



Animal experimentation and clinical studies: Ethical recommendations to ensure participants' safety in early drug development

**Report of an EFGCP workshop held at the Renaissance Hotel, Brussels, on
11 June 2008.**

1. THE WORKSHOP AND ITS AIM

This report summarises the discussion and conclusions of a unique workshop, a first for Europe, that took place in Brussels on 11 June 2008. This Europe-wide meeting, organised by the European Forum for Good Clinical Practice (EFGCP) with support from the European Federation of Pharmaceutical Industries and Associations (EFPIA), drew participants from a particularly broad range of interests – researchers, clinicians, patients, policy makers, regulators, ethicists and proponents of animal welfare. They came together to discuss ethical principles and possible recommendations which can apply when a drug candidate is used in first-in-man trials.

The dilemma faced by industry, ethics committees and regulators is that on the one hand they are trying to reduce animal testing for the sake of animal protection (and to reduce testing costs in order to maintain competitiveness), and that on the other hand they are looking to guarantee the highest possible safety for clinical trial subjects. The workshop's aim was clear, but far from easy, since it tackled one of the most complex and often controversial issues associated with ethics and patient safety in early drug development.

Around 35 invited participants listened to presentations on the dilemmas faced by all the stakeholders, and sought to reach conclusions. It is not in the nature of discussions on such topics that the outcome is a list of unanimous recommendations, and this report does not seek to imply that all participants agreed on all points. Given the widely differing standpoints of the various stakeholders, the concept of a "majority view" would be quite inappropriate.

Opening the workshop, Ingrid Klingmann from the EFGCP said, "We want to have a tangible outcome that we can discuss with the public." The conclusions on ethical principles that did emerge should, therefore, be seen as items for further discussion – a structuring of the ethical agenda – rather than as a blueprint for legislators.

The meeting took the form of an opening plenary session with a number of keynote introductions focusing on the dilemmas as seen by the various stakeholders. A discussion of the statements and areas of conflict was followed by agreement on the questions to be considered in breakout groups. The results from these breakout groups were then discussed in a final plenary session, during which some preliminary conclusions and suggestions for further debate (with the provisos above) emerged.

In order to achieve the greatest possible exchange of views, the meeting was conducted under Chatham House rules – that is to say, the contributions of participants are identified only with their consent, and then only in relation to the keynote introductions. In accordance with the spirit of the meeting, this report makes no attempt to attach names to contributions to the general discussions. It was compiled by rapporteur Peter Wrobel, a science writer, in consultation with the meeting’s programme committee.

2. KEY MESSAGES

The workshop addressed a controversial and, for some, emotional subject – the use of animals in the development of medicinal products for human use – in a broad, deliberately heterogeneous forum. Importantly, the workshop proved not only that such discussion can take place, but that it can also be highly productive.

It also revealed how much ethical common ground there is among researchers, patients and animal welfarists, between industry and policy makers; in fact, among all stakeholders. This common ground is centred around the ethical principles of doing no harm to study participants, and of replacing and avoiding animal use wherever possible in the research and development of new medicinal products.

There should be no secrets about animal research. For example, people taking part in clinical trials should be informed about prior tests of their clinical trials medication on animals, why the tests were carried out, and about their limitations in predicting absolute safety.

But much as everyone would like to see the use of animals in biomedical research phased out, it is clear that this is a long-term goal. If animal use in Europe were to be stopped tomorrow without appropriate alternatives in place, it would have a damaging effect on the safety of new medicines for humans, restrict the number of new medicines coming onto the market and could result in a shift in the research and development of medicines away from Europe.

On the other hand, there are initiatives that have been implemented for some years to reduce the number of animals used in research and drug development, for example by avoiding unnecessary animal tests, ensuring that tests are statistically robust and by developing alternatives to animal use. These ideas are encompassed within the ‘3Rs principles’: reduction, refinement and replacement of animal studies.

In the ongoing discussion about this whole issue, ethics has a central role to play. It is, furthermore, a discussion that must not be confined to those undertaking drug development, animal testing or clinical trials: it is a question for society at large.

3. SETTING THE SCENE

The question “When is the right moment to start a clinical study in humans?” has no absolute answer. Physicians, ethics committees and regulatory agencies have to make this decision based on data derived from human pharmacological studies and animal experimentation. But research can only go so far: there is

never a guarantee. What risk is acceptable to study participants? At what point would it be unethical to continue experiments with animals? This discussion required input from a broad range of views and backgrounds. It cannot be done with “silo thinking”, confined to discrete interests and disciplines.

A policy view

The welfare of animals, including those used for the development of medicines, is a subject that the public is keenly interested in, as Neil Parish MEP, co-chairing the first session, explained: “I get more letters and emails from people concerned about animal welfare than anything else I deal with.” As a politician, he would love to be able to say that no animal testing should take place. But it has to be done, he said, “We do want safe medicines.” He added that the more he hears, the more he is torn between the two sides of the argument. As a farmer, he said, he knows how medicines alleviate animal suffering; on the other hand, he does not want to see animals experimented on. So, we have to have a set of rules on how and when to do animal experimentation. What we have to decide is, are the present rules too vigorous, or not vigorous enough? And he had his own take on risk: the patient is the best judge, but can only decide on the basis of the right information.

A pharma industry view

In a broad review of principles that pharmaceutical companies use to assess the safety of new medicines, Tim Hammond from AstraZeneca, United Kingdom, explained how pre-clinical studies are used to identify potential hazards and assess risk before administering new candidate drugs to humans for the first time. Preclinical studies are used to define the nature of potential toxicity and to define the dose response. There are clear legally binding regulatory requirements that define a minimum set of tests to ensure the highest possible safety of drug candidates. It was recognised that preclinical studies – although imperfect – are the best way currently available to identify toxicity and guide selection of the first dose to be given in first time in man studies. “We would still conduct these studies even without regulatory requirements,” he said. First-in-man studies are designed to assess safety and tolerability of new drugs and as such usually dose to the maximum tolerated dose in human volunteers. Consequently, it is essential to understand the full dose response of both the pharmacological and toxicological dose ranges in studies in animals to select a safe starting dose and set clear stopping criteria in the clinical study. As development progresses the clinical knowledge increases and the balance shifts from total reliance on preclinical data to reliance on both preclinical and clinical safety data. Exceptions to this are in assessing reproductive toxicity – the potential to induce adverse effects upon the unborn child – and the risk of the compound inducing tumours. Preclinical studies remain the only available means to assess risk in these areas. In many areas of toxicity assessment alternative methods are increasingly used, but currently there is no alternative to the integrated assessment that comes from evaluation of in vivo studies.

An ethics committee view

For John Hudson from the UK Association of Research Ethics Committees, ethics committees were in the “increasingly uncomfortable position” of reaching subjective decisions on the basis of interpreting increasingly complex objective data. And there’s no shortage of data: the problem is turning a 40-centimetre stack of papers into meaningful information for ethics committees and human volunteers to use in the process of informed consent. “Bare statistics are often quite damagingly uninformative,” he said. He pointed to a number of dilemmas in relation to animal testing. For some conditions there are well established animal models, he said, while acknowledging that cutting edge science now raises some unanswered and even unanticipated questions. At the end, he said, there is always a decision to be taken. “It has to be taken in as objective a fashion as possible, but ethical decisions will always be subjective decisions.”

An animal protection view

Penny Hawkins from the UK Royal Society for the Prevention of Cruelty to Animals (RSPCA) acknowledged that the use of animals in research and testing is “a very broad issue”, because animals are used for a wide range of different purposes. Every project raises its own ethical, scientific and animal welfare issues. The RSPCA’s ultimate goal is to replace or avoid the use of animals in research and testing. In the meantime, recognising that animal experimentation will continue, it wants to see a reduction in animal numbers and suffering, and immediate improvements in animal welfare. Animals are sentient and capable of experiencing pain, suffering and distress, and this matters. Animals do suffer in biomedical research, for example as a result of scientific procedures and their effects. Suffering is also caused by other factors such as the stresses of transport and laboratory housing, and procedures such as euthanasia using carbon dioxide, which is widely used but can cause pain and distress. Literature from industry groups in support of animal use mentions suffering obliquely, she said, but it does not explain what that suffering is. Animal experiments can lead to medical and veterinary advances, she said, but that “does not detract from serious moral concerns”. “We’re not naïve,” she said, explaining that animal use is intrinsic to veterinary medicine, which the RSPCA uses to treat the many animals in its care.

“Ultimately, animals and humans both matter,” said Hawkins, pointing to “a significant conflict of interest between animals and science”. Avoiding and replacing the use of animals wherever possible has to lead to scientific and societal benefits, and a benefit to animals, she said. “The goal should be to alleviate human suffering without causing animals suffering. That goal is a long way off, but we have to have a positive approach to achieving it.”

A patient view

Patients, said Cees Smit from the Dutch Genetic Alliance, are interested in the results of good research: “If that can be done without the use of animals, that’s perfect. If animal experimentation is necessary, it must be humane and careful.” From that perspective, patients are not “in favour of animal research”, just like researchers. But if animal experimentation has to be done, then it must be

properly regulated, he said. Smit pointed to the fact that almost 15% of animal research was for veterinary medicines – a growing market, with companion animals, for example, falling victim to typically human illnesses such as diabetes and obesity. There are also crossover diseases, such as bird flu and BSE.

Smit was clearly exasperated with public hearings on research where it seems as if all that is heard is objections to the use of animals on the basis that it is either “only” for fundamental research, or “only” a rare disease, and so on – even that people with genetic diseases should stop having children. The way forward, he said, included greater involvement of patient groups in ethics committees, as well as an international research agenda that would reduce the number of animals used.

Alternatives to animal testing should be validated and internationally recognised. Finally, said Smit, the “more radical” animal protection groups should invest in good relations with other stakeholders in research – and sometimes recognise the value and necessity of research.

4. THE DISCUSSION

The key conclusions, suggestions for further debate, emerged from four parallel breakout sessions, each considering two key aspects of this broad issue. Each breakout group had a brief to consider the ethical principles involved, and their results were reported back to a plenary session and elaborated in discussion. As said above, there is no suggestion here that all participants were necessarily in agreement on all of the conclusions. Together, though, these conclusions might be seen as a platform for further discussion.

The questions

The following questions were provided to the breakout groups:

1. How to define ‘risk’? What is acceptable for a trial subject? Who decides? How to ensure the adequate information for trials subjects about the relevance of animal tests performed for their safety?
2. Does the current evidence-base for animal testing justify the present regulatory requirements? What impact would less animal testing have on the conduct of clinical research?
3. Under what conditions might it be possible for regulators to approve a first trial for a medicinal product which has not been tested in animals?
4. Would the objectives of a trial, e.g. pharmacodynamics, efficacy, impact the required amount of animal data? How do you ensure that trial subjects are adequately informed about the relevance of animal tests performed for their safety?

The answers

How to define ‘risk’? What is acceptable for a trial subject? Who decides? How do you ensure that trial subjects are adequately informed about the relevance of animal tests performed for their safety?

The answer from the breakout groups was clear: trial subjects must be informed in a meaningful way about all relevant tests performed in animals and about what the results indicate about risks potentially connected to the administration of the new drug. In addition, any limitations of the tests in terms of their predictability of safety need to be pointed out.

Does the current evidence base for animal testing justify the present requirements of regulators and investigators? In other words, is the current regulatory framework for animal research appropriate?

The answers provided to these questions were mixed. Some find the current regulatory framework is appropriate. Others believe that the regulatory requirements for doing tests in animals are not always justified, although that does not necessarily mean that the whole “toolbox” is wrong. Many drug candidates drop out during animal experimentation due to detected safety issues, and the incidence of serious adverse drug reactions in clinical trials is rare; this indicates that, overall, the regulatory framework works. But given the regulatory system for developing a medicinal product and getting a marketing authorisation for it, toxicologists might think it safer to do all the tests rather than only what is necessary.

The current toolbox of experiments was defined by science, not by regulators. So the toolbox should be continuously reviewed in line with progress in biomedical research – and, if appropriate, reduced rather than enlarged. Trial sponsors have to justify when they diverge from the toolbox; and they should stop doing studies in animals that are formally required but known to be useless in this particular situation. It would be, therefore, helpful if the Scientific Advice procedure is more extensively used to enhance early discussion between trial sponsors and regulators about particular animal studies.

Certainly, more harmonisation of requirements both within the EU and between the EU, the United States and Japan would help to reduce the number of animals used in experiments. It was also suggested, controversially for some people, that there should be specialist first-in-man ethics committees that would have the expertise to look at the issues involved. There was agreement, though, on the general principle that ethics committees considering first-in-man trials should have demonstrable access to acknowledged first-in-man experts.

What impact would less animal testing have on the conduct of clinical research?

There were several aspects to this particular question. Some animal testing may be redundant, but it is not currently clear how much. Furthermore, some animal models are of limited validity and it would presumably be acceptable to reduce animal use in cases where no suitable animal models exist.

A reduction in animal testing would put additional moral responsibility on ethics committees. They would also need to have a stronger knowledge of pharmacology. It was recommended that ethics committees should be particularly vigilant in examining protocols from less experienced trial sponsors

in order to help the sponsors to better understand the processes and background (which, of course, is already the case now).

However, the key principle is that less animal testing must not impact negatively on patient safety.

Under what conditions might it be possible for regulators to approve a first trial in humans of, or give marketing authorisation to, a medicinal product that has not been tested in animals?

Generally, requests for a marketing authorisation without animal testing will be very rare. The view expressed at the workshop was that this might be possible if the product were derived from the patient's own cells, or if there were no suitable animal models or – controversially discussed – if the only suitable animal model were the chimpanzee.

Also, clinical trials for new drugs are very rarely performed without prior animal testing. Exceptions relate to biotechnology-derived products where there is no relevant animal model and no transgenic animal can be produced.

Reduced testing may be appropriate in the development of medicines containing plant extracts or small molecules where toxicological experience had been accumulated over years, or in the development of medicines containing a different salt or ester of a previously tested substance.

Reduced safety data is acceptable in first-in-man trials involving patients suffering from end-stage cancer or other life-threatening diseases – but this can raise special issues with the process of informed consent.

The overall principle is that if sufficiently reliable safety data are available from other types of experiments, regulators should approve the conduct of first-in-man trials with drug candidates that have not been tested in animals before.

The workshop also looked at a hypothetical question: If there were a global ban on animal research and testing tomorrow, what techniques could be used to generate data to provide information about each compound before starting first-in-man trials? The answer was that researchers would have to turn the techniques they use now – in vitro tests and computer simulations, including new techniques such as QSAR (Quantitative Structure Activity Relationship – though the workshop heard that it will still take “a long time” to make this technique work). One thing was obvious: such a ban, tomorrow, would raise risk for participants in clinical trials, and would reduce the research and development of new products.

How do the objectives of a trial – for example, pharmacodynamics and efficacy – impact the process of animal testing?

Considerations of pharmacodynamics – the effect drugs have on the body – affect which animal species are chosen for the study, and the duration of the study. For example, in medical diagnostics, animal studies might be only of two weeks' duration; in antibiotics, four weeks; longer for drugs that target tumours. But if the drug is intended for pregnant women, for example, then tests would need to

be prolonged in order to assess possible effects on the next generation. Prolonged testing in animals might be needed with drugs intended for very elderly patients as well, or for rare diseases and, very rarely, treatments that involve administering a number of drugs at the same time (so-called multi-drug therapies).

Does it make a difference whether the initial clinical trials in people are intended to be carried out in healthy volunteers or in people who are already ill with the disease to be treated? Yes, in part, was the answer. To some extent, it is possible to derive data on toxicity from cancer patients and, rarely, to move to doses in people that you would not use in animals. Overall, though, the properties of the molecule being tested will determine whether healthy or sick volunteers are sought.

In any event, if you see clinical toxicity in trials, you need to understand the mechanisms. But if you have good applicable data from humans, the workshop agreed, it is unethical to repeat the experiment in animals just to “tick the boxes” in the list of regulatory requirements. However, researchers warned that it may be necessary to repeat experiments in animals in order to understand the mechanisms and to identify at-risk groups as well as to validate these findings.

The ethical principles are clear: the extent of knowledge about the safety of a drug candidate used for a first-in-man clinical trial may differ between different patient populations. There are especially vulnerable populations, such as pregnant women and children. Testing in these patient populations occurs later in the drug development process, and a greater degree of animal experimentation is necessary to avoid harm to them as much as possible. At the same time, everything possible should be done to avoid unnecessary harm to animals as well.

5. SUGGESTIONS FOR FURTHER DEBATE ON ETHICAL PRINCIPLES

- In clinical research it is required to do no harm to study participants. At the same time, animals should be used in research only when necessary and suitable to minimise the risk to the study participants and when unavoidable for the research and development of new medicinal products. As an absolute global ban on animal experimentation would affect the research and development of new medicines and would increase risk for clinical trial participants, the use of animals is today unavoidable to a certain extent.
- It should be accepted that – depending on the medicinal product and the scientific knowledge – it may sometimes be possible to reduce the number of animals used in testing without compromising the safety of volunteers taking part in clinical trials.

It should also be accepted that animals and their welfare matter, and that replacing animal use is a legitimate and desirable goal.

- After appropriate information and received consent, reduced safety data is already acceptable in first-in-man trials involving patients suffering from end-stage cancer or other life-threatening diseases.
- In the development of medication targeting vulnerable patient groups such as pregnant women or children, a greater degree of animal experimentation might be necessary to avoid harming them. It is likely that previous adult human data will be available before clinical trials in pregnant women or children are considered. At the same time, everything possible should be done to avoid unnecessary harm to animals as well.
- The “toolbox” used in research and development of medicinal products containing animal testing is to be defined by science rather than by regulation. The current regulatory framework for required animal testing needs to be continuously reviewed and updated along with the progress made in biomedical research. Harmonisation of the regulatory requirements in all regions needs to be further promoted with the aim of avoiding duplication of animal tests and avoiding animal use in general.

The Scientific Advice procedure should be more extensively used to enhance early discussion between trial sponsors and regulators about particular animal studies.

- Before entering the clinical trial, participants need to be properly informed about the potential risk, about the animal tests that have been performed, and about the limited predictability of such tests.

Ethics committees considering first-in-man trials should have demonstrable access to acknowledged first-in-man experts.

- Researchers in industry and academia do apply, and should be encouraged to apply further, the 3Rs principles; regulators and ethic committees should be vigilant in this respect.

The views expressed by participants from the European Commission are purely personal and may not in any circumstances be regarded as stating an official position of the European Commission

Glossary

3Rs. The principles of Replacement, Reduction and Refinement (most often referred to as the 3Rs), first proposed in 1959 by William Russell and Rex Burch as the key strategies for humane experimental techniques.

EFPIA represents 32 national pharmaceutical industry associations and 43 leading pharmaceutical companies operating in Europe. Its mission and priorities are to improve the competitiveness within Europe in a regulatory and political environment, which will above all stimulate R&D and reward innovation.

In vivo refers to experimentation done in or on the living tissue of a whole, living organism as opposed to a partial or dead one or a controlled environment.

Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect.

Pharmacology is the study of how drugs interact with living organisms to produce a change in function.

Toolbox – the type and duration of animal testing required to be performed during drug development in order to get a marketing authorisation for a medicinal product granted by health authorities

Scientific Advice procedure. Regulatory procedure, where health authorities give the industry advice by answering questions connected with the development of medical products.

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