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Adoption of animal welfare principles by UK regulators

Abstract

Regulatory authorities involved in safety and risk assessments have a primary duty to protect humans, animals and the environment. Safety evaluation studies, to assess the potential hazards and risks posed by products and substances, currently depend predominantly on animal testing as a limited number of non-animal methods have been developed and received regulatory acceptance. The ways in which regulatory authorities can assist in replacing animal procedures and in reducing the suffering caused to animals in safety testing were highlighted in 1997, when a set of principles on animal welfare was drawn up by them in collaboration with the Home Office. The principles are based on the replacement, reduction and refinement of animal experiments, known as the Three Rs. Focus on Alternatives (FOA), an umbrella group of organisations working together to advance the replacement of animal experiments, wrote to each of the UK regulatory authorities asking them how, and to what extent, they have implemented these principles. This paper reviews how well the various authorities are implementing the five principles, and also presents FOA's recommendations on where further effort is needed. These animal welfare principles and FOA recommendations may also apply to similar regulatory authorities worldwide.

Keywords: Regulatory toxicology; Animal welfare; UK regulators; Three Rs; Alternatives

1. Introduction

Regulatory authorities such as the Health and

Safety Executive, the Veterinary Medicines Directorate and the Department of the Environment, Transport and the Regions¹ have a primary duty to protect humans, animals and the environment. In order to assess the potential hazards and risks posed by products and substances such as new pesticides or pharmaceuticals, the authorities require safety assessment tests to be conducted. At present, safety evaluation studies depend predominantly on animal testing as a limited number of non-animal methods have been developed and received regulatory acceptance.

Both national and European legislation requires that non-animal, alternative methods should be used in place of animal procedures where possible, and that animal use and suffering should be minimised (known as the Three Rs: replacement, reduction and refinement). The development and regulatory acceptance of alternative methods has shown that strenuous efforts are required, and that all stakeholders, including regulatory authorities (hereafter referred to as regulators), have a role in this process. Regulators can influence the number of animals used for safety testing, for example, by preventing the unnecessary repetition of animal studies. They can also have an active role in encouraging the development and regulatory acceptance of non-animal alternative tests.

¹ The DETR has undergone reorganisation and some of their responsibilities are now part of the Department for the Environment, Food and Rural Affairs (DEFRA).

The ways in which regulators could assist in replacing animal procedures and in reducing the suffering caused to animals in safety testing were highlighted in 1997, when a set of principles on animal welfare in the assessment of safety and risk was drawn up by the regulators in collaboration with the Home Office (Anon, 1998). Focus on Alternatives (FOA), an umbrella group of organisations working together to advance the replacement of animal experiments, wrote to each of the UK regulators² in 2000 asking them how and to what extent each agency has implemented these principles (indicated below in italics). Furthermore, we asked them whether they had publicised the principles and produced any reports of progress in achieving these aims and, if so, whether they are in the public domain.

UK Government Department and Agencies differ in their roles and responsibilities. The DH and DEFRA provide the lead for national input into the Organisation for Economic Co-operation and Development (OECD) test guidelines programme. Agencies within these departments, for example the MCA and MDA in the DH, are involved in requesting data for safety assessment. Other regulators, such as the FSA, are not involved in regulatory testing except on occasions when committees recommend animal studies, for example to assess whether a certain chemical should be permitted in food. Thus, not all of the five principles applies to every regulatory authority and regulators did not necessarily respond to every question.

This paper reviews how the various regulators are implementing the principles and identifies any obstacles preventing their implementation. The emphasis is on how each principle is being achieved, rather than by whom, and therefore the information provided by the regulators is unattributed. The paper also presents FOA's recommendations on how more could be achieved.

1.1. Encourage the development of alternative methods through co-operation with or participation in national and international initiatives aimed at refining, reducing or replacing the use of animals

The regulators provided examples of how they encourage the development of alternative methods. Unfortunately, only three of the eight regulators stated that they fund research projects to develop alternative techniques such as in vitro or computer-based methods. In one case, research was being funded for the optimisation and preservation of precision-cut human tissue slices, and generation of cell lines for in vitro modelling of absorption through the human intestine. Projects were either funded at the national level, or part funding was given to European initiatives. In two cases, regulators indicated that details of research projects are available on the Internet. Thus, some regulators are proactive in funding and promoting their research to develop alternative methods, although it is not possible to gauge what portion of their budgets this constitutes.

Funding research is just one way in which regulators can encourage the development of alternatives. Regulators have access to vast amounts of data, derived from both animal and non-animal methods, which have been submitted to them for regulatory purposes. These data can be used to help validate non-animal tests, as well as to minimise animal use and reduce levels of suffering. However, only one regulator provided an example: it had reviewed the number of animals used to test for skin sensitisation and this revealed that the same classifications could generally be obtained using half the normal animal group size. In light of these findings, the standard European Union (EU) method and the OECD guideline were modified to reduce the minimum number of animals needed. Clearly, this approach has the potential to be very effective in improving animal welfare if applied more widely. The joint UK government and the European Centre for the Validation of Alternative Methods (ECVAM) meeting on progress in toxicological testing recommended that regulators should be strongly encouraged to publish data that have the potential

² Department of the Environment, Trade and the Regions (DETR); Department of Health (DH); Food Standards Agency (FSA); Health and Safety Executive (HSE); Medicines Control Agency (MCA); Medical Devices Agency (MDA); Pesticides Safety Directorate (PSD); Veterinary Medicines Directorate (VMD). The UK Government Departments and Agencies listed above granted permission to be cited in this manuscript.

to influence the development of testing strategies (Tichias et al., 1998).

Other approaches include the promotion of the Three Rs by UK regulators to various audiences. For example, regulators cited examples of promoting refinements to the classical LD₅₀ test; and the use of tiered-testing approaches, with non-animal data being used in the initial assessments, such as with eye irritation testing. Most UK regulators stated that they were involved in progressing national, European and international recognition of validated non-animal methods, or methods which are refinements to existing protocols. A case in point is the local lymph node assay (LLNA), a less severe animal test for skin sensitisation whose recognition was progressed by UK regulators at multinational committees and scientific conferences. The assay also received funding for further development. UK regulators can also play a vital negotiating and co-ordinating role in support of alternative methods at the OECD, whose test guideline programme is used worldwide.

1.2. Seek to influence international harmonisation initiatives to ensure that policies and practices take full account of the ethical duty to protect the welfare and minimise the numbers of animals used in safety assessments

International harmonisation of test protocols provides the means to substantially reduce animal use and minimise suffering worldwide. There are different international harmonisation processes, such as for human and veterinary pharmaceuticals and for medical devices. In these processes, UK regulators have a key input to negotiations, and the majority of regulators contacted by FOA mentioned this role.

UK regulators described several instances where they have been proactive towards ensuring that a single data dossier, generated in one region, will be equally acceptable for authorisation purposes in other regions. Two regulators stated that they participate in the International Conference on Harmonisation (ICH), which is a pharmaceutical harmonisation initiative involving industrial and regulatory authorities representing the EU,

the USA and Japan. Some successes were reported; for example, a set of ICH-approved reproductive toxicity protocols are now accepted by all regulators. One regulator indicated that they pragmatically recognised other countries' reproductive toxicology protocols even before this agreement was achieved.

One regulator is using and actively promoting within Europe a system of batch release of immunological products that relies on quality assurance inspection of manufacturers' testing facilities rather than repeat testing of products in animals by state laboratories. In another example, a regulator has resisted an attempt to introduce a newly developed animal screening test to screen for reproductive toxicity into the EU base-set requirements for notified chemicals. This decision was based, in part, on the view that, with new tests, preference should be given to non-animal methods. Instead, it was recommended that ECVAM be asked to oversee the development of a non-animal assay for eventual incorporation into the base-set testing requirements.

The International Standards Organisation (ISO) and the OECD are other fora in which regulators can advance the Three Rs through harmonisation. One UK regulator stated that the most significant aspect of its work lies in the progress made through the ISO in writing the standards that set out scientific principles and methods for safety assessments. For example, in respect of medical devices, there is an international biological safety standard on animal welfare. With input from the UK, this will shortly be revised to ensure that it is brought into line with European minimum standards of care and accommodation, OECD guidelines on humane endpoints, and any changes in the implementation of the US Animal Welfare Act. In other ISO working groups, UK representatives are pushing for the addition of the LLNA to the standard on skin sensitisation in place of the more severe guinea pig test, and the deletion of the LD₅₀ test from the systemic toxicity standard.

1.3. Alert applicants/clients to instances where data submitted in support of registration or safety evaluation are considered excessive in terms of

animal suffering or numbers or where internationally accepted alternatives replacing, reducing or refining animal use have not been employed

Four regulators suggested that they have detected instances where animals may have been used excessively or inappropriately and do alert applicants in these cases; one regulator highlighted that action had particularly been taken when this involved the use of primates. Obviously this retrospective approach is too late to prevent animal suffering on that occasion; however, such action may help to avoid a similar situation in the future.

A better approach is that of preventing over-testing in the first place. However, only four of the regulators contacted provided examples of how they were achieving this. Two regulators responded that they informed applicants on how to meet regulatory requirements by using the fewest animals and minimal suffering, and of changes in testing requirements that help achieve the same goals.

In a similar vein, a flexible approach to animal test requirements with judgments based on a scientific and rational basis (rather than blindly following the recommendations given in guidelines) was highlighted by two regulators. In an example provided, repeat-dose toxicity testing data would not be required for humanised monoclonal antibodies developed against a human antigen for which there is no animal counterpart. Meaningful studies could not be conducted in animals, as exaggerated pharmacological responses could not be detected and, if neutralizing antibodies were produced in test animals, the product might be inactivated. In another example, no dermal absorption studies for chemicals were required when worker risks were considered negligible, even though EU guidelines stipulate that testing is normally required. The need for greater flexibility with respect to the data required from notifiers for regulatory approval was highlighted in the report of recommendations from the joint UK government/ECVAM meeting on progress in toxicological testing (Tichias et al., 1998).

One problem described by several regulators was that their scope for action is limited. A considerable amount of animal work is conducted abroad and the majority of products are developed on a global basis. Thus, companies usually design their animal study programmes to meet the needs of all the major regulatory authorities. Certain UK regulators felt that some testing above the minimum stipulated under EU regulations might be considered justified if applicants are submitting to other non-EU authorities with more-demanding requirements. Thus it is not always straightforward to define what constitutes genuine regulatory 'over-testing'. This again emphasises the importance of harmonising data requirements.

Another problem identified was that regulatory duties are sometimes delegated to third parties and therefore the regulator is not always in a position to monitor compliance with animal welfare principles. For example, with certain kinds of medical devices, marketing approval is delegated to other independent organisations (or is subject to self-certification by manufacturers), and these organisations review dossiers containing animal test results. It is important that these other organisations demonstrate support and compliance with the animal welfare principles.

1.4. Accept for assessment internationally recognised, non-animal alternative tests conducted to appropriate standards

Most regulators said that they are happy to review data from non-animal methods, where these are scientifically valid. There is, of course, an expectation for them to do so under EU Directive 86/609/EEC (EEC, 1986). UK regulators are also bound by EU statutory requirements for animal testing, although these requirements permit replacement by non-animal alternatives as they become available. For example, batch safety testing of rabies vaccines in mice has now been replaced by tissue culture tests. The OECD agreement on mutual acceptance of data should enhance worldwide acceptance of alternative test data where a member state has accepted a method as valid. A case in point is the identification of

severe eye irritants. Several countries have approved the use of ex vivo methods (such as the bovine corneal opacity and permeability test) and data from these assays should be accepted by other OECD members.

Some regulators have accepted data from non-animal alternative methods before receiving international regulatory approval. For example, one regulator had accepted skin penetration data from in vitro tests in advance of an OECD guideline being agreed. However, not every regulator condoned this approach. Two regulators expressed the view that it would not benefit animal welfare if one or a group of regulators accepted an alternative test before the wider international community does so. This is because companies that wish to market their product outside the UK will have to provide in vivo data despite the fact that such information is not needed in the UK. Whilst FOA acknowledges this problem, we argue that there needs to be an impetus for change and that agreement should be reached as soon as possible, not at the speed of the slowest decision-making process.

1.5. Not require repetition of data produced by the applicant for other safety evaluation regulators where such data accord with internationally accepted guidelines and have been generated in compliance with appropriate standards

Clearly, preventing the unnecessary duplication of animal testing is an important reduction strategy. Many products are now developed on a global basis and companies may design their animal test programmes to meet the needs of all the major regulators. Providing these studies have been conducted to internationally accepted guidelines and Good Laboratory Practice (GLP) standards, such data should be accepted by any regulatory authority. However, one regulator indicated a flexible approach by accepting data from studies performed in the spirit of GLP, and to a suitable protocol, rather than insisting on a repetition of animal studies to meet full GLP standards.

Related issues such as data protection and commercial confidentiality were highlighted by regula-

tors as major obstacles in preventing the unnecessary duplication of animal testing. These arrangements prevent the disclosure of data by regulators to third parties without the consent of the originator of the data. Understandably, companies generating safety data for regulatory purposes at great cost to themselves are reluctant to give third parties access to those data without compensation. One regulator indicated that legislation does allow some action in this area, but that imposing—rather than encouraging—a settlement would be fraught with difficulties, and demand considerable additional resources.

Notwithstanding this, half of the regulators contacted were able to provide examples of positive actions taken by them to prevent the unnecessary duplication of animal testing, including identifying overlaps in applications, encouraging data sharing, and promoting the better use of existing data.

Some directives and regulations require potential notifiers to contact regulators before starting tests on animals. This provides regulators with the opportunity to examine whether the substance to be tested is sufficiently similar to one that has already been notified (termed a ‘positive hit’). If so, the regulatory authority can inform the companies involved, making it clear that they encourage data sharing. One regulator reviewed data collated over a period of 6 years to show how effective this approach was in reducing repeat testing. Of 722 initial enquiries, 65 positive hits were identified; at least 34 of these resulted in UK notifications, some of which were based on data sharing. The regulator knew of only two instances over that time where the companies concerned failed to reach agreement and repeat testing was carried out. Clearly, directives and regulations that require potential notifiers to contact regulators prior to starting animal tests can enable data sharing and significantly reduce repetitive testing.

Two regulators indicated that, where data are available and well-reasoned arguments are provided, the re-interpretation of existing data (e.g. to extrapolate hazard classification of new products from relevant data on similar formulations) was encouraged. In some cases, regulators are proactive in adding to the amount of information

publicly available. For example, one regulator publishes a list of active ingredients for which data protection has expired. In another example, supporting dossiers from applicants are placed on the regulators' web page, allowing others to review existing safety data. The impetus for this action was new regulations that require routine disclosure, for public comment, of all non-confidential information provided by companies in support of an application.

2. Information in the public domain

The information summarized here was only obtained by directly writing to each regulatory authority. FOA asked whether reports of progress towards achieving the animal welfare principles were available in the public domain. Disappointingly, less than half of the regulators responded that they had taken steps to promote the five principles, although, at the Third World Congress on Alternatives to Animal Use in the Life Sciences, one regulator described how they do so (Evans, 2000).

None of the UK regulators indicated that they produce reports (e.g. annual reports) containing this information and only one said that it was considering making information available in the future. At one agency there was a discussion about mentioning the principles on its website, but this was over-ruled by senior management.

Regulators have a duty to function transparently and in an accountable manner. Public concern about animal testing is high and information needs to be in the public domain. For these reasons, and in order to develop and promote best practice, all regulators should take every opportunity to highlight their efforts to implement the Three Rs.

3. Conclusions and recommendations

Although these animal welfare principles were drawn up and accepted by UK regulators, they apply to similar regulatory authorities worldwide. Regulators in the EU are bound by EU legislation

that requires non-animal, alternative methods to be used in place of animal procedures where possible, and that animal use and suffering should be minimised. Furthermore, regulators worldwide involved with requesting animal data from industry, have an ethical responsibility to implement the Three Rs.

Regulators are ideally placed to identify opportunities for developing alternatives. The positive actions taken by some UK regulators are indicated in this paper. However, this review has revealed that there are many opportunities for developing and encouraging the use of alternative methods. FOA makes the following recommendations to regulatory authorities:

- More funding is required for the development of replacement methods. Regulators should indicate the percentage of their funding budget used for this purpose.
- The review and analysis of data submitted to regulators is an essential means of helping to validate non-animal tests and minimise animal use and suffering. As a priority, resources should be made available for this activity.
- Continued and improved efforts should be directed towards the harmonisation of international testing guidelines.
- Regulators should be more proactive in preventing excessive or repetitive animal testing, for example, by applying test requirements more flexibly, and making judgements based on a scientific and rational basis rather than rigidly applying test guidelines.
- The possibility of eliminating duplicate testing (such as with biologicals) by state and company laboratories should be explored, for example, by implementing a system of quality assurance inspection at the company laboratories.
- Where testing has been conducted which is considered excessive in terms of animal suffering or numbers, regulators should advise applicants accordingly. Better still, regulators should advise and update likely applicants on how to meet regulatory requirements while using the fewest animals and minimizing suffering.

- All applicants should be informed that, where validated and approved alternatives exist, animal tests should not be conducted.
- Requirements for potential notifiers to contact regulators prior to starting animal tests can enable data sharing and significantly reduce repetitive testing. Regulations which require this should be implemented, and others introduced in areas where they do not presently exist.
- Regulations that require the public disclosure of all non-confidential information provided by companies in support of an application should be applied rigorously.
- Where approval for marketing is delegated to other organisations or to manufacturers, such as with testing certain medical devices, compliance with the Three Rs should be ensured and monitored by the appropriate regulatory agency.
- The animal welfare principles should be promoted as widely as possible, for example on each authority's website. Reports of progress towards achieving these principles should be published regularly by the regulators.

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