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

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

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

**EFPIA and animal welfare**

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

<table>
<thead>
<tr>
<th>EU institutions and agency interaction</th>
<th>EU initiatives</th>
<th>Alliances and collaborations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Directive 2010/63/EU</strong></td>
<td><strong>EFPIA</strong></td>
<td><strong>ELSA</strong></td>
</tr>
<tr>
<td><strong>EFU</strong></td>
<td></td>
<td>Engage with stakeholders – open dialogue including with animal protection organisations</td>
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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).

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**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.**

- Selection of models to be tested
- Protocols to be followed
- Interpretation of results generated are being optimised, reducing the use of animals overall
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

IMI2

1. 1,638 Billion €
2. 1,638 Innovation
3. 3,276 Billion €

What are the results?

The public contribution
The private Industry in-kind contribution

Public Partners in IMI consortia
Private Partners in IMI consortia

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

Why IMI?

Prioritisation
Combining 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 business models
## Impact on pharma value chain

<table>
<thead>
<tr>
<th>DISCOVERY</th>
<th>LATE DEVELOPMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>New lines of enquiry in drug development (thanks to large data sets)</td>
<td>Definition of regulatory endpoints, e.g.; for autism, sarcopenia, asthma, pain</td>
</tr>
<tr>
<td>Identification of new hits and leads (screening center with proprietary compounds)</td>
<td>Development of antibiotics and Ebola vaccines and diagnostics</td>
</tr>
<tr>
<td>First human Beta cell line for diabetes research</td>
<td>Clinical trial networks and fast-fail cohorts (pediatrics, antimicrobial resistance, autism)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EARLY DEVELOPMENT</th>
<th>PATIENT ACCESS &amp; USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory qualified safety biomarkers</td>
<td>Continued dialogue on merits of outcomes based and adaptive models</td>
</tr>
<tr>
<td>In silico predictive models and early biomarkers for non-genotoxic carcinogenesis</td>
<td>Definition of evidentiary standards for pragmatic trials</td>
</tr>
<tr>
<td>Normalised and structured data of about 8,000 legacy GLP toxicology reports from 13 Pharma companies, and about 100 predictive algorithms</td>
<td>Methodological standards in pharmacovigilance</td>
</tr>
</tbody>
</table>

## A few examples: how does IMI address…

### Unmet medical need
- Solutions for diseases with high burden and cost for patients and society

### Efficiency in value chain
- Tracking and addressing science gaps and inefficiencies from discovery to disease management

### New business models
- Challenging current models & focus on value for patients and sustainable healthcare

### Market access
- AMR – balancing rational use and profitability
- Definition of outcomes
- Access to and generation of outcomes data

### Real world evidence
- Digital and IT tools to generate quality data (including social media)
- Registries in adaptive models and outcomes based healthcare systems

### Unmet medical need

<table>
<thead>
<tr>
<th>Disease</th>
<th>Effort</th>
<th>New business models</th>
</tr>
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<tbody>
<tr>
<td>Diabetes</td>
<td>Surrogate markers for CVD complications Beta Cell function Patient stratification NASH, Diabetic Kidney Disease Hypoglycemia</td>
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<td>Alzheimer</td>
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<td>Infections</td>
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</table>

### Safety and Efficacy
- Safety and Efficacy
- Safety and Efficacy
- Safety and Efficacy

### New trials design
- New trials design
- New trials design
- New trials design

### Patient centricity
- Patient centricity
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- Patient centricity
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

<table>
<thead>
<tr>
<th>Eliminating poorly predictive models</th>
<th>Developing new improved models</th>
<th>Replacing animals with better in vitro &amp; in silico models</th>
<th>Alternative tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s Disease</td>
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<td>Diabetes</td>
<td>Biomarkers</td>
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<tr>
<td>Diabetes</td>
<td>Diabetes</td>
<td>Cancer</td>
<td>Novel cell lines</td>
</tr>
<tr>
<td>Asthma</td>
<td>Asthma</td>
<td>Schizophrenia</td>
<td>2D and 3D cell cultures</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>Chronic Pain</td>
<td>Chronic pain</td>
<td>Imaging</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Schizophrenia</td>
<td>Drug safety</td>
<td>Computation</td>
</tr>
<tr>
<td>Depression</td>
<td>Depression</td>
<td>Parkinson’s Disease</td>
<td>Simulation</td>
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<tr>
<td>Autism</td>
<td>Autism</td>
<td></td>
<td>Pooling &amp; novel analysis of existing data</td>
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IMI projects with foreseen 3Rs impact

Beyond Compliance

Innovative Medicines Initiative - world's largest public-private partnership in the life sciences driving medical innovation and IMI projects

The Innovative Medicines Initiative (IMI) is a public-private partnership between the European Union and EFPIA. Its mission is to improve people’s lives by speeding up the development of new and improved treatments and care through unconventional partnerships between public and private sectors.

Beyond Compliance

A drug and disease models library will be developed, as well as modelling frameworks and simulation tools to support the use of animals in research.

www.efpia.eu

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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 to be explored for causes of hypoglycaemia and consequences of hypoglycaemia to be documented in animal models. Mentions in vitro to be explored.
- **Topic 2:** FAIRification of IMI and EFPIA data
  - database/data sharing especially toxicity data may indirectly lead to reduction in animal use
- **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 4:** Biomaterial manufacturing 2020. Development of innovative high throughput analytical tools and methods to characterise cell culture fluid during development and commercial cell culture processes.
  - Focus is on animal cell culture production
- **Topic 5:** Biomaterial manufacturing 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 6:** Personalised medicine approaches in autism spectrum disorders
  - In vitro (pluripotent patient stem cells) and generic animal models need aligning

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**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 (ESColab)
  - 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, neurodegenerative 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

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.