breeding of animals; and
- To improve the transparency to the general public.

Review report published 8 November – Too early to measure impact on objectives. No amendments proposed.

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EFPIA and animal welfare

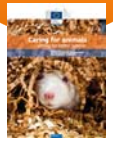
- Directive 2010/63/EU, visible and proactive engagement on 3Rs and welfare

EU institutions and agency interaction

EU initiatives

Alliances and collaborations

Directive 2010/63/EU



EURL ECVAM European Union Reference Laboratory for Alternatives to Animal Testing

ESTAF

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The European Partnership for Alternative Approaches to Animal Testing

ELSA

Engage with stakeholders – open dialogue including with animal protection organisations

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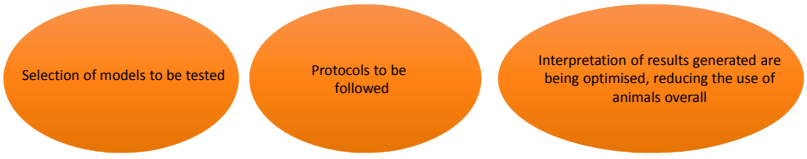
Project: Culture of Care

- **User Survey in 2016** - EFPIA members reflected on the concept of a Culture of Care and how it is understood and applied across research institutions and companies in Europe. This reflection process was facilitated by a survey containing a series of questions.
- Via the EFPIA website, this **list of questions** is shared (in English, French and German) with the wider research community as a "checklist" to help engage in or enhance discussions on a Culture of Care within your establishments.
- **Users workshop** in February 2017 – the relationship between culture of care and Dir 2010/63/EU. (reported on at NCP13).

Link with IMI and animal welfare

- **IMI helps to drive animal welfare and 3Rs – Presently numerous IMI consortia impact on the use of animals and IMI projects contribute to the 3Rs.**
- **IMI successes have addressed and brought results in 3Rs or new research paradigms or more predictive testing tools that do not require – or require fewer – animals**
- **IMI projects are contributing to a better understanding of the challenges faced in using animal models and are impacting on the use of laboratory animals in research and development.**



innovative medicines initiative

The Innovative Medicines Initiative: the largest public-private partnership for health research worldwide

€5 billion – 2008 to 2024

Part of the Framework Programme and EU Horizon 2020 R&D funding

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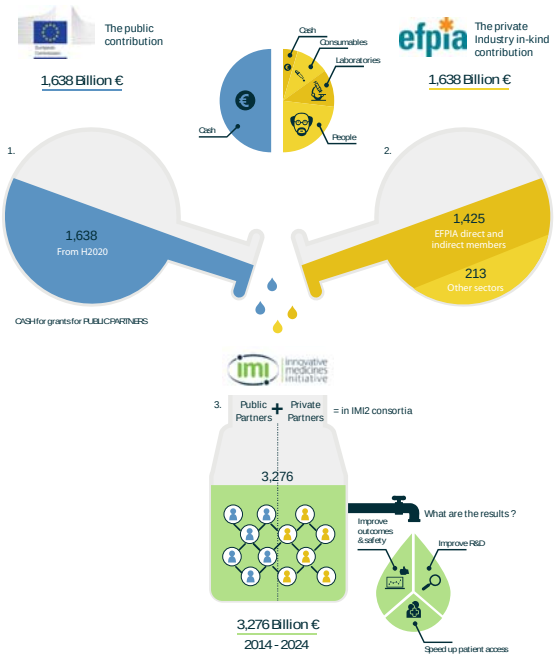
IMI2



Source: http://www.efpia.eu/topics/innovation/innovative-medicines-initiative-imi

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Industry does not receive EU funding: we co-invest with the Commission 50/50

Industry* defines the projects,

invests in kind

does not select public partners

Commission gives grants to public partners*

to work with industry on equal footing

* Big and small companies from EFPIA, EBE, Vaccines Europe, Partners in Research

* Any organisation which is not a company with turnover above €500 mln

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Why IMI?

Prioritisation

Combinining healthcare, science and industry agendas

Collaboration

across stakeholders groups, including decision-makers

From First to Last Mile

from discovery to uptake and business models

Flexibility

different sectors, different assets, different busines models

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Impact on pharma value chain

DISCOVERY New lines of enquiry in drug development (thanks to large data sets) Identification of new hits and leads (screening center with proprietary compounds) First human Beta cell line for diabetes research	**LATE DEVELOPMENT** Definition of regulatory endpoints, e.g.; for autism, sarcopenia, asthma, pain Development of antibiotics and Ebola vaccines and diagnostics Clinical trial networks and fast-fail cohorts (pediatrics, antimicrobial resistance, autism)
EARLY DEVELOPMENT Regulatory qualified safety biomarkers In silico predictive models Novel epigenetic mechanisms and early biomarkers for non-genotoxic carcinogenesis Normalised and structured data of about 8,000 legacy GLP toxicology reports from 13 Pharma companies, and about 100 predictive algorithms	**PATIENT ACCESS & USE** Continued dialogue on merits of outcomes based and adaptive models Integration of patient voice in benefit risk evaluations Definition of evidentiary standards for pragmatic trials Methodological standards in pharmacovigilance

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A few examples: how does IMI address…

Unmet medical need	Efficiency in value chain	New business models
Solutions for diseases with high burden and cost for patients and society	Tracking and addressing science gaps and inefficiencies from discovery to disease management	Challenging current models & focus on value for patients and sustainable healthcare
Diabetes Surrogate markers for CVD complications Beta Cell function Patient stratification NASH, Diabetic Kidney Disease Hypoglycemia	Safety and Efficacy Biobanks, databanks, qualified biomarkers In silico prediction of toxicities Vaccines benefit/risk Mechanism-Based Integrated Systems for DILI	Market access AMR – balancing rational use and profitability Definition of outcomes Access to and generation of outcomes data
Alzheimer Taxonomy Biomarkers Adaptive Trials Prevention Real world evidence	Pediatrics Preclinical platform for pediatric oncology Pediatric clinical trials network	Real world evidence Digital and IT tools to generate quality data (including social media) Registries in adaptive models and outcomes based healthcare systems
Infections Antibiotics: Discovery; Hit to lead Clinical development; Investigators networks; New business models Ebola: vaccines, manufacturing, deployment, diagnostics	New trials design Modeling and simulation Adaptive trials in AD and AMR Pragmatic trials	Patient centricity Meaningful patient involvement in R&D Patient preference elicitation in benefit/risk Patient reported outcomes Impact of adaptive models

Benefits from Projects

- Proactive dissemination of relevant IMI project results and available tools

WHY?

Stricter research and testing environment

Questions, tools and regulations are evolving, driven by scientific progress, public concerns and collaboration.

- **New and changing legislative requirements**
  - E.g. Directive 2010/63/EU on the protection of animals used for scientific purposes
    - challenges scientists to change their perspectives and way of thinking, to drive for change
  - Regulations, OECD and European pharmacopeia incorporating 3R approaches
- **New, evolving technologies and techniques**
  - Human relevance
  - Computer, simulating techniques
  - More predictive models
  - Organ on a chip technologies

Shift in way of working

- **Reason for the need to adapt**
  - Important that Europe remains a world leader in medical research and biological innovation in order to address the unmet medical needs of its citizens and to preserve its capacity to shape its health strategies.
  - There is a general change in way of working, paradigm shift – Different ways of addressing scientific challenges

Examples of IMI outputs that support new research paradigms

- Identification and validation of new drug targets and novel hit and lead discovery
- Establishment of robust, validated tools for preclinical drug development
- Development of biomarkers and tools predictive of clinical outcomes (efficacy and safety)
- Clinical trials - improved design and process
- 'Big data' solutions to leverage knowledge
- Implementation of data standards

IMI projects deliver 3Rs – examples

Eliminating poorly predictive models	Developing new improved models	Replacing animals with better *in vitro* & *in silico models*	Alternative tools
• Parkinson's Disease • Diabetes • Asthma • Chronic Pain • Schizophrenia • Depression • Autism	• Parkinson's Disease • Diabetes • Asthma • Chronic Pain • Schizophrenia • Depression • Autism	• Diabetes • Cancer • Schizophrenia • Chronic pain • Drug safety • Parkinson's Disease	• Biomarkers • Novel cell lines • 2D and 3D cell cultures • Imaging • Computation • Simulation • Pooling & novel analysis of existing data

IMI projects with foreseen 3Rs impact

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Beyond Compliance (Practice | Science | Training) · Leading by Example (Sharing | Enforcing) · Open Communications (Dialogue | Reporting)

Beyond Compliance

Innovative Medicines Initiative - world's largest public-private partnership in the life sciences driving animal welfare and 3Rs

The Innovative Medicines Initiative (IMI) is a public-private partnership between the European Union and EFPIA. IMI is pursuing the goal of developing the next generation of vaccines, medicines and treatments by improving research practice; getting new healthcare solutions to patients faster; and improving health outcomes thanks to new tools, methodologies, research infrastructure and big data.

Established in 2009, and further expanded in 2014, the IMI consortia (involving industry, academia, SMEs, patients, regulators, etc.) have a direct or indirect impact on the use of animals and IMI projects are contributing enormously to the 3Rs.
IMI successes have brought results in 3Rs or new research paradigms (different ways of addressing scientific challenges) or more predictive testing tools that do not require – or require fewer – animals by removing from pipelines harmful molecules before animal studies are conducted. IMI funded projects are contributing to a better understanding of the challenges faced in using animal models and what impact their results are having on the use of laboratory animals in research and development. Through the unique approach and collaborative platform of IMI, the 3Rs are addressed on multiple different levels such that the selection of models to be tested, protocols to be followed and the interpretation of results generated are being optimised, reducing the use of animals overall. Examples of such projects from the 100 project IMI portfolio include:

◊ ABIRISK - Anti-Biopharmaceutical Immunisation - Prediction and Analysis of Clinical Relevance to Minimise the Risk: develops tools for determining patient response directly, i.e. without the use of animals
◊ COMPACT - Collaboration on the optimisation of macromolecular pharmaceutical access to cellular targets: sets up sophisticated in vitro models of biological barriers and appropriate animal models to identify and exploit novel cell pathways for effective delivery of biopharmaceuticals
◊ DDMoRe - Drug Disease Model Resources: A drug and disease model library will be developed, as well as modelling and simulation solutions for better prediction and the reduction of animals used
◊ EBiSC - European Bank for induced pluripotent Stem Cells: iPS cells help to reduce the use of animals in research.
◊ EMTRAIN - European Medicines Research Training Network: pan-European platform for education and training. In this framework SafeSciMET - European Modular Education and Training Programme in Safety Sciences for Medicines: implements training for a new generation of safety specialists
◊ eTOX - Integrating bioinformatics and chemoinformatics for the development of expert systems allowing the in silico prediction of toxicities: combination of this knowledge will enable them to create more reliable computer models
◊ EU-AIMS - European Autism Interventions - a Multicentre Study for Developing New Medications: construct for the first time cellular models of ASD with construct validity
◊ EUROPAIN - Understanding chronic pain and improving its treatment: elucidate the mechanisms of pain, using novel experimental models, human volunteers and clinical data of pain
◊ IMIDIA - Improving beta-cell function and identification of diagnostic biomarkers For treatment monitoring in diabetes: pancreatic β-cell line for drug efficacy testing in diabetes R&D as well as for a preclinical model for cell replacement therapy
◊ IPiE - Intelligent Assessment of Pharmaceuticals in the Environment: based on existing data help identify which 'legacy' APIs are most likely to pose a risk to the environment and so should be prioritised for testing – reduction of overall number of animals used
◊ MIP-DILI - Mechanism-Based Integrated Systems for the Prediction of Drug-Induced Liver Injury: develop new tests that will help researchers detect potential liver toxicity, including combinations of non animal models
◊ NEWMEDS - Novel methods leading to new medications in depression and schizophrenia: develop improved experimental models that mimic schizophrenia or depression in humans
◊ Pharma-Cog - Prediction of cognitive properties of new drug candidates for

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PUTTING ANIMAL WELFARE PRINCIPLES AND 3Rs INTO ACTION - European Pharmaceutical Industry Report - 2016 Update

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Beyond Compliance (Practice | Science | Training) · Leading by Example (Sharing | Enforcing) · Open Communications (Dialogue | Reporting)

Beyond Compliance

neurodegenerative diseases in early clinical development: development of experimental human models for the study of drugs ameliorating cognitive impairment
◊ Predect - New models for preclinical evaluation of drug efficacy in common solid tumours: focus on complex but transferable next generation in vitro and in vivo models
◊ PreDICT-TB - Model-based preclinical development of anti-tuberculosis drug combinations: in silico modelling for the prediction of efficacy of novel drug regimens for tuberculosis
◊ SAFE-T - Safer and Faster Evidence-based Translation: focus on measuring sets of safety biomarkers across a variety of patient populations
◊ STEMBANCC - Stem cells for biological assays of novel drugs and predictive toxicology: supply of cells that mimic more accurately what happens in the human body
◊ U-BIOPRED - Unbiased biomarkers for the prediction of respiratory disease outcomes: will be linked to results of preclinical models, in order to facilitate future drug development
VAC2VAC – Vaccine batch to vaccine batch comparison by consistency testing: aims to develop and validate quality testing approaches for both human and veterinary vaccines using non-animal methods

In 2015, IMI launched several new calls for proposals with new topics with 3Rs impact, such as translational imaging methods in safety assessment or quantitative systems technology. In 2016 additional topics with direct 3Rs impact were launched such as on data quality and reproducibility in Central Nervous System research or on preclinical data sharing.

Approaches to Animal Testing – from bench to industrial application

EFPIA and a number of its members are founding members of the EPAA (European Partnership for Alternative Approaches to Animal Testing) – a cross-sectoral and multidisciplinary partnership between five European Commission services and seven industry sectors. The mission of the EPAA is to promote 3Rs in regulatory testing, and facilitate the development and implementation/regulatory acceptance of alternative testing strategies.

After a first decade, during which the EPAA started to deliver tangible results (see 2015 activity report), the Commission and the industry decided to prolong the partnership for the new five-year term.

◊ In 2015 and 2016, the pharmaceutical sector led the industry delegation at the Steering Group.
◊ EFPIA and its members play important roles on the EPAA Project Platform focusing their work on skin sensitisation, vaccines and other biologicals as examples.
◊ A successful project identified differences in legal requirements for vaccines testing between different regions (Europe, US, China, Japan, Brazil, etc) and brought together regulators from these regions to align views on usefulness of alternatives to four safety tests and kick off actions to remove obsolete tests from national and international guidance. Two in vivo safety tests were recognised as obsolete by 12 regulators from 4 regions who committed (and started the relevant processes) to kick off deletion in European Pharmacopoeia, WHO and OIE guidelines, and national legislation as appropriate.

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IMI accelerating the medicines development process

- 34 *in vitro* models and tools
- 70 animal models
- 316 *in silico* models
- 12 novel imaging techniques
- 95 novel robust assays
- 1500 stem cell lines

IMI call 9

- **Topic 3: Data quality in preclinical research and development**
  - Direct impact as it calls for the need of good animal models for development and safety studies.
  - Also talks of 3Rs in preclinical research
- **Topic 4: Next generation of electronic translational safety – NexGETs**
  - Direct impact as it calls to advance the assessment of the relevance of animal findings for humans
  - It also states that the abundant use of data will impact on 3Rs
- **Topic 5: Identification and validation of biomarkers for non-alcoholic steatohepatitis (NASH) and across the spectrum on non-alcoholic fatty liver disease (NAFLD)**
  - Calls on the development of novel animal models that have good concordance with the human pathobiology of NASH and NAFLD.
  - This may have an indirect impact. The call for Novel animal models needs to be closely followed to ensure this also includes good models, leading to better animal welfare.

IMI Call 10

- **Topic 1: Understanding hypoglycaemia: The underlying mechanisms and addressing clinical determinants as well as consequences for people with diabetes by combining databases from clinical trials.**
  - Direct impact as it calls for suitable animal studies are to be explored for causes of hypoglycaemia and consequences of hypoglycaemia to be documented in animal models. Mentions *in vitro* to be explored.
- **Topic 3: Improving the care of patients suffering from acute or chronic pain**
  - Direct impact as it notes that some current animal models lack validity (for retrograde menstruation)
  - States that animal models for BPS (bladder pain syndrome) differ from the clinical situation
  - For PK, in vitro assays are also to be used
- **Topic 5: Biomanufacturing 2020. Development of innovative high throughput analytical tools and methods to characterize cell culture fluid during development and commercial cell culture processes.**
  - Focus is on animal cell culture production
- **Topic 6: Unlocking the solute carrier gene-family for effective new therapies (unlock SLCs)**
  - Requires experts in cell culture, in vitro high throughput screening
  - Includes the development of HTS cell-based and cell free cultures
- **Topic 8: Personalised medicine approaches in autism spectrum disorders**
  - *In vitro* (pluripotent patient stem cells) and generic animal models need aligning

Call 12

- **Topic 2: FAIRification of IMI and EFPIA data**
  - database/ data sharing especially toxicity data may indirectly lead to reduction in animal use
- **Topic 6: Discovery and characterisation of blood-brain barrier targets and transport mechanisms for brain delivery of therapeutics to treat neurodegenerative & metabolic diseases**
  - An overall objective is to establish and characterise models relevant for healthy and disease conditions for evaluation of disease-modifying agents (human *in vitro* cell based, and *in vivo*). Could lead to reduction and refinement.
  - Concern over robustness of some *in vitro* models
- **Topic 7: European Screening Centre: unique library for attractive biology (ESCulab)**
  - Possible relation in the fact that it relies on high throughput screening and cell biology however there may be no prior link or need for animals.

CRISPR

- CRISPR has many likely applications for medicine – with potential for preventing or treating diseases or going as far as editing the genes of human embryos.
- Researchers are embracing CRISPR to create animal models of the diseases – cancer, neurodegeneration.
- Recent applications and developments in oncology, translational safety, AMR, clinical trials, neurogenerative diseases, immunology, genetic disorders etc
- Leads to the production of more animals, in more complex ways, using a wider range of animal species, however with ultimately leading to much needed medical breakthroughs.

Limitations of CRISPR/Cas9-mediated animal modeling

- Mosaicism and off-target effects

CRISPR

Ethical and animal welfare issues

- Animal welfare concerns: using animals increases the perception of animals as 'research tools' or 'commodities', rather than sentient beings. In addition, the technique has huge potential to cause pain, suffering, distress and lasting harm to animals.
- Ethical concerns include: Regulation of patenting; Possibility of non-therapeutic interventions like enhancement (athletes) using genome editing; Formation of animal chimeras for organ transplantation raises ethical questions…

Take up of the Three Rs

- It is important to implement the precautionary principle and fully take up the Three Rs approach.
- Welfare assessment of animals is essential to ensure any signs of pain and distress are detected as soon as possible, so that relevant refinement alternatives or humane endpoints can be implemented.
- CRISPR has benefits for animal welfare whereby it ensures better use of the animals involved, also it covers cell culture so *in vitro* techniques can be considered and improved.