Factors Stimulating or Obstructing the Implementation of the 3Rs in the Regulatory Process

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Summary

Approximately 30% of animal use within the European Union (EU) is done to meet regulatory requirements. The tests are often repetitive in nature and may cause severe suffering, due to the procedures used and to rigidly predefined end points. In addition, product evaluation procedures often take long and are very expensive. Over the last decades the heavy reliance on animal experimentation in this area has met serious objections, both ethical and economical in nature. This study describes obstacles and opportunities to implement the 3Rs in regulatory animal testing. The findings are based primarily on interviews with legislators, regulators, industry, science and animal welfare organisations and reflect shared perceptions of these respondents. In order to increase the application of the 3Rs in regulatory testing a number of technical, political and social obstacles must be overcome. This study offers insight into the persistent character of regulatory animal testing and can function as a starting point for further discussion on how to tackle these problems. To this end, several recommendations are made ranging from strategic test approaches and data sharing to strengthening the policy network and improving communication between 3Rs experts and regulators. The study is an initiative of the national project group "Regulatory Animal Testing", which consists of a group of Dutch experts on animal testing working for a variety of organisations in the field.[1] They felt the need for cooperation to initiate a discussion at relevant levels and to identify possible solutions in order to implement the objectives of the three R's in testing for regulatory purposes without loss of scrutiny in safety and/or efficacy evaluation needed for product release.

Zusammenfassung: Was fördert und was hemmt die Einführung der 3R bei amtlichen Zulassungsverfahren?

Etwa 30% der Versuchstiere in der Europäischen Union (EU) werden in behördlichen Zulassungsverfahren verwendet. Die Tests wiederholen sich naturgemäss oft und können schweres Leiden verursachen, abhängig vom Versuch und von den strikt vorgegebenen Endpunkten. Darüber hinaus dauert die Klassifizierung von Produkten oft lange und ist sehr teuer. In den letzten Jahrzehnten wurde das grosse Vertrauen, das bei diesen Verfahren in die Tierversuche gestzt wurde, ernsthaft erschüttert, aus ethischen, aber auch aus ökonomischen Gründen. In dieser Studie werden Hemmnisse und Möglichkeiten beschrieben, die 3R in amtlichen Zulassungsverfahren einzuführen. Die Resultate basieren in erster Linie auf Interviews mit Abgeordneten und Angehörigen von Behörden, der Industrie, der Wissenschaft und von Tierschutzorganisationen; sie reflektieren die Auffassungen der Befragten. Um der Anwendung von 3R Methoden bei amtlichen Zulassungsverfahren stärkeres Gewicht zu verleihen, müssen eine Reihe von technischen, politischen und sozialen Hindernissen beiseite geräumt werden. Diese Studie bietet einen Einblick in den gegenwärtigen Stand der Zulassunsgverfahren und könnte als Ausgangspunkt für weitere Diskussionen dienen, wie die Probleme gelöst werden könnten. Zu diesem Zweck werden einige Empfehlungen ausgesprochen, die von strategischen Testabläufen und Datenaustausch bis zur Verstärkung des politischen Netzwerks und einer verbesserten Kommunikation zwischen 3R Experten und Zulassungsbehörden reichen. Die Studie ist eine Initiative der nationalen Projektgruppe "behördlich vorgeschriebener Tierversuche", die aus einer Gruppe holländischer Experten für Tierversuche besteht, die für verschiedene Organisationen auf diesem Gebiet arbeiten[1]. Sie erachteten eine Kooperation als dringend geboten, um eine Diskussion auf relevanten Ebenen zu starten und mögliche Lösungen aufzuzeigen. Die 3R Prinzipien sollen bei amtlichen Zulassungeverfahren eingeführt werden, ohne einen Verlust an Sicherheit und Wirksamkeit bei der Produktfreigabe befürchten zu müssen.

Keywords: regulatory animal testing, registration, regulatory requirements, 3Rs, validation, alternatives, stakeholders, stream model, policy

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[1]Underlying findings of this article are available at at http://www.bio.uu.nl/scienceshop/ ; under publications.

1 Introduction

In 2002, approximately 10.7 million animals were used for experimental purposes in the European Union.

The experiments were conducted in the following areas:

About 30% of these animal tests are carried out to comply with regulatory requirements (from within the following categories: R&D for medical, veterinary and dentistry products, toxicology/safety evaluation and production and quality control)[2]. These legal requirements prescribe which experiments must be conducted in order to licence and release a compound or product onto the market for human, animal or environmental applications. This implies that these tests are mainly applied in the areas of production and quality control of human and veterinary medicine and of toxicological and safety evaluation of other compounds or products, e.g. pesticides, household products, cosmetics, food additives. Many national and international parties, often with divergent interests, are involved in setting these requirements, aiming at efficacy, consumer safety and environmental protection.

Regulatory animal testing is usually laid down in standard protocols. It is often repetitive in nature and more likely to cause severe suffering than other types of animal testing, due to the procedures used and predefined experimental end points, in contrast to most other types of animal research. Because of these characteristics, regulatory animal testing is an important area to evaluate for 3R policy opportunities.

In 1959, W. M. L. Russell and R. L. Burch proposed the implementation of the 3Rs principle to animal experimentation in "The Principles of Humane Experimental Technique" (Russell and Burch, 1959).

1. Replacement: the substitution of insentient material for conscious living higher animals.
2. Reduction: reduction in the numbers of animals used to obtain information of a given amount and precision.
3. Refinement: any decrease in the incidence or severity of inhumane procedures applied to those animals, which still have to be used.

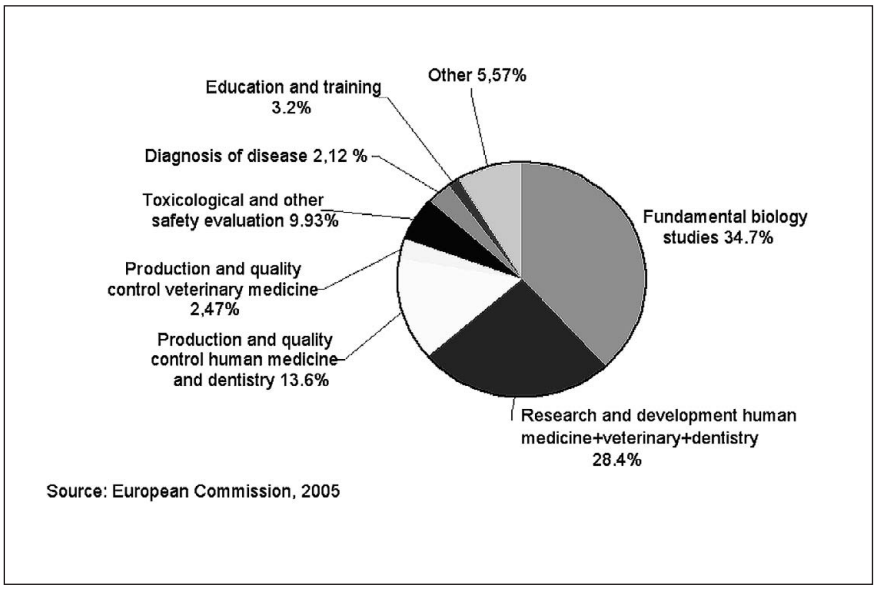

Fig. 1: Purposes of experiments

Much can be gained in testing for regulatory purposes with respect to the 3Rs (replacement, reduction, refinement) by looking critically at the approach to animal testing, the necessity of the test, the way tests are conducted, the possibilities to use alternative methods, etc. (IVTIP, 2000).

It must be emphasised that when this article mentions alternatives to animal testing, this refers to all three R's and not exclusively to the R of "replacement".

In practice however, it proves difficult to implement the 3Rs as an important concept in testing for regulatory purposes. In order to identify opportunities and obstacles in implementing the 3Rs within testing for regulatory purposes this study examines the decision-making process underlying regulatory animal testing.

2 Investigative approach

A policy-making process is typically surrounded and influenced by a variety of factors and actors. The process is permanently subject to conflicts (of interest) between the various stakeholders in society and on the administrative level itself. Both the object and the result of the policy are the outcome of a permanent political (power) struggle. In order to explain how various factors and actors influence the policy-making process, this analysis makes use of the stream model (Kingdon, 1995). Although the theory of the stream model is designed to analyse the process of agenda setting, it proved to be a very useful model in this context to describe and understand the factors influencing the implementation of the 3Rs in the regulatory process.

In the stream model, the policy-making process is regarded as an organised anarchy in which problems, parties and solutions each behave according to their own dynamics. The model postulates three streams: problems, solutions and political/administrative developments. The problem stream represents the multitude of issues in society that need to be addressed. The political/administrative stream reflects the political and administrative actors caught up in a continuous battle for votes, budget and support. Finally, the solution stream reflects the ideas, plans and pilot projects – developed by parties, lobby groups and civil servants – which may lie around unused for years. Developments within these streams determine whether opportunities arise for the streams to connect. Such opportunities for the confluence of streams are known as policy windows.

[2]In the Netherlands this percentage is 29% (Food and Consumer Product Safety Authority (VWA), "Zodoende"; Annual Report on Animal Experimentation and Laboratory Animals, 2005, The Hague, The Netherlands)

When the streams meet, it is possible to effect changes in policy or to initiate new policy (Walraven et al., 2002).

Chances to produce new policy or to modify existing policy can be created and used by a so-called policy entrepreneur (Hart't et al., 1995). The entrepreneur has capacities to function as the initiator of new policy. The personal characteristics of the entrepreneur and the social relevance of the group he or she represents are two of the factors that determine how successful a confluence of streams will be.

In terms of the stream model, this study also aims at providing insight into the influences and entrepreneurs that can ensure that the various streams successfully converge to create a policy window.

The European legislative process is long and complicated. It involves many different actors who have either a formal or an informal opportunity to contribute to policy shaping and lobbying the decision-makers. The multitude of stakeholders and the barter of issues from other policy sectors make it hard to predict how a particular initiative will fare. In view of these characteristics, the legislative process is also difficult to predict. At the European level, one can hardly speak of coherent and strong policy-making. The stakeholders of influence do not operate in a focussed formal framework but rather in a network with flexible relationships.

This survey is exploratory and descriptive in nature. The identification and description of factors influencing the policy-making process is based on the qualitative research methods of desk research and a series of interviews. Approximately thirty stakeholders were interviewed in-depth to get an overview of their views on the complex issue of regulatory animal testing. The survey is therefore mainly based on the respondents' ideas and perceptions of the factors they see as influential in the decision-making process at the European level. Many categories of putative stakeholders were considered first. From these, several categories of stakeholders were selected based on their assumed significance. The following categories were defined to select respondents for this research:

- Legislators (policymakers);
- Regulators (governmental agencies and authorities responsible for the implementation and maintenance of laws and regulations, with the authority to approve or reject the release of products on the market);
- Science (academia, research institutes);
- Industry;
- Animal interest organisations.

The respondents came from the European and Dutch context and were selected in close consultation with the project group "Regulatory Animal Testing". A complete list of respondents can be found in the acknowledgements.

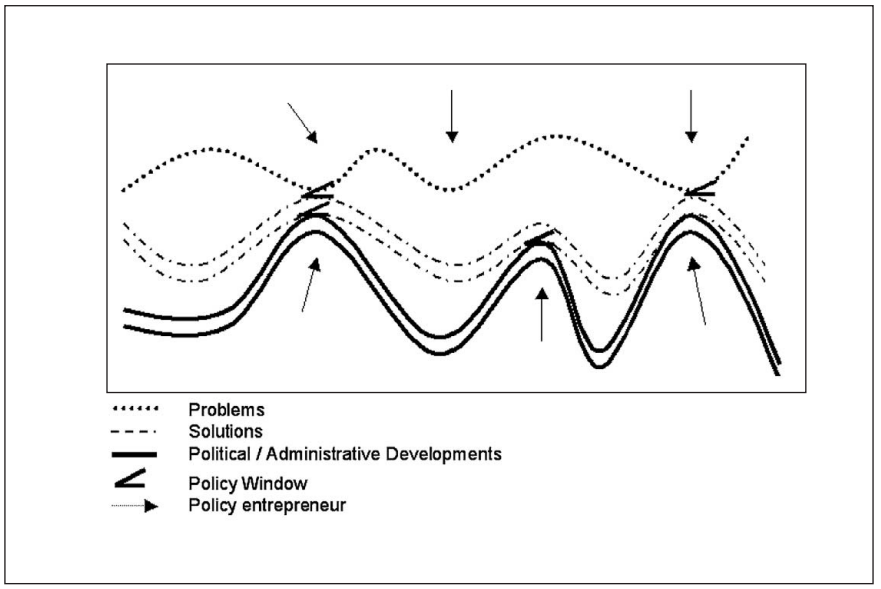

Fig. 2: Representation of the Stream Model
Sources: Walraven et al., 2002; van de Graaf and Hoppe, 1989

3 Results

Regulatory animal testing is a persistent element in assessment procedures for licensing a compound or product for release onto the market. Even though the number of alternative test methods keeps increasing, these new methods are not automatically implemented in the guidelines for assessment procedures in order to replace the more classical animal tests. This is due to a combination of technical, political/administrative and societal factors. In order to accelerate the implementation of alternative methods in regulatory testing, a number of obstacles must first be overcome. What follows below is an overview of the most relevant factors influencing the use of the 3Rs in assessment protocols. These factors have been grouped using the problem stream and the solution stream of the above mentioned stream model. The political and administrative factors are the focus of this study. Next to these factors, several technical and societal factors have been identified.

3.1 Problem Stream

The problem stream represents a combination of problems, which have to be addressed in order to reduce the extent of animal use for regulatory requirements.

3.1.1. Technical problems

Availability of alternative methods

Most alternative test models developed so far are intended to replace relatively simple test methods e.g. for local toxicity / one target organ. However, most remaining animal experiments are complex tests for which it is difficult to find alternatives. For example, many animals are needed for tests in reproductive toxicology (embryo toxicity) and systemic toxicology, which are much more complicated to entirely replace. Science is now facing the task of developing such complex alternative test methods, either by refinement, reduction of the number of animals needed per test, or replacement. Opinions on the feasibility of this task are divided.

Technical expertise

For the methods that have been developed in the area of the 3Rs, there might be more room for application and acceptance. Up till now, such methods are often insuffi-

ciently or too narrowly publicized and are known to a limited audience and therefore used to a limited extend.

Technical expertise is a crucial factor in the decision making process whether or not to implement the 3Rs in safety and efficacy testing for regulatory requirements. Since the field is very complex, only a select number of experts are able to contribute to discussions on the matter. Legislators and regulators might have limited knowledge of alternative methods when they do not have detailed and updated scientific information at their disposal. This makes it difficult for them to evaluate the merits of these test models. They are therefore strongly influenced by the extent of scientific consensus concerning animal experiments and alternatives. Without this type of scientific backing, politicians are reluctant to take a political stand. Furthermore, scientists who do have expertise on alternative test models often lack the knowledge of, and access to, the policymaking process, and therefore cannot effectively inform legislators and regulators about these possibilities (Sauerborn et al., 1999). This hinders the necessary communication between legislators and regulators on the one hand and scientists in the field of the 3Rs on the other. Much of the knowledge with regard to the 3Rs remains unused, according to the experts consulted.

Availability of data

Another important barrier with regard to implementing the 3Rs in regulatory animal testing is that, for reasons of competitiveness, industry is reluctant to make research data available. This means that a vast volume of valuable information regarding the 3Rs already exists but is not available to third parties. And although much is undertaken to harmonize the registration requirements between countries and to accommodate the mutual acceptance of test results across borders, this lack of available data still leads to unnecessary use of classical "non 3R" testing models.

"Traditional" versus "new" methods

The present generation of regulators was mainly educated some 20 to 30 years ago when the credo still was "*in vivo veritas*". The new generation of regulators will most likely incline towards *in vitro* methods. There is, however, a risk that each "school" will exclude the other methods to a certain extent. The new generation of scientists/regulators may run a risk by making the transition too quickly, thus missing the opportunity to convince others by demonstrating valid evidence, while the older generation may be too dismissive of novel *in vitro* methods. This would impede the acceptance of alternatives. It should be emphasised that a "stand-alone" position, of either *in vivo* or *in vitro* methods, is neither feasible nor desirable.

Validation process

Before newly developed alternative methods can be put into practice, these methods first have to be validated. Although the number of alternative tests developed and accepted has risen sharply in the recent past (Balls, 2002), validation is looked upon as a difficult and time consuming process dominated by a small number of interest parties. The process often leads to interpretation problems, since the scientific prestige of the various players may be at stake. Validation of alternative methods has therefore become a process that takes many years. This shows a sharp contrast to *in vivo* methods that have never been formally validated and are widely accepted.

Implementation

Furthermore, the process after validation is often even more time consuming, since alternative methods must prove themselves many times over before they are accepted by regulators and become part of legislation (Spielmann, 2000).

Why acceptance takes such a long time will be discussed in the following paragraphs.

3.1.2. Political and administrative problems

The main political and administrative factors considered to be barriers when trying to implement the 3Rs for regulatory purposes are: agenda setting, legislative/regulatory context and acceptance of validated methods.

Agenda setting

The EU concerns itself primarily with the internal market of the now 27 European states. Other issues near the top of the agenda are safety and risk limitation. Animal welfare as such has a lower priority. This also means that governments and industry have limited budgets for developing alternatives, particularly because they are aware that an alternative method, once developed and validated, will be subject to a very time consuming period of negotiations before it can be accepted for regulatory purposes. The growing concern regarding consumer safety and environmental impact is translated into more regulatory requirements for products, and will therefore result in an increase of the number of animal tests used for regulatory purposes.

Legislative/regulatory context

Two types of legislation are relevant to the use of experiments on animals. The first is "horizontal legislation" pertaining to animal experimentation and multilateral agreements. The second is "vertical" or "sectorial legislation". The latter regulates the activities of a particular sector, for example the approval of pharmaceuticals, which indirectly affects animal experimentation. In principle, vertical legislation must take horizontal legislation into account. For example, Directive 86/609/EEC, which regulates the protection of animals used for experimental and other scientific purposes, should be taken into account by vertical legislation (Article 21). Directive 86/609/EEC applies the "no, unless" principle. This directive stipulates that alternatives, if available, should be used (Article 7). Some vertical European legislation already explicitly refers to this directive. Moreover, even when this is not the case, the provisions in the horizontal legislation about animal testing must be respected in all other regulations. In practice, however, this is often done insufficiently or not at all due to a combination of factors. There is too little cooperation between the EU committees that draft "safety and efficacy regulations" and those that develop "animal welfare regulations" (de Leeuw, 2004). As a result, when directives are revised, they continue to include requirements for animal tests even after alternatives have been validated and used by corporations. This is why different directives can, and often do, conflict. There are no traffic regulations indicating which directive has priority in case of conflicting rules in different directives (de Leeuw, 2004).

In addition, Member States are given relatively great discretion to interpret European directives within the limits of national law, for instance in the area of pharmaceuticals. In the EU alone, there are more than 800 laws, regulations, directives and other documents regulating the use of laboratory animals to ensure the safety of humans, animals or environment (de Leeuw, 2004). These regulatory requirements are often used in quite a rigid manner, the so-called "tick box approach". This refers to a rigid method of quality and safety control by assessors of products and compounds. One can speak of the tick-box approach when assessors simply request every test prescribed in the protocol to be executed without having a critical look at the necessity of conducting all these tests. This results in great differences between EU Member States and the extent to which they are open to alternatives.

Finally, European legislation dealing with market related issues usually outweighs animal welfare issues. Animal welfare issues are primarily seen as the responsibility of the individual Member States, even as Article 22 of the Directive 86/609/EEC obliges the Commission to collect information about the legislative framework for regulatory purposes in each of the Member States, and to evaluate these for the protection of animals.

Acceptance of validated methods
As mentioned in paragraph 3.1.1, successful validation does not guarantee acceptance. The slow pace of acceptance is caused by a combination of factors. Firstly, legislators and regulators are facing increasing demands for consumer safety and risk minimisation. These authorities are expected to take this increasing demand for safety into account when developing and implementing policies. In the area of policy implementation, the regulators in particular are considered to be reluctant to implement the 3Rs in evaluating testing protocols and dossiers for product registration. One main reason for this reluctance is the heavy responsibility regulators bear for the safety of products they allow onto the market. In addition, regulators are often relatively unfamiliar with the properties and scientific qualities of relevant, but relatively new, alternative test methods. They therefore tend to adhere to classic (animal) models and are sceptical towards accepting new methods with different scientific end points. A number of respondents believe legislators and regulators are waiting for a scientific consensus before taking the risk of incorporating alternatives into policy. This process of reaching scientific consensus, by the very nature of scientific methodologies, is difficult to achieve and takes a long time. As a consequence, so are the changes in policies.

Along the same lines, industry is identified as a conservative force, preferring to play safe by anticipating the strict registration requirements regulators will set. As a result, industry tends to stick to the old, animal based models, even when alternative models are available.

3.1.3. Societal problems

The societal factors that are perceived as barriers when trying to reduce the extent of animal use for regulatory purposes can be divided into two categories: public opinion and risk minimisation.

Public Opinion
Although there is public resistance to animal testing in general, the growing focus on consumer safety has so far taken priority over the concern for animal interests. Public opinion on animal testing depends also on the purpose for which the animals are used. For example, animal testing for medical purposes is much more accepted than safety testing of cosmetics (Aldhous et al., 1999).

Public opinion has a powerful potential to influence the attitude of politicians and industry towards animal testing and alternative methods and is of great importance to the image of companies and products. This has prompted various companies to promote alternatives as part of a Corporate Societal Responsibility concept. Moreover, if animal testing is in the public eye, it usually becomes of more interest to politicians too. However, when product safety is a hot topic, the concern about the welfare of animals used in experiments tends to loose any priority.

The influence of public opinion is therefore ambiguous. It has the potential to encourage the development and implementation of alternative methods in case there is a high public concern regarding animal welfare. Currently it is more likely to hamper the implementation of the 3Rs due to the growing emphasis on consumer safety.

Risk minimisation
The tendency within Western society towards a so-called "zero risk" concept is a serious threat to replacing, reducing and refining regulatory animal testing. The ongoing call for extra research based on the precautionary principle is a manifestation of this. According to many respondents, the advocates of the "zero risk" concept are insufficiently aware of the consequences this has in terms of the increased use of animals for testing purposes.

3.2 Solution stream

The solution stream contains several possibilities to overcome (some of) the barriers described above. In order to effectively reduce the number of animals used for regulatory purposes a mix of technical, political/administrative and societal solutions is needed.

3.2.1 Technical solutions

Options for reduction and refinement
Although it is difficult to develop alternative methods for more complex tests, much progress has been made in reducing the use of animals and in refining methods for complex end points, such as local acute toxicity, some vaccine tests and pyrogen testing. When it comes to the more complex experiments, reduction and refinement seem to offer the best prospects for the time being. Respondents expect good results in the near future from developments aimed at reducing the number of laboratory animals used to test scientific hypotheses and refining tests to limit the suffering of laboratory animals. The most substantial gain according to interviewees is expected from strategic test approaches and data sharing.

The strategic test approach, also referred to as step-by-step approach in toxicity tests and consistency approach for biological products, offers a chance to reduce the number of animal tests (Health Council of the Netherlands, 2001). It is important to apply strategic planning before carrying out any animal experiments in an effort to ensure appropriate implementation of the 3Rs. For example, there is tremendous potential for the increased use of screening tests to assist in prioritising chemicals for further test-

ing for their pharmaceutical potential (Combes et al., 2002). This could result in cancelling subsequent *in vivo* tests in case *in vitro* tests indicate a compound to be toxic. Currently, animal experiments are often carried out regardless of such initial results.

The merit of sharing data is widely accepted. It is essential for verification purposes, secondary analyses and the information can be used for (computerised) modelling of pharmacodynamic and putative properties of compounds. In order to be able to maximise the implementation of the 3Rs, scientific inquiry must be open to the public domain. Since the advantages of data sharing are sufficient, a considerable amount of energy should be put into overcoming one of the main hurdles by finding ways in which data can be shared without jeopardising privacy or breaching confidentiality promised to data providers (Fienberg, 1985).

Broaden communication on the 3Rs
As mentioned, scientific knowledge is often underused due to the poor communication of results by scientists to other stakeholders (Sauerborn et al., 1999). In order to promote the implementation of scientific developments with regard to the 3Rs, these developments should be made public to a wider audience of legislators and regulators than is done presently.

3.2.2 Political/administrative solutions

Influencing agenda setting
Animal welfare organisations represent important actors in the struggle to get animal welfare and the 3Rs on the political agenda and keep them there. Therefore, ongoing attention from these non-governmental organisations (NGOs) to this subject is an important driving force.

Harmonisation of legislation and regulations
Even though harmonisation is an onerous and time-consuming process, it seems to be a precondition to reduce any unnecessary testing caused by insufficient coordination between various legislations and regulations. This has been achieved for pharmaceuticals through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)). Harmonisation can give an important boost to reduce unnecessary testing. Furthermore, Mutual Acceptance of Data (MAD) ensures that research is not needlessly duplicated. Therefore, it is of great importance to develop a Mutual Recognition Agreement, or MRA. However, as is the case with harmonisation, developing an MRA is a laborious process.

Towards acceptance of validated methods
Acceptance of validated methods is a mixture of awareness of the problem, commitment to change, availability and knowledge of alternatives and positive experiences with these methods, finding them reliable to reach the relevant scientific end points. The new generation of assessors/regulators (expert reviewers of test data in the process of registration of products) is expected to have awareness of the concept of the 3Rs because of greater exposure to the issue during education.

Combination of technical expertise and political intuition
Experts involved in elaborating safety requirements and tests have mainly technical expertise. In order to effectively bring about change, experts should also be familiar with the policy-making process and forces at play in politics and administration. In risk assessment, the public perception of product safety is also relevant, e.g. recent incidents may cause (public, political) risk perception to change for a short or longer term, and administration is bound to be sensitive to risk perception as a political fact. Adequate awareness of factors of a different nature than just scientific/technological expertise and fact-finding creates a better chance to effectively exert influence.

Ethical review committees
Practically all Western European countries have procedures for the ethical review of a proposed animal test. Although Member States vary widely in terms of the organisation of the review process (composition of review committees, their tasks, status, and the levels at which tests are reviewed), ethical review committees could play an important role in being loud and clear when they believe certain regulatory tests are outdated and could be replaced or modified, e.g. by contacting the national representative in the regulatory bodies.

In order to bring the potential contribution of alternative approaches for risk assessment to the attention of regulators, it is important to have 3Rs experts represented at expert committees of regulatory authorities, both at the EU and at the national level.

3.2.3. Societal solutions

Risk communication
To tackle the problem of the tendency towards "zero risk level", better information about the risk/benefit balance must be provided. First, it is necessary to clearly convey the message that zero risk cannot be achieved by any means. Second, open communication about potential risks creates an opportunity to bring risk acceptance back to proportions that are more realistic and fosters individual freedom of choice.

3.3. Stakeholder analysis

Four stakeholder groups are seen by the respondents as most dominant in the policy-making process and the implementation of 3 Rs for regulatory purposes:

1. *Regulators*, being the assessors of new products and compounds, have most influence on the implementation of legislation, and, therefore, on the feedback loop between applicant and authority. Regulators also exert direct influence on the policy-making process in their position as experts who advise legislators on drafting new policy or revising existing policy. Regulators also have authority over the industry regarding application and release of their compounds and products.
2. *Industry*, in turn, exerts great influence on legislators through strong lobby and expertise as well.
3. *Animal welfare organisations* influence the policy-making process directly (political lobby) and indirectly (through public opinion). This influence is aimed primarily at the initial stages of the process: the agenda-setting stage and partly the policy-making stage. It is mainly by their competence to mobilise public opinion that these organisations have power to influence the political agenda. Therefore, they

can be a driving force behind reforms that implement the 3Rs. However, animal welfare organisations have very little direct influence on regulators, respondents remarked, since regulators take their cues first and foremost from the heavy responsibility they bear.

4. *Experts*, who are shown in this study to have a great deal of influence on the development of policy, are mainly found within the stakeholder groups: regulators, scientists and industry.

Although more and more legislation is now formulated at EU level, the Member States themselves can ultimately be regarded as dominant actors in the political arena. After all, it is the Member States that provide the experts who help draft and revise regulations at every level. The Member States' influence is even greater because of the necessity to implement EU regulations into their national legislation. European legislation usually leaves Member States enough discretionary room for their own interpretation of policy. Consequently, (national) experts play a dominant role in policy-making, while regulators play a dominant role in policy interpretation and implementation.

4 Conclusions and Recommendations

Regulatory animal testing is perceived by a vast majority of the respondents as a very persistent element in the assessment procedures for licensing a compound or product for release onto the market. Even though the number of alternative test methods keeps increasing, even scientifically validated alternative methods are not easily included in assessment procedures. In order to effectively replace, reduce or refine animal testing for regulatory purposes, first of all a common understanding about the nature and importance of the problem needs to be established. Only a concise problem definition will enable tackling the problem in an effective manner. Therefore, there seems to be a fair level of consensus about the fact that there is a problem. Stakeholders however seem to have different opinions on the level of priority it must have in comparison to other problems that need to be addressed. To tackle the problem of regulatory animal testing, it is of special importance that regulators and industry grant it priority. Experts in the field of the 3Rs and NGO's concerned about animal welfare can play an important role in keeping this issue on the agenda of these stakeholders. The problem of regulatory animal testing should be addressed by combined technical, political/administrative and societal solutions.

Three categories of opportunity can be used to tackle the problem of the large number of animals used within regulatory testing.

1. Technology: There is a need for the development and validation of new, supplementary techniques that need to be accepted by a process of expert peer review to replace, reduce or refine animal experimentation.
2. Communication: There is considerable room for improvement of the exchange of knowledge between stakeholders about methodologies, results, etc. The necessary improvements would start with basic awareness, leading up to the implementation of a communication strategy.
3. Co-ordination/harmonisation: Supported by a better communication strategy, the stakeholders should coordinate their actions more closely. The desired result is harmonisation, i.e. the dovetailing of legislation and regulations in various regions and sectors.

In terms of the stream model, these three categories each contribute in their own way to a convergence and confluence of the three streams (the solution, problem, and political/administrative streams), which then can create a policy window. The technology category deals with new ways to enlarge and improve the solution stream, while the communication category offers a way to bring the political/administrative stream and the problem stream closer to the alternatives stream. Coordination and harmonisation have a great potential to reduce regulatory animal testing.

In order to create new implementation opportunities for the 3Rs within the regulatory framework, progress is needed in all three streams, and the resulting improvements must subsequently be brought together. Entrepreneurs or "advocates" who seek to improve conditions for the application of the 3Rs principles can facilitate this. The dominant actors who are leading toward implementing the 3Rs in regulatory animal testing can play the role of policy entrepreneurs. Some examples of such actors are: innovative companies in the field, experts in the field of the 3Rs, animal welfare organisations, ethical review committees, the inspectorates and committed individuals in any stakeholder group.

Conclusion

Regulatory animal testing is deeply ingrained in the procedures for evaluating compounds and products before they are allowed onto the market. Society, however, is growing increasingly critical of such animal tests required by protocol. Hence, initiatives from a variety of backgrounds are taken to reduce regulatory animal testing. This study is one of those initiatives. By analysing the technical, political and administrative and social factors that influence the use of regulatory animal testing, the researchers aimed to contribute to the quest for possible solutions and to stimulate further discussion in order to reduce regulatory animal testing. Both the respondents in the qualitative inquiries, and the discussions in different stakeholder debates, have shown that the problem is recognized and that progress in this field would be much welcomed, for various reasons (protection of animals, cost of testing, and access to a common market by harmonized regulatory processes) and is therefore viable.

In order to stimulate further reduction of regulatory animal testing this article ends with the following recommendations:

Recommendations

- Invest in data sharing, retrospective analyses and strategic test approaches;
- Use risk communication in order to influence the level of risk acceptance;
- Make the costs of conducting animal tests more visible;
- Visualise the limitations of current animal testing procedures;
- Widely publicise available (validated) alternatives;
- Improve communication between stakeholders;
- Strengthen the policy network;
- Harmonise various laws and regulations concerning product registration.

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