Science Shop

Biology

Regulatory Animal Testing

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Universiteit Utrecht

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A Survey of the Factors Influencing the Use of Animal Testing to Meet Regulatory Requirements

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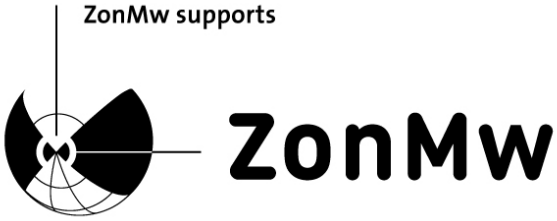

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Summary

Thirty percent of the animal tests conducted annually in Europe are performed to meet regulatory requirements pertaining to the authorization and release of a substance or product onto the European market. Regulatory animal testing is often repetitive in nature and more likely to cause severe suffering than other types of animal testing due to the procedures used. Because of these characteristics, regulatory animal testing is very interesting in terms of the 3R policy (Replace, Reduce and Refine).

The Science Shop for Biology at Utrecht University asked the Utrecht School of Governance to conduct a survey into the actors and factors that affect regulatory animal testing. The project was commissioned by the 'Regulatory Animal Testing' Research Project Group, which consisted of representatives from industry, science and an animal welfare organisation. The study was conducted in the framework of the ZonMw 'Limits to Animal Testing' programme.

This study surveys and describes the factors and actors that influence the use of animal testing to comply with regulatory requirements. Wherever possible, the research focussed on animal testing required by protocol for the authorization and release of pharmaceuticals. The research findings are based primarily on interviews with representatives of the main stakeholder groups (legislators, regulators, industry, science and NGOs). In other words, this study provides a survey of perceived influences. These findings are meant to help identify possible follow-up projects at the European level in order to reduce regulatory animal testing wherever possible.

Regulatory animal testing is a persistent element in the assessment procedures for registering a substance or product for release onto the market. Even though the number of alternative test methods keeps increasing, these new methods are not automatically included in assessment procedures. In order to increase the use of alternative methods to comply with regulatory requirements, a number of obstacles must first be overcome. What follows below is a list of the most obvious factors influencing the implementation of the 3Rs in assessment protocols. These factors have been grouped into the following categories: technical, political/administrative and social.

Technical factors

Respondents indicated that most alternative test models developed so far are intended to replace relatively simple tests. However, most animal experiments are part of complex tests for which it is difficult to find alternatives. Science is facing the task of developing such complex alternative test methods. Opinions on

the feasibility of this task are divided. In terms of the 3Rs, respondents expect the most 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. In this field the greatest gain is expected from so-called strategic test approaches, data sharing and retrospectively analysing existing data.

Another factor influencing the implementation of the 3Rs in regulatory animal testing is that legislators (policy makers) and some regulators (regulatory authorities) have limited technical expertise concerning alternative methods which makes it difficult for them to evaluate the merits of alternative test models, whereas scientists may have little understanding of regulating processes. Experts on the 3Rs can play a key role here by providing legislators and regulators with the information needed.

Political / administrative and social factors

Once a new method has been validated, it usually takes many years before this test method is actually accepted by legislators and regulators.

The slow pace of acceptance is caused by a combination of factors. To begin with, legislators and regulators are facing increasing demands for consumer safety and risk minimization. When compared to these concerns, animal welfare has relatively low priority. Legislators and regulators are expected to take this increasing demand for safety into account when developing and implementing policy. In the area of policy implementation, it is the regulators in particular who are reluctant to implement the 3Rs in evaluating protocols, according to respondents. One main reason for this is the heavy responsibility regulators bear for the safety of the products they allow onto the market. In addition, regulators are often relatively unfamiliar with alternative test methods and they therefore tend to adhere to existing models. Along the same lines, the industry is identified as a conservative force, preferring to play safe by anticipating the strict registration requirements regulators will set. As a result, more animal tests are conducted than strictly necessary.

Finally, coordination between policy makers at the European level -- and hence between various legislation and regulations in different policy areas – is not optimal. This leads to unnecessary testing. Harmonization of legislation and regulations is a precondition for reducing regulatory animal testing.

This survey identifies and describes the various opportunities and threats for the implementation of the 3Rs in regulatory animal testing. As mentioned before, this study is the basis for a follow-up project focusing on one or more of the factors identified. To this end, this report makes the following 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 transparent;
- Widely publicize available alternatives;
- Improve communication between stakeholders;
- Strengthen the policy network;
- Harmonize various laws and regulations.

Chapter 1

Introduction

1.1 Motivation

This research project focuses on animal testing carried out to meet regulatory requirements pertaining to the authorization and release[1] of a substance or product on the European market. Article 1 (1) of the Dutch Animal Testing Act [Wet op de dierproeven (WoD)] defines animal testing as:

> *any act or series of acts carried out upon a living vertebrate or living invertebrate of a species to be designated by Order in Council..*[2]

A few figures provide insight into the number of animal tests done and the fields in which these are used. In 2003, a total of 620,875 tests were performed on animals in the Netherlands, 14% less than in 2002.[3] In the European Union, some 10 million animals are used annually for experimentation.[4]

The pie chart in Figure 1.1 shows the fields of research that use animal testing. In 2003, most of the animal tests in the Netherlands were conducted for purposes of scientific research (52%)[5].
In 2003, 26% (162,680) of all experiments on animals in the Netherlands were performed to comply with regulatory requirements.[6] In Europe, approximately 30% of the animal tests conducted annually are

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[1] Release means the authorization of substances, a batch at a time, for use in pharmaceuticals and biological products.

[2] …. for the purpose of:

a) manufacturing or testing serums, vaccines, diagnostics or other medical, veterinary or biological substances, or conducting biological calibrations;

b) carrying out toxicological or pharmacological research;

c) identifying or detecting pregnancy, disease or other bodily conditions or characteristics of humans or animals or corresponding conditions or characteristics of plants, other than in the normal and proper veterinary treatment of the animal in question;

d) acquiring or developing knowledge of the human or animal body or dexterity in performing operations thereon;

e) resolving a scientific problem, insofar as it is reasonable to suppose that the animal may suffer distress or that the intended or possible consequence is the birth of an animal that would suffer distress.'

http://www.nca-nl.org/English/legislation-uk.html, consulted on June 5, 2005

[3] Voedsel en Waren Autoriteit (The Dutch Food and Consumer Product Safety Authority), 2003.

[4] Ministry of Health Welfare and Sport, 2001

[5] Voedsel en Waren Autoriteit, 2003

performed to meet regulatory requirements.[7] In figure 1.1, regulatory animal testing is represented by the segments labelled 'Development and production of serums and vaccines', 'Development and production of drugs' and 'Toxicity research'.

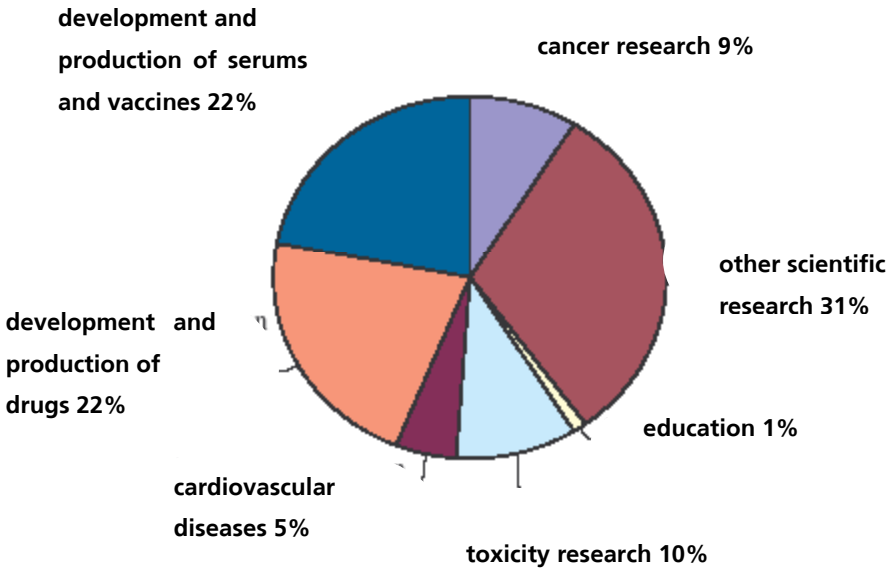

Figure 1.1 **Purposes of animal testing**[8]

Experiments on animals are conducted in various areas, namely the pharmaceutical field[9], vaccines/ biological products, existing and new chemicals, plant protection, biocides and food additives. A substantial proportion of these animal tests is carried out to comply with regulatory requirements pertaining to the authorization and release of a wide range of substances and products for human, animal or environmental applications. In short, approximately one quarter of all animal testing is conducted to meet regulatory requirements.

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[10]. Because it has these characteristics, regulatory animal testing falls within the scope of 3R policy[11] and this is one reason why the 'Regulatory Animal Testing' Research Project wishes to scrutinize such tests.

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[6] Ibid.

[7] Swart, J. et al. (2004)

[8] L.F.M. van Zutphen, et al. (2001)

[9] Animal testing for pharmaceutical purposes is defined as: experiments on animals for the purposes of developing and authorizing (veterinary) drugs with the aim of submitting these to the Commissions authorized to evaluate the drugs' compliance with the registration requirements. This is the so-called 'narrow definition'.

[10] Science Shop for Biology (2003)

[11] Replace the use of animals by other research methods, Reduce the numbers of laboratory animals and Refine the experimental procedures to minimize suffering.

Various national and international parties, often with divergent interests, are involved in setting these regulatory requirements. The question is, how does this decision-making process take place? In addition, authorities seem to interpret risk management in very different ways, which leads to discrepancies in how different countries use experiments on animals. This begs the question to what extent the protection of laboratory animals is taken into consideration at social, political and administrative levels.

On behalf of the 'Regulatiory Animal Testing' Research Project, the Science Shop for Biology at Utrecht University has asked the Utrecht School of Governance to examine whether the decision-making process surrounding regulatory animal testing can be influenced. This study is financially supported by the ZonMw[12] 'Limits to Animal Testing' programme.

1.2 Definition of the Problem

The research question this study focuses on is:

> *Which factors and actors influence at EU level the policy making process in reference to the use of animal testing to meet regulatory requirements and in which ways?*

This core question has been subdivided into four sub-questions:

I. What laws and regulations exist concerning animal testing and how is this legislation developed in the European Union?
II. Which factors affect the policy-making process[13] at EU level and which actors are involved?
III. How do these factors and actors influence the use of animal testing to meet regulatory requirements?
IV. Which factors affect legally required animal testing for quality control of veterinary vaccines, and how?

The aim of this research is to gain insight into the factors influencing the possible reduction of regulatory animal testing. These insights will aid in the formulation of a proposal for an international follow-up project. The aim is to secure European subsidies to help fund the project.

This report refers frequently to alternative methods and the 3Rs. In 1959, W.M.L. Russell and R.L. Burch proposed an alternative approach to animal testing in *The principles of humane experimental technique*. They introduced the 3Rs: Replacement, Reduction and Refinement of animal experimentation.[14] This principle has also been adopted in the Netherlands:[15]

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[12] ZonMw is the Netherlands Organization for Health Research and Development, a combination of ZorgOnderzoek Nederland and Medische Wetenschappen (Medical Sciences), formerly one of NWO's (Netherlands Organisation for Scientific Research) departments.

[13] In this study, the term 'policy-making process' refers to the process which leads to the development and/or revision of the regulatory requirements to be met in order to authorize and release a product or substance on the market.

[14] Russell W.M.S. and Burch R.L. (1959)

[15] Weerd, H. van de and J. van der Valk (2004)

- Replacement: replacing vertebrate animals with invertebrate animals, organic material or non-biological material.
- Reduction: reducing the number of laboratory animals for a specific problem.
- Refinement: limiting the pain, suffering, distress or lasting harm experienced by laboratory animals before, during and after the experiment.

It must be emphasized that when this report mentions alternatives to animal testing, this refers to the 3Rs and not exclusively to the R of 'replacement'.

Although there is still a long way to go in the development and implementation of alternative test methods, the 3Rs have made significant inroads in the past few years. The number of alternative tests developed has increased in the recent past.[16] Some examples have been included in section 3.4.

1.3 Scope

Because this study is a survey which had to be completed in a relative short span of time, the research was limited in the following ways.

In consultation with the project group, the researchers decided to focus wherever possible on the pharmaceutical field, since animal testing is applied in so many different fields of research. The pharmaceutical field was chosen because the project group expects it to function as an example for other fields[17]. Animal experimentation for pharmaceutical purposes (for a definition, see footnote 9) comprises approximately 15% of the total number of tests on animals.[18] Despite this focus, the lion's share of the findings in this report still has a bearing on regulatory animal testing in general. This can be explained partly by the choice of respondents, and partly by the fact that many respondents answered from a general perspective.

Secondly, the researchers opted to focus on the decision-making process at the European level because the playing field where decisions about animal testing are made is distinctly European. The national and global levels are of less importance. Where necessary, links to the global and Dutch national context are mentioned.

Thirdly, this research has yielded findings at the technical, political/ administrative and social levels. Because the technical aspects are beyond the expertise of the project team members, the recommendations at the end of this report deal mainly with the social and political/administrative aspects which the project team was commissioned to investigate.

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[16] ECVAM (2002)

[17] According to some respondents, however, pharmaceuticals are an exception rather than the rule. These respondents contend that the public is less concerned with animal testing in the pharmaceutical field than in other fields and that pharmaceuticals face greater restrictions than other sectors due to the global requirements dictated by FDA/ICH.

[18] Voedsel en Waren Autoriteit (2003)

Another important constraint is that the findings were derived mainly from interviews with respondents. Therefore they reflect the respondents' ideas and perceptions of the factors they see as influential in the decision-making process at the European level. The findings therefore reflect perceived influence.
This report focuses particularly on the more widely held views; where a cited opinion is more of a dissenting standpoint, this will be indicated.
To encourage candid responses, all interviews were conducted on condition of strict anonymity. As a consequence, this report can only indicate in the broadest terms where the findings come from.

1.4 Analytical Frame of Reference

To interpret the research findings this study has made use of the analytical frame of reference shown below. This model allowed the researchers to structure the results of this study.

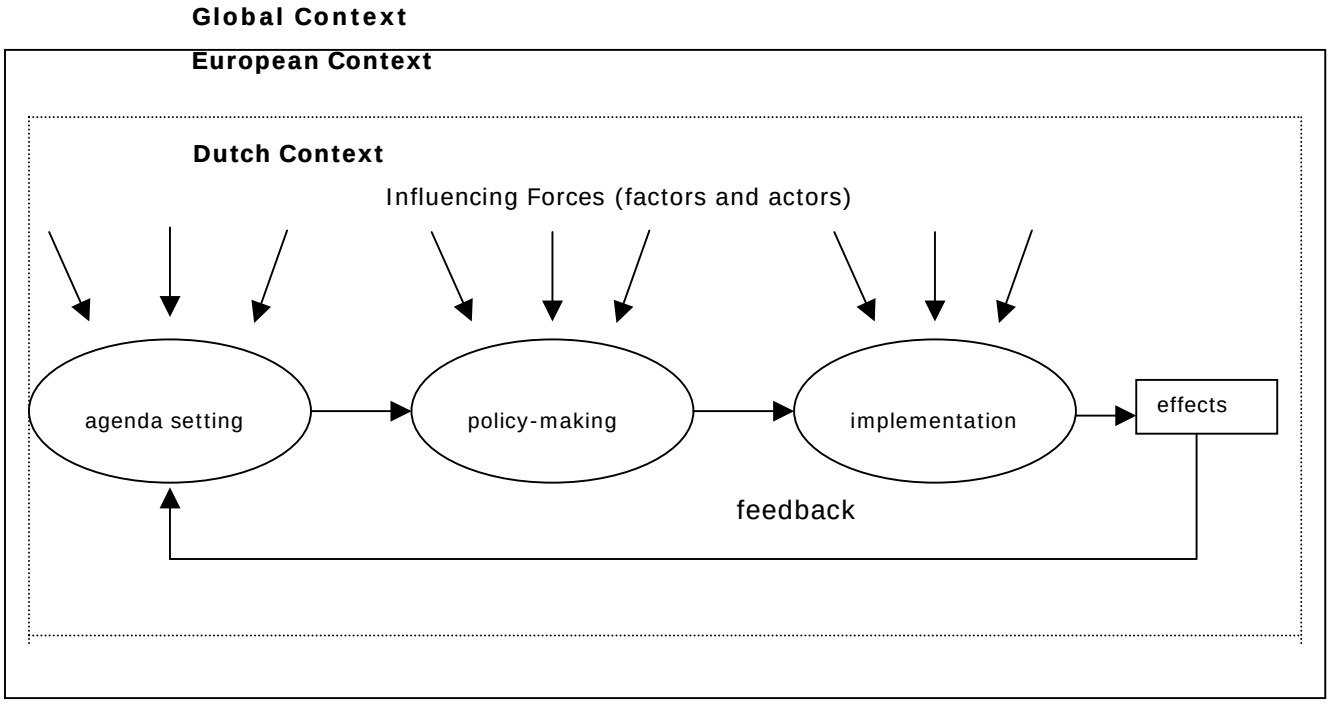

Figure 1.2 Analytical model

In this model, the policy-making process has been subdivided into three stages: agenda setting, policy-making and policy implementation. These stages are linked to the institutional characteristics of the legislative and regulatory process and to the authorities, special interest groups and others involved in this process.[19] The policy-making process can be charted using this model.

The analytical model also shows that the policy-making process is surrounded and influenced by a variety of factors and actors. The process is permanently subject to conflicts (of interest) between the various

[19] Hoogerwerf, A. et al. (1993)

stakeholders in society and within 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, the analysis makes use of the stream model[20].

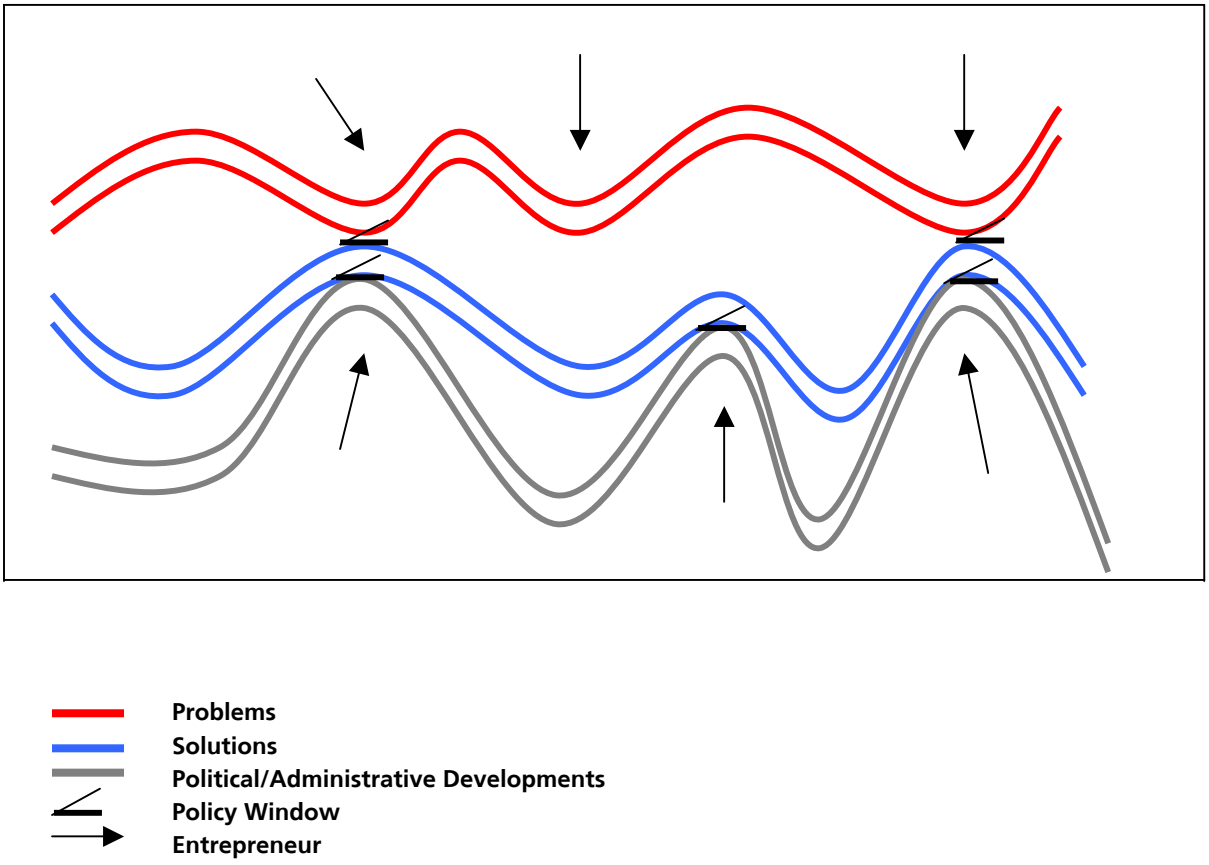

Figure 1.3 Representation of the Stream Model[21]

In the stream model, the policy-making process is regarded as an organized 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 a 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 in a desk drawer 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. When the streams meet, it is possible to effect changes in policy or to initiate new policy.

[20] The stream model was introduced by John W. Kingdon in Agendas, Alternatives and Public Policies (1995)

[21] Walraven, G., S. van Erp and M. Knegtel (2002)

Chances to produce new policy or to modify existing policy can be created and used by a so-called entrepreneur.[22] In other words, the entrepreneur, also known as the advocate, functions as the initiator of new policy. The personal characteristics of the advocate 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 some places in the model, only two of the streams meet. If no link is established with the third stream, the first two will drift apart again. The political agenda is largely determined by the confluence of the problem stream with the political/administrative stream. A subsequent connection with the stream of alternatives, followed by a selection process in which some alternatives are selected and others rejected, narrows the political agenda down to a policy agenda. In terms of the stream model, this study attempts to provide insight into the influences and entrepreneurs that can ensure that the various streams successfully converge to create a policy window.

1.5 Approach

This pilot study is exploratory and descriptive in nature. Qualitative research methods, such as document analysis and in-depth interviews, have been used to investigate which factors influence the European policy-making process and how. Because this study is essentially a survey, the researchers decided to take a wide angle perspective. The aim is to provide an overview of the important actors and factors with an impact upon European policy-making. The results can serve as a basis from which to select aspects worth investigating in possible follow-up projects.

The decision to use qualitative research methods was also based on the anticipated complexity of the field. In-depth interviews provide an opportunity to ask more (and more probing) questions about certain issues and to check earlier findings.

The study was initiated and commissioned by the "Regulatory Animal Testing" research project group. This group was composed of representatives from various stakeholder groups (see Appendix 1) who have expertise in the field of (alternatives to) animal testing. The initiator saw to the selection of an advisory committee which handled the daily supervision of the Utrecht School of Governance project team. This advisory committee was closely involved in the selection of respondents, brainstorming about the sub-points to be studied, and the evaluation of interim reports and discussion of progress.

In addition to the Project Group and the advisory committee, a group of experts was established whose members specialize either in the development or implementation of policy and guidelines requiring animal experimentation. Each of this group's members provided input by giving an interview, discussing the findings in this report and contributing to a joint discussion on possible follow-up projects.

The chart below shows the research project's structure. Names of the various bodies' members can be found in Appendix 1.

[22] Hart, P. 't et al. (1995)

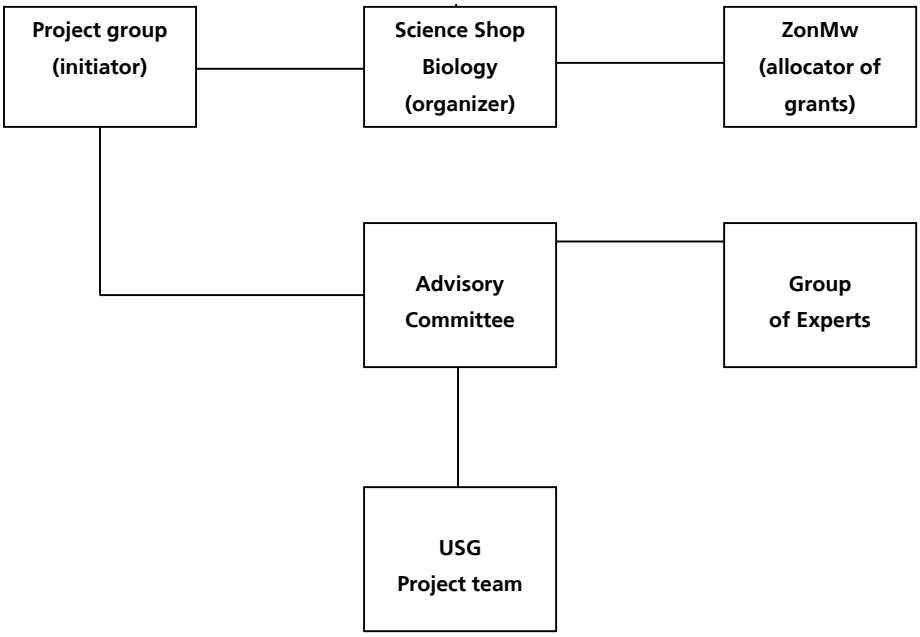

Figure 1.4 **Research project's structure**

The research project has been subdivided into the following stages:

Stage 1 Orientation and Legal Framework

The researchers familiarized themselves with the subject by studying documents and interviewing members of the advisory committee. They mapped out all laws and regulations pertaining to the subject in order to gain an understanding of the national and international legal framework of animal testing for the authorization and release of drugs. The context given in this report results from a study of Dutch and European policy documents and laws, and information gathered from interviews conducted during the next stages.

Stage 2 Identification of Factors and Actors

The identification and description of factors influencing the policy-making process is based on desk research and a series of interviews. In this stage, twenty-five stakeholders were interviewed in-depth. The respondents gave their views on the complex issue of regulatory animal testing. The respondents came from the European and Dutch policy-making contexts, from politics, the (pharmaceutical) industry, science and special interest groups. For an overview of the respondents, see Appendix 2. The respondents were selected in consultation with the advisory committee.

In processing the results of this stage, a decision was made to combine factors and actors into a cluster rather than discuss them separately, so as to avoid duplication. The actors involved are introduced in the descriptions of the legal context, the development of EU legislation and the relevant technical, political/administrative and social factors.

A separate document with an overview of the actors was presented to the project group. A diagram summarizing this overview can be found in Appendix 3.

The study differentiated between the following main categories of stakeholders:

- Policy-makers/Legislators
- Regulators (regulatory agencies and authorities at the European and national Dutch level)[23]
- Science (academia, research institutes)
- Industry
- NGOs/special interest groups (such as animal welfare organizations, environmental organizations, consumer organizations and patient organizations)
- General Public

In consultation with the initiator, the researchers selected which actors would be approached for interviews. The interviewees represented all the main stakeholder categories, with the exception of the general public.

The key aim of these interviews was to identify possible incentives and impediments to changing animal testing policy in favour of the 3Rs. The interviews focused on themes deemed relevant during the orientation phase.

Stage 3 Case Study: Quality Control of Veterinary Vaccines

To take stock of the practicalities surrounding the authorization and release of a product on the European market, a case study was chosen to chart this process. The case study was intended to verify the findings from Stage 2. The case was selected in consultation with the advisory committee based on the following criteria:

- the case had to pertain to the development or implementation of regulations and/or policy at the European level regarding the release of a product or substance onto the European market.
- the case had to offer the opportunity to analyze the involvement of actors and factors in policy formulation, decision-making or implementation.
- the researchers had to have access to the main documentation and case data concerning both public and private actors.

The researchers would have preferred a case involving drugs for human use, but none was available. Therefore, they opted for a case in the field of quality control of veterinary vaccines. Although this was not the first field of choice, the expectation of the Project Group was that valuable lessons could be learned from it. The case study provides insight into how the regulatory requirements that prescribe animal testing lead in practice to re-testing vaccines. The information necessary for this case study was obtained through document analysis and two in-depth interviews with stakeholders from the pharmaceutical industry and of the European Commission staff.

[23] Governmental agencies, responsible for the implementation and maintenance of laws and regulations, with the authority to approve or reject the release of products on the market. In the pharmaceutical field, these include the MEB at the national level and CHMP (EMEA) at the European level.

Stage 4 Report and Workshop

The research project resulted in this report, which provides an overview of the most important factors that have an impact on the use of animal testing as well as an analysis of the political arena.
The structure of the report is explained in more detail in the next section. A draft of the report has been submitted to the project group and the group of experts.

In addition, the project concluded with a half-day workshop with members of the group of experts and the project group. The purpose of the workshop was to check the insights gained from the research project and to generate additional input to be used in the European proposal for a follow-up project.

1.6 Structure of the Report

The report follows the order of the subdivision of research questions. Following this introduction, Chapter 2 sketches in broad lines how policy is made at the EU level. The remainder of the chapter is devoted to charting legislation and regulation at the global, European and Dutch national levels.

Chapters 3, 4 and 5 subsequently describe the factors that influence the policy-making process. The findings have been categorized into three kinds of factors: technical, political/administrative, and social. Chapter 3 focuses on the technical aspects, such as expertise and ways of realizing valid alternatives. Chapter 4 deals with the political and administrative factors such as the political agenda and the activities of lobby groups.
Finally, Chapter 5 sheds light on the influence of social factors including public opinion and the degree of risk that society is willing to accept.
The findings in the Chapters 3, 4 and 5 were obtained from respondents and therefore mainly reflect the opinions of stakeholders on various themes. For every theme, the interviewees' more widely held opinions are summarized, followed where applicable by specific pharmaceuticals-related aspects within the theme.
Chapter 6 is devoted to the case study of the authorization and release of a veterinary vaccine onto the European market. After summarizing the facts of the case, the chapter lists the main factors influencing the possibility of reducing the number of regulatory animal tests.
Chapter 7 provides a survey of the factors and actors that can be characterized as dominant and describes how they influence the policy-making process. This chapter sketches the forces in the political arena.
Chapter 8 states conclusions and offers recommendations for drafting a project proposal for possible follow-up research projects.

Chapter 2

Legislative and Regulatory Context

2.1 Introduction

This chapter provides an overview of the legislation and regulations relevant to the research topic. It subsequently describes how legislation and regulation is developed at the European level.

Two types of regulation are relevant to the use of experiments on animals. The first is horizontal regulation pertaining to animal experimentation and multilateral agreements. The second is vertical or sectorial regulation. The latter regulates the activities of a particular sector, for example the approval of drugs, which indirectly affect animal experimentation. Figure 2.1 below shows both types of regulation.

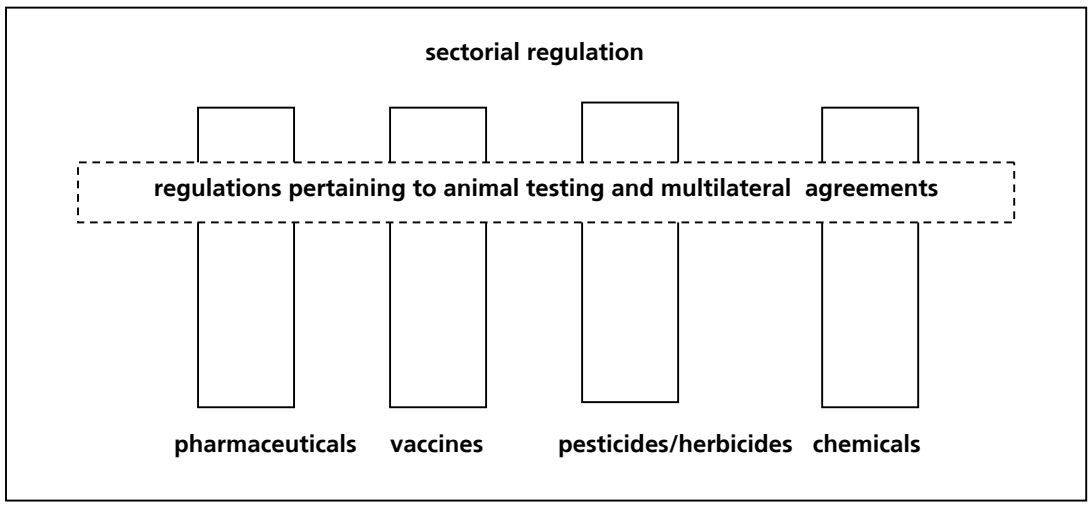

Figure 2.1 Horizontal and vertical regulation

This study focuses not only on legislation and regulations pertaining to animal testing, but also on the laws and regulations in a particular sector - in this case pharmaceuticals - that indirectly affect animal testing. Any additional regulations pertaining to the case study about the authorization of veterinary vaccines are reviewed in Chapter 6.

In principle, vertical regulation takes horizontal legislation and regulation into account. Some vertical European regulations explicitly refer to horizontal regulations on animal testing. Even when this is not the case, the provisions in the horizontal regulations about animal testing must be respected in all other regulations.

Apart from this distinction between horizontal and vertical regulation, it is important to establish at which level regulations are set. This report distinguishes between three different levels: the global, European and Dutch national level.[24] In this study, the emphasis is on the European level.

Section 2.2 describes how regulations are developed at the European level in order to provide an overview of the characteristics of the formal process. Section 2.3 charts the horizontal legislation regarding animal testing. Section 2.4 discusses horizontal legislation created to accommodate multilateral agreements, while section 2.5 describes the vertical legislation and regulations with regard to pharmaceuticals.

2.2 The Development of European Union legislation

The development of legislation in the EU is a complex process in which many institutions, actors and (formal and informal) rules play a role. By far the largest part of EU policy - and this applies to animal testing as well - eventually manifests itself in European law (regulations and directives). Therefore it is important to gain insight into the formal legislative process followed in the EU. Within this formal, institutional framework, various actors use all kinds of influence and pressure with the aim of obtaining the desired legislative results. At the European level, lobbying is part and parcel of the legislative process. In many cases, consultation with special interest groups is a fixture in the formulation of policy.

Like the development of Dutch legislation, the EU legislative process -- as part of the wider policy-making process -- is subdivided into several stages. In this respect it fits in well with the policy-making stages identified in Chapter 2.

In keeping with the subject of this study, the description of the legislative process focuses on the policy areas that influence the number of experiments on animals, such as animal welfare and the authorization and release of drugs. The following sections deal with the structure of the EU decision-making process, the institutions involved in this, and their role in the legislative process.[25]

2.2.1 How the EU Decision-making Process Works

Broadly speaking, the EU decision-making process is currently structured as follows:

[24] In some cases, (additional) regulations are drawn up by local governments or representative organizations in a given sector. These fall outside the scope of this study.

[25] In the new European Constitution, the development of directives is simplified. Whether and when this Constitution is ratified depends on the outcome of referendums and decision-making processes in the member states. We are basing ourselves on the current situation.

Commission stages:

1 European Commission initiative
2 European Commission action plan
3 European Commission expert stage

Council stages:

4 Presentation of new Commission proposals to the European Council and the European Parliament
5 Discussion in Council working groups [26]
6 Decision-making in the COREPER[27]
7 Decision-making in the Council of Ministers

Implementation stages:

9 Implementation by the European Commission (comitology)
10 Implementation and compliance at the national level

The European Convention has various pillars (clusters of policy areas), each of which has its own manner of shaping and making decisions. The lion's share of EU policy is developed in the first pillar-this is the regular 'Community policy'. In this pillar, policy-making begins in the European Commission, which has the right of initiative. It is difficult to trace the exact origin of Commission initiatives, but they are usually the result of contacts with national civil servants, special interest groups, etc. This stage, and the subsequent expert stage, are crucial moments in the effort to get one of the many issues vying for attention on the European policy agenda. In order to effectively anticipate and monitor the progress of these policy-making processes, national policy-makers in the individual member states must also time and co-ordinate their own moves. This entails permanent *issue linking* and *package dealing*: success in one area is sometimes set off against failure in another. Sometimes 'winning' on one issue consists of no more than avoiding 'losing' on another, or creating a possible future trade-off.

In practice European decision-making obviously does not follow these stages like clockwork. Sometimes coincidence seems to be the organizing principle, at other times the political clout of one particular actor seems to decide the issue.[28] [29] Easy access to decision-makers is indispensable. But even when policy-making seems to have strayed from rationality, the legislative process remains the institutional guideline for decision-making, simply because it is laid down in the European Treaties. It is important to consider how the margins in this process are utilized by other stakeholders. European decision-making used to be a sort of 'black box', but these days there are many studies available that describe and analyze the forces at work in the decision-making process.[30] [31] Such research has shown that the first stages of the decision-making process are the determining factor. It has been said that some 80 per cent of decisions are settled at the

[26] See figure 2.2

[27] COREPER: French acronym by which the Permanent Representatives Committee is known

[28] Schendelen van, M.P.C.M. et al (2003)

[29] Schendelen van, M.P.C.M. (2002)

[30] Nugent, N. (2003)

[31] Richardson, J. (2001)

COREPER level.[32] There has also been a steady increase in insight regarding the ways in which member states and other actors anticipate and implement European policy.[33]

2.2.2 Actors in the EU Legislative Process

The political agenda is set first and foremost by the European Council and the European Commission. The European Council consists of the heads of government and the ministers of Foreign Affairs. The European Council outlines the main contours of EU policy on important international issues. While it is not an EU institution, it does, to a great extent, determine the political agenda of the EU. As a political body, the European Commission also has many responsibilities and plays an important role in the EU political process because it is the main actor enforcing EU regulations. The Commission is supposed to act on behalf of the EU as a whole. This means that its main task is to harmonize national interests.

The subsequent legislative process involves a number of institutions, namely the European Commission, the Council of Ministers and the European Parliament. Figure 2.2 shows these three legislative institutions and the various organizations and working groups that support them in their tasks.[34]

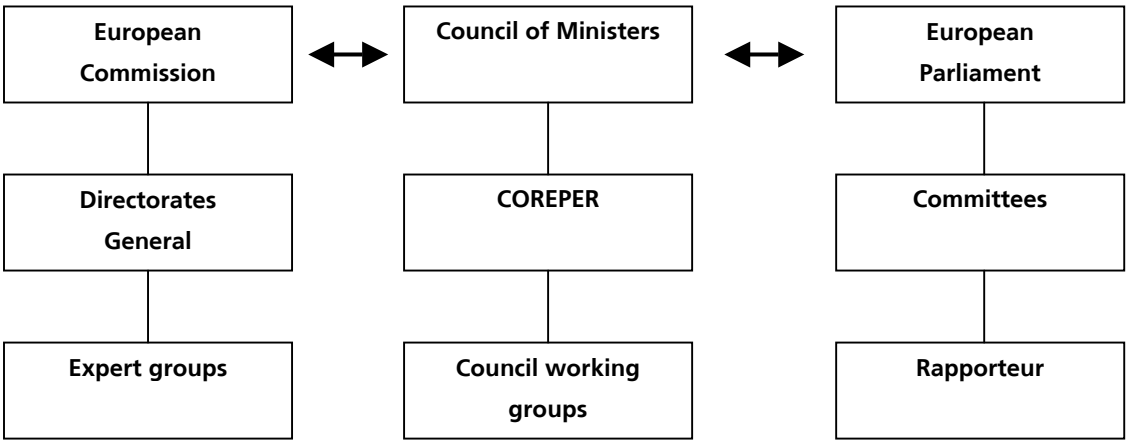

Figure 2.2 EU legislative institutions and their supporting bodies

It is up to the European Commission to initiate policy and regulation. The EC has the exclusive 'right of initiative': the right to draw up a proposal. The Council of Ministers and the European Parliament may request that a particular initiative be taken. No proposal is introduced without prior research and consultation with committees of national civil servants.

Because of its key role in the structure of the European Union, the European Commission maintains special ties with every other EU institution. It cooperates closely with the Council of Ministers and European Parliament in preparing EU regulations. It attends sessions of the Council and Parliament. The Commission President also attends the semi-annual meetings of the European Council.

[32] Raad voor het openbaar bestuur (2004) p. 22.

[33] Raad voor het openbaar bestuur (2004)

[34] Thanks to Sebastiaan Princen, USG June 2005

The Council of Ministers, which consists of the ministers of the member states in any one policy area, is the most important decision-making body in the European Union and has the final say on all legislation. The Council's tasks and decisions are prepared in the COREPER, the Permanent Representatives Committee of the member states. The COREPER is supported by some 250 commissions and working groups.
The European Parliament consists of 732 representatives from the member states. Apart from its advisory function, Parliament has co-decision powers on European regulations in various policy areas. EU legislative power therefore resides with the Council and Parliament. Members of Parliament are also members of one or more Parliamentary Commissions that prepare plenary sessions.

2.2.3 The EU Legislative Process

The European Union has various procedures for developing regulations, depending on the policy area concerned and other factors. Of these procedures, the co-decision procedure is of particular relevance to this study and is therefore discussed in more detail below.[35]

The co-decision procedure for developing instruments of general validity (regulations and directives) has been laid down in Article 251 EC. In practice, the co-decision procedure has become by far the most important procedure. It is also the most relevant to this study since it is applied to directives on the creation of a single market, public health, specific measures to protect consumers, research programmes, the pursuit of the environmental protection objectives referred to in Article 174 EC and the implementation of environmental protection programmes.

The co-decision procedure has created 'equality of arms' between Council and EP. It denies the Council the right to adopt its common position if efforts to reach agreement with Parliament fail. This increases the incentive to reach a compromise in the conciliation procedure as the entire legislative process must otherwise be abandoned. In that case, the maxim is: "no policy is also a policy". The co-decision procedure consists of three readings.[36]

Once a European directive has been fully developed, all member states are bound by it. The directive must then be translated into national regulations.[37] In practice, however, implementation of directives in and by member states sometimes turns out to be a problem. In some cases, member states do not meet the deadline to adopt national regulations in keeping with new EU regulations. If a member state violates a regulation or is late implementing a directive in its national laws, the Commission can start infringement procedures against this member state (Article 226 EC). The Commission often bases its actions on official inspections or complaints from organizations or individuals. In infringement procedures, the Commission issues a member state a substantiated warning and gives the member state the opportunity to respond before a certain date. If the dispute is not settled at that stage, the Commission may institute an action in the European Court of Justice.

[35] European Union, www.eu.int/eur-lex/nl/about/abc/abc_21.html, consulted on November 23, 2004

[36] Nugent (2003), pp. 350-351.

[37] This is different from a European regulation that is directly effective in the member states.

2.3 Animal Testing: Horizontal Laws and Regulations

This section outlines the existing regulations on animal experimentation. This concerns so-called horizontal legislation. At the global level, animal testing has not been regulated explicitly at all. However, there is some global regulation that has a bearing on animal testing; this is described in section 2.4. and 2.5.1 The section below focuses on European and Dutch laws and regulations.

2.3.1 European Animal Testing Legislation

Council of Europe[38]

The Council of Europe's Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes (1985) is based on the premise that humans have a moral obligation to respect all animals and to have due consideration for their capacity for suffering and memory. It aims to limit, and wherever possible, replace the use of animals for experimental and other scientific purposes, by seeking alternatives and encouraging their use.

All the signatories of the Convention were bound to take the necessary steps to give effect to the provisions of the Convention within five years.[39] Parties to the Convention are free to adopt stricter animal protection measures for animal testing in their own country.[40] The remaining articles of the Convention deal with laboratory animal care, accommodation, breeding and handling. The document also requires countries to gather and publish statistical data on animal testing. Every five years the Council of Europe organizes multilateral consultations to examine the application of this Convention. In 1986, a year after the Convention was signed, EU animal testing regulations were enacted.

European Union

There is no legal basis for animal welfare in the European Conventions. On May 1, 1999, the Commission and the member states undertook to comply with the Protocol concerning the protection and welfare of animals (Protocol annexed to the Treaty of Amsterdam). This establishes that in formulating and implementing the EU's agriculture, transport, internal market and research policies, the member states will take the welfare requirements of animals into consideration, while respecting the legislative or administrative provisions and customs of the member states relating in particular to religious rites, cultural traditions and regional heritage. However, the Protocol is not a binding instrument and cannot be enforced. A similar provision is included in Article III-121 of the European Constitution. This article stipulates that any new EU regulations must be checked for compliance with requirements relating to animal welfare.[41]

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[38] The Council of Europe is an intergovernmental organization, founded in 1949, whose aim is to achieve a greater unity between its members, to promote democracy and the constitutional state and to defend human rights. The Council of Europe can make recommendations to member states. These are legally binding for the states that have ratified the Council of Europe Treaties.

[39] Council of Europe (1985), Article 3.

[40] Council of Europe (1985), Article 4

[41] http://www.grondweteuropa.nl/9326000/1f/j9vvgjnazrhmix9/vgoneuhzxou4: consulted on May 11, 2005

http://europa.eu.int/eur-lex/lex/en/treaties/dat/12004V/htm/C2004310EN.01005501.htm, consulted on June 3, 2005

"In formulating and implementing the Union's agriculture, fisheries, transport, internal market, research and technological development and space policies, the Union and the Member States shall, since animals are sentient beings,

The EU has not set any minimum standards for animal welfare. In general, regulation is aimed at minimizing animal suffering and obliging animal owners/caretakers to observe minimum welfare requirements. This means that individual member states may set higher welfare norms.

EU legislation regarding animal welfare is drawn up in close cooperation with the Council of Europe. EU regulations concerning animal testing largely correspond to Council of Europe conventions and the rules set by the Organisation for Economic Cooperation and Development (OECD). For example, the European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes was translated into EU Directive 86/609/EEC.[42] This directive concerns the protection of laboratory animals by ensuring they are properly cared for and not made to suffer unnecessarily. The EU Directorate General for the Environment is responsible for the implementation of this directive.

A remarkable difference between the EU directive and the Council of Europe's Convention is that the former was not inspired by the moral obligation to protect animals, but by the wish to approximate the provisions laid down by law, regulation or administrative provisions in the member states so as to avoid affecting the establishment and functioning of the common market.[43] The aim is clearly to allow the common market to function without distortions of competition or trade barriers. Beyond that, the contents of the directive correspond largely to those of the European Convention. The member states committed themselves to take the measures necessary to comply with this directive by the end of 1989. Once every three years, the member states inform the Commission about the national legal provisions they have adopted in the field covered by the directive and provide statistical data on the use of laboratory animals.[44] Just as in the Council of Europe Convention (Article 6), the member states are required to encourage the development of alternatives to animal testing.[45]
Directive 86/609/EEC also bans unnecessary duplication of experiments. The 'no, unless' principle applies, i.e. no experiments should be duplicated unless a member state deems further testing necessary to protect public health and safety.

2.3.2 Dutch Animal Testing Legislation

The main Dutch legislation regarding animal testing is the Experiments on Animals Act (Wet op de dierproeven; WOD).[46] The first WOD dates from 1977. It was supplemented by the Ministerial Decree on Animal Experimentation in 1985. Since the inception of the Experiments on Animals Act, policy has been aimed at the 3Rs.[47] In 1996, the Experiments on Animals Act was amended to implement European Directive

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pay full regard to the requirements of animal welfare, while respecting the legislative or administrative provisions and customs of Member States relating in particular to religious rites, cultural traditions and regional heritage.".

[42] EC (1986)

[43] EC (1986), Article 1

[44] EC (1986), Articles 25, 26, 13

[45] EC (1986), Article 23

[46] Other regulations targeted more at the actual conducting of experiments on animals, are: Regulations for Conducting Tests under the Experiments on Animals Act, Ministerial Decree on Animal Experimentation, Exemption to the Ban on LD50/LC50 Animal tests, the Animal Tests Regulation, the Exemption to the Ban in Article 11 of the Experiments on Animals Act, Policy for Exemptions to the Experiments on Animals Act, Regulation of Laboratory Animal Housing and Care.

[47] Bordes, E. de and E. Evertsen (2004), pp. 244.

86/609/EEC.[48] The key element of the Act is the licensing system. No animal experiments can be performed without a licence from the Ministry of Health, Welfare and Sport.[49] In granting animal experimentation licences, the Minister is advised by the Central Commission on Animal Testing (Centrale Commissie Dierproeven; CCD). In principle, licences are issued for an unlimited period of time,[50] so licensees are not required to apply for a licence for every single experiment. Recommendations to conduct animal experiments are issued by official Animal Experiments Committees (Dierexperimentencommissies; DECs) to the licensee at a licensed institution.

Since the Experiments on Animals Act took effect, the number of laboratory animals used has been reduced from 1.5 million to 700,000 per year.[51]

The Ministry of Health, Welfare and Sport holds chief responsibility for animal testing policy. Licensees must inform this ministry annually about the number of experiments actually conducted on animals. These data are the input for the annual review published by the Dutch Food and Consumer Product Safety Authority (Voedsel en Waren Autoriteit; VWA).[52]

2.4 Multilateral Agreement: Horizontal Laws and Regulations

Global horizontal legislation pertinent to the use of animal experiments is developed by the Organization for Economic Cooperation and Development (OECD). The OECD produces internationally agreed instruments, decisions and recommendations to promote rules of the game in areas where multilateral agreement is necessary for individual countries to make progress in a globalised economy.
One of the OECD recommendations relevant to this study is the Decision of the Council concerning the Mutual Acceptance of Data in the Assessment of Chemicals 1981 (amended in 1997). This states that OECD member states which comply with the principles of Good Laboratory Practice (GLP) will accept each other's research findings. The OECD Working Group on Good Laboratory Practice developed a guidance document for the application and interpretation of the OECD Principles of GLP to *in vitro* studies with the purpose of to facilitate the proper application and interpretation of the GLP Principles in this area. [53]

This harmonisation prevents duplication of safety testing of chemicals, which is labour intensive and costly. In principle, therefore, the MAD Council Act also has a positive impact on the use of animal testing. Because fewer tests are necessary, fewer animals are used for experimentation. Although many countries have accepted this guideline, it is not legally binding. The European Union also adopted the guideline in 1986[54] and the Netherlands in turn implemented the guideline in the Environmentally Hazardous Substances Act (Wet milieugevaarlijke stoffen). This stipulates that all safety testing of drugs for human and veterinary use must comply with GLP principles.

[48] Ibid., pp. 243.
[49] Ibid., pp. 243
[50] Ibid., pp. 244.
[51] Ibid.
[52] Voedsel en Waren Autoriteit (2002)
[53] OECD (2004)
[54] EC (2004)

GLP was introduced after a study by the US Food and Drug Administration (FDA) showed that laboratory experiments were of poor quality and integrity.[55] In order to increase the quality and reliability of test results and to improve the welfare of laboratory animals, the OECD introduced GLP and GMP (Good Manufacturing Practice). GLP is a set of rules and criteria for an organization to comply with and a list of conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. GLP does not include guidelines detailing when experiments on animals are justified, but it does prescribe how animal tests must be performed and where data must be stored. In addition to the GLP guidelines, there are Good Manufacturing Practice (GMP) guidelines for the production and quality control of pharmaceuticals. Testing and production of veterinary vaccines is also subject to GLP and GMP (for more information on this see Chapter 6).

Currently, GLP instructions are being developed for requesting and reporting on GLP inspections. This is covered by Directive 2004/9/EC and Directive 2004/10/EC. Both directives include provisions (Article 4 and Article 9 respectively) stating that it is desirable to restrict the number of experiments on animals in accordance with Council Directive 86/609/EEC.

The requirements for testing and producing substances included in OECD recommendations often presuppose that the test methods will use laboratory animals. The alternatives are few and far between. One respondent called it "a drop in a bucket". Despite this view, some respondents mentioned that quite a few initiatives have been taken to include alternative test methods in laws and regulations.

Sharing the results of animal testing makes it possible to reduce the number of experiments on animals. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (see also 2.5.1) is a programme of test guidelines that make it possible to exchange test results within the EU and with Australia, Japan and the USA. The European Commission has also taken measures to reduce duplication of tests (Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances, and Council Regulation (EEC) No 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances). Apart from reducing the number of animal tests, there is an added advantage of exchanging test results. It saves both time and costs. It is important, however, to lay down an agreement on sharing test data and costs so as to ensure fair competition.

2.5 Pharmaceuticals: Vertical Laws and Regulations

The pharmaceutical field includes drugs, vaccines, hormones, serums and medicinal devices (implants and equipment). The regulations described below deal with 'registration' (authorization of new drugs) and 'release' (bringing existing drugs onto the market). In the pharmaceutical field, there are pertinent guidelines at different levels (global, European and Dutch). These regulations are widely divergent, which is why global and European harmonization of these guidelines is a priority. In practice such harmonisation is very difficult, however, because views on quality and safety vary widely. The sections below sketch as complete a picture as possible of the existing guidelines.

[55] Jonkman, J.H.G. (1997), pp. 49-56.

2.5.1 Global Regulations Regarding Pharmaceuticals

In 1990, the regulatory authorities responsible for evaluating a new drug before release onto the market[56], in cooperation with the pharmaceutical industry in the EU, the USA and Japan, started a joint project entitled the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[57] Its purpose is to harmonize the various national and international registration requirements so as to reduce the need to duplicate testing. The ICH mainly deals with the registration of new drugs because most new drugs come from these three regions. The requirements are aimed at safeguarding the quality, safety and efficacy of new drugs. The guidelines drawn up by the ICH are subsequently transformed into European and national laws and regulations.

2.5.2 European Pharmaceuticals Legislation

The **European Pharmacopoeia**[58] [59]plays an important role in the development and production of drugs. It is a collection of standardized specifications for researching drugs, ingredients, blood, blood products and vaccines. These so called monographs generally deal with substances used in the preparation of drugs, but may also pertain to (general) quality standards of end products: pharmaceutical, immunobiological and biotechnological drugs. The Council of Europe's Directorate for the Quality of Medicines in Strasbourg is responsible for managing and updating this 'Bible' of the pharmaceutical world. Various delegations from the associated countries keep the Pharmacopoeia up to date. These delegations are comprised of a number of selected national experts who take part in the Pharmacopoeia in their private capacity.

The Netherlands is one of the member states of the European Union that has signed the Convention to develop the European Pharmacopoeia (Ph.Eur.) The Dutch delegation on the European Pharmacopoeia Commission is involved in the decision-making on the development of quality standards (monographs) for human and veterinary drugs. Under the authority of the Health Care Inspectorate, the Centre for Quality of Chemical-Pharmaceutical Products (KCF) acts as the secretariat for the Dutch delegation. The delegation participates in various working groups to draft, revise and test the monographs detailing the descriptions and specifications of methods. Quality standards are elaborated in direct collaboration with the manufacturers involved.

European Union

In the European Union, Directive 2001/83/EC deals with pharmaceuticals. Unlike the directive on animal experimentation, this one falls under the EU Directorate General for Enterprise & Industry. Directive 2001/83/EC clusters and replaces a number of previous directives, including 65/65/EEC and 75/318/EEC. EU Directive 2001/83/EC describes which processes must be completed before a drug is approved. Generally speaking, European regulations regarding pharmaceuticals are not very detailed. The regulatory requirements set forth in the pharmaceuticals regulations do not explicitly refer to animal experimentation.

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[56] These regulatory authorities are the US Food and Drug Administration (FDA); the European Medicines Agency (EMEA) and the Pharmaceuticals Unit of the EU; the Pharmaceuticals and Medical Devices Agency (PMDA) and the Ministry of Health, Labor and Welfare (MHLW) in Japan.

[57] ICH, www.ich.org, consulted on March 28, 2005; June 4, 2005

[58] NIWI, www.niwi.knaw.nl, consulted on June 15, 2004.

[59] RIVM, www.rivm.nl/overrivm/vgz/kcf/farmacopee.jsp, consulted on June 15, 2004. Since June 1, 2005:
http://www.rivm.nl/over-rivm/organisatie/vz/kcf/farmacopee.jsp;
http://www.rivm.nl/en/aboutrivm/organization/vgz/kcf/supporting_upkeep_pharmacopoeia.jsp, consulted on June 5, 2005

These have been laid down in the ICH field standards, which list in concrete detail which tests must be conducted to create an acceptable dossier.

2.5.3 Dutch Pharmaceuticals Legislation

Dutch pharmaceuticals legislation corresponds largely to European regulations. The Drug Provision Act (Wet op de Geneesmiddelenvoorziening) is the relevant Dutch legislation in the field of pharmaceuticals. This act contains provisions detailing which natural or legal persons are licensed to produce and dispense drugs to consumers. It also lists the steps a company must take to register a drug before it may be sold.[60] In addition, the following Dutch laws contain requirements concerning the quality, efficacy and safety of drugs:

- Medicinal devices act (Wet op de medische hulpmiddelen)
- Health act (Gezondheidswet)
- Veterinary drugs act (Diergeneesmiddelenwet)

One respondent indicated that the Netherlands already carries out EU policy and that other EU member states do the same. In short, the ICH guidelines form the basis for EU legislation which is in turn adopted by the individual member states. Therefore, although the ICH guidelines are not legally binding in a formal sense, they do have such a status in practice.

2.6 Conclusions

This chapter has given an overview of the laws and regulations relevant to this study. It has also described the EU legislative process. The section on EU policy-making makes clear that the European legislative process is long and complicated. It involves many different actors who have either a formal or informal opportunity to contribute to policy-shaping and lobby the decision-makers.

The open nature of this process ensures that it is relatively simple to take part in it. 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 does not lend itself to predictions.
At the European level, one can hardly speak of coherent and strong policy-making. It would be better characterized as a patchwork blanket.
Furthermore, this chapter has sketched the problems of harmonizing legislation at the national, European and global levels, as well as between horizontal and vertical legislation.

[60] Franken, W.P.J. (2003.)

Chapter 3

Technical Factors

3.1 Introduction

The next three chapters give an overview of the identified factors which encourage or hinder a reduction of regulatory animal experimentation. The findings have been categorized into three kinds of factors: technical, political/administrative, and social. The results were obtained mainly from respondents and therefore provide insight into the opinions of stakeholders on various themes.

This chapter deals with the more technical and technique-related factors. These have been divided into five themes, namely: expertise, availability of data, validation, costs and other technical factors. For every theme, the interviewees' more widely held opinions are summarized, followed where applicable by specific pharmaceuticals-related aspects within the theme. The chapter ends with a brief overview of the technical factors affecting alternatives to animal testing.

3.2 Expertise

- **The Influence of Experts on Policy-making**
  In the field of safety testing and animal experimentation, politicians and policy-makers are most strongly influenced by the views of experts in the field. Technical expertise is a crucial factor at every stage of the policy-making process. Since the field is complex, only a select few are able to contribute to discussions on the subject. This makes the experts closely involved and very influential in policy-formulation and policy-making. Who these experts are depends greatly on the field in question. The experts most closely involved in the preparation and development of policy are therefore seen by other stakeholders as key figures. The experts are mainly found among regulators, civil servants at the national and European levels and a select group of scientists (in the field of pharmaceuticals and biological substances these include toxicologists, pharmacologists and microbiologists. They are often organised into expert groups. European expert groups consist of technical specialists from the various member states. In turn, these groups provide experts at the global level. Each area of expertise has its own 'forest' of commissions, working groups and advisory committees at the national, European and global levels. The large number of expert groups and the high degree of specialisation make it difficult for outsiders to get a grip on these expert groups.

- **Combination of technical and administrative expertise**

  The 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, according to a respondent at the policy-making level. This respondent suggested that experts who combine technical expertise with political intuition would have the best chance of ensuring that a change is embedded in policy.

  Sauerborn et al.[61] studied why knowledge from scientific research sometimes remains unused, and identified six factors that contribute to this. The first factor they mentioned, that "scientists' lack of knowledge about policy-making", underscores the point made above.

- **in Vivo versus in Vitro**

  The present generation of experts was educated some 20 to 30 years ago when the credo was 'In vivo veritas'. The new generation of experts is leaning increasingly toward in vitro methods. Respondents feel there is a danger that each 'camp' is excluding the other too much. They add that the new generation of scientists/regulators is in danger of making the transition too quickly, thereby throwing the baby out with the bathwater, while the older generation is often too dismissive of in vitro methods. This impedes the use of alternatives. Respondents indicated that a 'stand-alone' situation, of either in vivo or in vitro methods, is neither feasible nor desirable. Most respondents agree that for the time being the best possible scenario is a well-considered combination of both types of testing.

- **Statistical Expertise**

  According to one expert specialized in alternatives to animal experiments, statistics offer great opportunities for developing such alternatives. Mathematical analyses can provide a scientifically sound underpinning for in vitro methods because the tests are easily reproducible. However, regulators lack the ability to interpret these mathematical analyses, according to this respondent. This means they are insufficiently capable of judging alternative methods on their merits.

- **Influence of Research Infrastructure**

  According to several respondents, some scientists tend to adhere to existing test methodology in order to protect their 'return on investment'. This makes research institutions reluctant to disrupt the existing research infrastructure. In the case of animal testing, this impedes the replacement of animal experimentation with alternative methods. Respondents also point out that research institutes wish to keep test methods 'in-house' to keep up with other research institutes.

- **Scientific Consensus**

  A number of respondents believe politicians, policy-makers and regulators are waiting for a scientific consensus before they dare incorporate alternatives into policy. But this consensus is very long in the making, and consequently so are the changes in policy.

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[61] Sauerborn, R. (1999), pp 827-835.

3.3 Availability of Data

- **Accessibility of Data in the Industry**

  The industry is seen as reluctant to make existing research data available because that would harm its competitive position. According to respondents such access to available research data would give a strong boost to alternative methods since many duplications could be avoided.

  As one respondent put it:

  > *There are databases full of information, but these are not accessible because the industry owns them. A lot of the data concerning newly developed methods stays within the walls of the company. And these companies are only willing to share their knowledge when it is no longer commercially relevant.*

  Unlike pharmaceuticals, however, the chemical industry is setting up more and more knowledge-sharing networks, according to one respondent, although even there the data exchanged are not published due to the fear of losing ground to the competition. This respondent suggested a possible solution whereby governments fund the creation of databases with publicly accessible data. Another respondent pointed out that organizations such as the Netherlands Centre for Alternatives to Animal Use (NCA) could fulfil a facilitating role in such a project.

- **Retrospective Analyses**

  Several respondents indicated that retrospective analysis deserves more attention than it currently enjoys. According to respondents, retrospective analyses are a rich source of information and looking back at past experiments will teach valuable lessons. The data needed for such analyses is mainly in the hands of the industry. These are the same data that are submitted to the regulators. Another respondent argued that by putting the data acquired during the earlier stage of fundamental research to better use, the number of experiments on animals could be reduced significantly.

  However, respondents feel that the industry is not very motivated to cooperate in such efforts. One reason for this is a reluctance to make data available. One respondent mentioned that initiatives have been taken in the USA to set up databases in cooperation with the pharmaceutical industry, but there, too, the industry remains reluctant to publish its data.

  Another reason retrospective analysis is still insufficiently looked at is that long-term research that is not guaranteed to pay off. Therefore, there is no funding for such initiatives. An additional obstacle identified by this respondent is that scientists question the scientific basis of such analyses, often branding them as lacking in innovation.

  Respondents indicated that the EC's Directorate General for Research could play an important initiating role in this area, by allocating more funds to retrospective analyses and emphasizing their importance.

- **Measuring the Effectiveness of Animal Tests**

  Various respondents said the debate on animal experimentation has so far paid too little attention to quality measurement.

  In Germany, there is a trend towards effectiveness reporting, which evaluates whether an animal experiment has lived up to the researchers' expectations. In this approach, results from clinical practice play a much larger role in the planning of new experiments on animals.

  According to a number of respondents, science must also continue to evaluate the validity of extrapolations from the results of animal experiments to human beings. The British Union for the Abolition of Vivisection (BUAV) has published several reports on this subject.[62]

- **Mutual Acceptance of Data**

  Mutual Acceptance of Data (MAD) ensures that much research is not needlessly duplicated. Therefore, it is of great importance to develop a Mutual Recognition Agreement, or MRA (see also Chapter 6, case study). Some respondents pointed to one of the disadvantages of such an agreement, saying that with every research project, the researchers' flexibility would further decrease. This pinpoints one of the reasons why developing an MRA is such a laborious process. Many countries want to keep their own research structure intact. An MRA could jeopardize this because it would mean that most tests would only have to be performed in one country. As one respondent put it:

  > *There are countries where people are in favour of alternatives and other countries that couldn't care less. That's why this should be enforced via international agreements, the way MAD is used within the OECD.*

- **Publicizing Developments in the Area of Alternatives**

  A few respondents noted that scientific developments implementing the 3Rs are inadequately publicized and explained to the public. The articles that are published tend to end up in third-rate journals, according to one respondent, while in fact the results should be widely publicized to encourage implementation of the 3Rs. In listing the reasons why scientific knowledge is underused, Sauerborn et al. [63] mentioned the poor communication of results to stakeholders.

  Sauerborn et al. also state that research data are often of no use to stakeholders and that researchers lack the networks necessary to connect with stakeholders.

  As a consequence, knowledge about alternatives is insufficiently taken into account by policy-makers.

3.4 Validation of Alternative Methods

- **Validation Process**

  The European Centre for the Validation of Alternative Methods (ECVAM) optimises, standardises and validates alternative methods, while the OECD develops test guidelines. However, formal,

[62] Langley, G. (2004)

[63] Sauerborn, R., S. et al (1999): pp. 827-835.

external validation currently also takes place in some EU member states, the US and to minor extent within the OECD. Various stakeholders call validation a difficult process dominated by a number of big players intent on defending their own territory. This regularly leads to disagreements about the validity of test methods. Every country is convinced its own tests are superior to those of other countries, according to one respondent. Therefore, all countries want to take part in the validation process. The scientific prestige of the various countries is often a key factor here. Validation of alternative methods has therefore become a process that takes years.

- **Validation versus Acceptance**

  When a method has been validated does not yet mean that regulatory authorities will actually accept it. One respondent said alternative methods must be proven three times over to be just as safe, sensitive and specific as 'regular' methods before they are accepted in legislation.

  Therefore, a distinction can be drawn between validated and valid tests. As one respondent put it:

  Even if a test has been validated for the EU, a multinational will still have problems in Japan and the United States. This is because the European results are not automatically accepted in the rest of the world.

Although there is still a long way to go in the development and implementation of alternative test methods, the 3Rs have made significant inroads in the past few years. The number of alternative tests developed and accepted has risen sharply in the recent past.[64] One example of this was the EU's acceptance of three alternative test methods to evaluate possibly corrosive or phototoxic substances. Another important step in implementing the 3Rs was the OECD's December 2000 decision to gradually ban the infamous LD50 test.[65] The reason for this was the acceptance of three test models that required fewer laboratory animals and greatly reduced their suffering.[66]

The fact that an alternative method is only widely accepted if it is included in OECD guidelines is an extra impediment to reducing the number of animal tests. The fact is, the process of inclusion in an OECD guideline is even more time-consuming than the same process at EU level.

3.5 Costs

- **Costing Research by Numbers of Animal Tests**

  Policy-makers do not sufficiently take into account how many animal experiments their new policy will require, according to a number of respondents.

  Respondents would like the development of new policies - such as REACH (Registration, Evaluation and Authorisation of Chemicals) and SCALE (the EU strategy for the environment and health) - to include an assessment of not only the financial cost, but also of the numbers of laboratory animals needed to implement them. Several respondents see this as a possible stimulus for the use of

[64] ECVAM (2002)

[65] Lethal Dose 50. The LD50 value is the quantity of a solid or liquid substance that kills 50% of the laboratory animals (e.g. mice or rats) in one dose

[66] NCA, http://www.nca-nl.org/, consulted on June 22, 2005

alternative methods. However, one respondent noted that a number of impact studies are already available but have so far done little to reduce regulatory animal testing. Again, it seems that factors such as risk minimization dominate the issue.

- **Economic Impact of Alternatives**

  Animal experimentation is expensive. Conducting experiments is costly, and so are animal accommodation and care. Making these costs visible and comparing them to possible alternatives may encourage the use of alternatives.[67] Industry is eager to use existing alternatives if they are cost efficient. Respondents indicated that *in vitro* methods are already being widely applied in the developmental stage to trace new active ingredients. Respondents believe that cost reduction has great potential as an incentive.

- **Time Factor**

  Policy-makers and government institutions are increasingly raising objections to the length of time it takes to evaluate substances.[68] This is partly due to legal and administrative procedures, but mostly to the time-consuming nature of conducting animal experiments required by protocol.

Pharmaceuticals

Respondents made the following observations about costs in the field of pharmaceuticals:

- **The Pharmaceutical Industry and in Vitro Models**

  The pharmaceutical industry is constantly on the look-out for new active ingredients for drugs. In order to find one active ingredient, enormous numbers of substances must be screened for possible effectiveness first. Therefore, there is a clear need for inexpensive and fast screening methods. In this highly profitable business, the development of *in vitro* tests for the R&D stage is relatively inexpensive compared to the total cost of developing a new drug, respondents from the industry stated. Therefore, the industry often initiates the development of alternative methods.

  In the developmental stage, the pharmaceutical industry is highly motivated (for economic reasons) to develop *in vitro* methods. But for registration and release of a drug, tests on the entire organism - *in vivo* models - remain necessary.

3.6 Other Technical Factors

- **Technical Limits to Alternatives**

  Most respondents agree that the relatively easy work has been done when it comes to replacing animal experiments. By far the majority of animals is used for more complex experiments that are difficult to replace. For example, large numbers of animals are needed for tests in reproductive toxicology (embrotoxicity) and toxicology, while there are few opportunities to entirely replace such tests. At the same time, respondents indicate that much progress has been made in reducing

[67] One respondent qualified this by indicating that alternative methods are sometimes more expensive than animal testing.

[68] Gezondheidsraad (2001), pp. 21.

the use of animals and in refining methods for complex end points such as acute toxicity, some vaccine tests and pyrogen testing. So when it comes to the more complex experiments, Reduction and Refinement seem to offer the best prospects.

- **Strategic Test Approaches**

  A number of respondents indicated that strategic test approaches are so far used only sparingly. These approaches -- the step-by-step approach in toxicity tests and the consistency approach used for organic products -- offer a chance to reduce the number of animal tests.[69] Respondents gave examples, such as the decision to cancel subsequent in vivo tests if in vitro tests prove a substance to be toxic. Currently, such animal experiments are often carried out regardless of earlier results. The Dutch Health Council has published recommendations about this issue to reduce the number of unnecessary experiments.[70]

3.7 Conclusions

Below follows a list of the most important findings per theme:

Expertise

- A select number of experts have great influence on policy-making.
- Lack of transparency due to multitude of expert groups.
- Technical expertise combined with political expertise and intuition creates a better chance to effectively exert influence.
- Combining in vivo and in vitro methods remains necessary.
- Some regulators are unable to appreciate alternative test models due to a lack of statistical expertise.
- Experts have a self-interest in maintaining their scientific status. This is one of the reasons why a scientific consensus is elusive.

Availability of Data

- Inaccessibility of data owned by the industry leads to duplications of experiments.
- The effectiveness of animal tests is not measured often enough.
- As yet, not enough retrospective analyses are done, allowing valuable information to be lost.
- MAD has a potential impact on reducing the number of animal tests. However, developing an MRA is difficult.
- Developments in the area of the 3Rs are insufficiently or too narrowly publicized.

Validation

- Validation does not guarantee acceptance.

[69] Gezondheidsraad, (2001)

[70] Ibid.

Costs

- Calculating the costs of policy is generally not expressed in terms of the number of animal experiments it will 'cost'.
- The time-consuming nature of animal tests required by protocol.

Other Technical Factors

- The more simple health effects in the area of alternative methods have already been addressed. The challenge is to find alternatives for complex tests.
- Strategic test approach is still insufficiently applied.

Chapter 4

Political and Administrative Factors

4.1 Introduction

This chapter divides the relevant political and administrative factors into three categories: regulatory requirements, the political agenda and lobby groups. This is followed by a summary of the respondents' more widely shared opinions and, where applicable, any specific pharmaceuticals-related aspects. In Section 4.6, this chapter concludes with an overview of the political and administrative factors that influence the use of alternatives to animal testing.

4.2 Regulatory Requirements

Regulatory animal testing refers to animal experiments carried out to meet the regulatory requirements prescribing which experiments must be conducted in order to register and release a substance or product onto the market.[71]
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 or animals.[72]

Several stakeholders identified these regulatory requirements as a significant obstacle to the use of alternatives. The next subsection describes the factors responsible for this.

- **The Influence of Regulators**
  According to respondents, regulators at the national, European and global levels are usually reluctant to include alternative methods in registration procedures. There are various reasons for this (see also sections 5.3 on risk acceptance and 5.4 on attitude).

  In a general sense, new policy ideas often meet resistance from those who bear the responsibility for policy. After all, new ideas are to some extent risky, while no one can guarantee that they can

[71] Bosch, J. E. van den, Met het oog op wettelijk verplicht dierexperimenteel onderzoek, May 2000.

[72] Leeuw, W. de, "De ethische toetsing van dierproeven: wat heeft Europa ons te bieden", in: DEC's in discussie: de beoordeling van dierproeven in Nederland, J.Swart, J. Wolters and H. Zwart (eds.), Uitgeverij Damon, Budel 2004, p. 148

be successfully implemented.[73] Hence, any cost/benefit assessment usually favours an existing policy rather than a new one. New policy is often seen as a potential liability. This point is illustrated by a civil servant's comment on policy changes:

> *It's better not to change ten times, than to make nine changes for the better and one for the worse*.[74]

Many respondents observed that regulators have cause to be conservative. They bear the heavy responsibility of keeping risks to a minimum. This is especially true when it comes to the registration of substances and products that pose potential health or environmental risks.

Still, the reluctance of policy-makers and decision-makers to incorporate alternatives seems to result from a combination of factors such as attitude, knowledge and risk acceptance. Each of these three factors is discussed separately in this chapter.

It should be noted that the various regulatory agencies widely differ in their willingness to consider alternative methods. The Japanese agencies, for instance, are seen as very conservative authorities who take a so-called tick-box approach[75], while British, Dutch and German agencies are said to have a relatively open attitude towards alternative methods. Respondents indicated that these differences are due to the same combination of factors, in which cultural differences, the degree of risk acceptance and public opinion appear to play an important role.

- **The Influence of Directive 86/609/EEC**

  Directive 86/609/EEC regarding the protection of laboratory animals applies the 'no, unless' principle. This directive stipulates that alternatives, if available, should be used. However, the directive does not explicitly mention the 3Rs concept. Ideally, Directive 86/609 should be taken into consideration when decisions are made about the use of regulatory animal testing, but respondents indicated that other forces dictate which test methods are given preference and that Directive 86/609 has little weight. The industry is guided by registration procedures, for example. Although the directive states that everything possible should be done to limit the number of experiments on animals, it also leaves room for member states to duplicate tests to protect the safety of their citizens. Directive 86/609 does not forbid such duplication (see also Chapter 6: Case study).

  Furthermore, animal welfare is beyond the competence of the EU; it is the responsibility of individual member states. Respondents expressed doubt that the EU would assume authority over this issue in the future, because the member states do not see any need to do so. Member states prefer to keep the issue under their own control.

[73] Hart, P. ´t, A. Wille et al., Politiek ambtelijke verhoudingen in beweging, Boom Amsterdam, 2002, p. 181.

[74] Ibid., p. 181

[75] This refers to the evaluation of a dossier in a manner that disregards the quality of the data, focusing instead on a checklist and ticking off whether all regulatory tests have been conducted.

- **The Importance of Ethical Reviews**

  Directive 86/609 also does not require ethical reviews of proposed animal tests. Although there is no such requirement under current EU legislation, practically all western European countries have procedures for an ethical review of a proposed animal test. However, the member states vary widely in terms of the composition and tasks of their review committees, the status of their committees' findings and the levels at which tests are reviewed.[76]

  Ethical review committees (in the Netherlands these are called Animal Experiments Committees (Dierexperimentencommissies; DECs)) usually have limited room to manoeuvre when it comes to regulatory animal testing.

  Reviews are usually marginal and the committees have little or no means of putting conditions on the design and conduct of tests.[77] In such cases, it is felt that ethical review committees should raise the alarm. Referring to the Dutch context, Swart et al. stated:

  > *That means that the DECs will have to be loud and clear when they believe that certain regulatory tests are outdated and could be replaced or modified. Even when there are alternatives, there is often a long way to go before the regulatory agencies accept these. The more experts and organizations support them, the greater the chances of success. DECs and researchers can definitely play an important role in this.*[78]

- **Cooperation Between Various Policy-makers**

  There is too little cooperation between the EU committees that draft 'safety regulations' and those that develop 'animal welfare regulations'.[79] As a result, when directives are revised, they continue to include requirements for animal tests even after alternatives have been introduced. The following is an example:

  > *A revised food safety directive requires that member states must annually test four times as many shellfish intended for human consumption for the presence of certain toxins. These tests are performed on mice and may cause a great deal of distress. Experts point out that there are alternatives to tests on mice. Directive 86/609 states that such alternatives have to be implemented.*[80]

  There are no traffic regulations indicating which directive has priority in case of conflicting directives.[81] [82]

- **The Impact of the EU Cosmetics Directive and REACH**

  Respondents agree that the revised Cosmetics Directive (2003/15/EC amending Directive 76/768/EEC) has boosted implementation of the 3Rs. This has forced various actors in science, the

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[76] Swart J. et al. (2004), pp. 146.

[77] Ibid., p. 149

[78] Ibid..

[79] Ibid.

[80] Ibid., p. 148.

[81] Ibid.

[82] Chapter 6 of this report (the case study) mentions the option of asking the European court to decide on how the directives should be prioritized.

industry and policy-making to consider ways of replacing experiments on animals. According to several respondents, REACH has had the same effect. It forces actors to think about alternative methods to test chemicals.

Pharmaceuticals

Respondents made the following observations regarding regulatory testing in the field of pharmaceuticals.

- **The Influence of the ICH**

  Europe plays only a modest role in the pharmaceutical industry and this is even more true of individual member states. The main regulatory framework in pharmaceuticals is the global ICH system of guidelines (see Chapter 2).

  The 3Rs will only begin to play a role in the registration and release procedures for pharmaceuticals if they are included in the ICH guidelines, respondents stated. To achieve this, a scientific consensus would have to be reached first. Then there would have to be an administrative consensus within the ICH. It is here that most resistance can be expected (see 3.2). Respondents name Japan as the most conservative player in this field. The ICH is structured like a giant pyramid. Every guideline and every topic has its own expert working group that includes both industry and policy representatives from all three regions (USA, Japan and EU). The Dutch government can influence ICH decisions through the CHMP (EMEA) in London which includes representatives from all EU member states. Influence can also be exerted via the pharmaceutical committee of the European Commission, in which every EU member state has two representatives. In addition, different EU member states represent the EU in various ICH working groups. These representatives often hold key positions and are therefore of great interest to various stakeholders.

- **The Importance of Harmonization**

  Harmonization of legislation tends to have a positive effect on limiting animal tests, respondents stated. In the pharmaceuticals field, harmonization is the responsibility of the ICH. According to one respondent from the pharmaceuticals industry, the ICH is indeed working on harmonization, but so far it has had only marginal success. The respondent stated that all the stakeholders are willing to harmonize, but only if their own standards are accepted as the norm.
  Therefore, harmonization is a difficult process, dominated by cultural differences and competition, both scientific and economic.

- **The Implementation of EU Pharmaceuticals Legislation in Member States**

  The provisions in EU Directive 2001/83 are so broadly formulated that national regulatory authorities have ample room for interpretation. Responsibility for risk assessment is left to the individual member states. EU pharmaceuticals legislation leaves the member states room for their own interpretation. This means that one regulatory agency may attach greater importance to some issues than another. Respondents named Ireland and Sweden as examples of more conservative authorities.

4.3 Political Agenda

- **Animal Welfare's Place on the Political Agenda**

  The EU concerns itself first and foremost with the internal market.

  Other issues near the top of the agenda are safety and risk limitation. Animal welfare has lower priority. Ethics comes into play only if safety is guaranteed and there is no significant effect on the market, various respondents stated. This also means that the government and industry make available limited budgets for developing alternatives. The Dutch Ministry of Health, Welfare and Sport recently halved the budget for alternative methods, according to one respondent. This cut was the result of a policy change that assigned higher priority to other issues, in this case the health care sector which is high on the public and the political agenda.

  In the struggle for scarce resources such as time and money, animal welfare usually loses. Members of parliament never have enough time, according to one respondent from politics. There are too many meetings for one person to attend, so choices have to be made. However, the European Parliament is currently very keen on alternatives to animal testing, according to several respondents. They ascribe this to the recent revision of the Cosmetics Directive and the debate surrounding REACH.[83] This has raised awareness of the 3Rs. Many respondents said that European politicians and national governments are sometimes inconsistent in their views. They want maximum safety and at the same time as little animal testing as possible.

- **The Influence of Current Affairs and Personal Commitment on Political Agenda**

  Politicians are mainly drawn to issues on which they can score politically, respondents say. This can have both positive and negative effects on implementation of the 3Rs. When animal testing is in the public eye, politicians usually sit up and take notice too. But when product safety is a hot topic, animal welfare tends to get snowed under. One respondent from politics mentioned that politicians' personal interests also play an important role. For example, the Intergroup on animal welfare consists of members of the European Parliament (MEPs) who have an interest in animal welfare. Membership is based on personal commitment to the issue. As one respondent noted, its composition generally reflects the cultural differences in Europe regarding animal testing and the political and social prioritization of animal testing in the various member states. Thus, the Intergroup has a high percentage of UK and Dutch members. Germany is also fairly well represented, but the southern member states have fewer representatives.

  According to one respondent, MEPs tend to identify with the interests of the sector they are part of. MEPs on the Committee on Industry, Research and Energy set greater store by industrial interests, while MEPs on the Committee on the Environment, Public Health and Food Safety put environmental issues first. Conversely, parliamentarians normally do not end up on a particular committee by accident. Their membership is linked to their background and personal affinities. These factors combine to create a fixed division of roles within a commission. According to one

[83] On 29 October 2003, the Commission adopted a proposal for a new EU regulatory framework for chemicals. The proposed new system is called REACH (Registration, Evaluation and Authorisation of CHemicals), www.europa.eu.int/comm/environment/chemicals/reach.htm, consulted on April 13, 2005.

respondent, commission members often know who will take what position before a meeting even starts. This depends on personal and sectorial interests as much as political leanings.

- **The Political Agenda's Impact on Regulatory Testing**

  Respondents said it would be ideal if the need for animal testing was determined mainly by experts in the field. In reality the need to test is primarily a political decision based only to a limited extent on scientific grounds. One example of this is the re-testing of vaccines produced and tested in the USA. Various member states require these vaccines to be re-tested when they enter the EU (see also the case study in Chapter 6). There is no scientific reason for this, but the law offers member states the opportunity to re-test where it is felt to be necessary for public health protection. Respondents have different theories as to why re-testing is often demanded. The most commonly mentioned are risk minimization and protectionism (protecting a state's own market and test structure).

- **Politicians' Expertise on Animal Testing and Alternatives**

  Several respondents pointed out that politicians know too little about animal testing and alternatives. This makes them very dependent on the expertise of external specialists. Because of their lack of insight they are also easily swayed, which often leads to inconsistent opinions about animal welfare, according to respondents. Some respondents cited examples of politicians who advocate both a reduction of animal testing and an increase in research to enhance food safety. It seems many politicians do not understand that such research would require extensive animal testing, various respondents stated.

  One expert in alternative test methods said it was practically impossible for politicians to judge the merits of animal and alternative testing. On the one hand, this explains why politicians sometimes expect too much from alternatives, for example in the case of the 7th amendment of the Cosmetics directive which aims to replace all animal testing within 10 years. Experts from various backgrounds have called this scientifically unrealistic. On the other hand, politicians have underestimated the potential of alternative test methods in several cases.

  Two factors that inhibit the consideration of alternative options are: research data that are indecipherable to stakeholders and researchers' inability to clearly convey results to stakeholders.[84]

[84] Sauerborn R., S. Nitayarumphong and A. Gerhardus (1999): 827-835. Sauerborn et al. distinguished six factors that contribute to knowledge from scientific research remaining unused:

1. lack of knowledge on the part of the researchers about the policy-making process;
2. lack of 'ownership' of the research agenda on the part of the main stakeholders;
3. unsuitability of research data for the stakeholders;
4. poor communication of the results to the stakeholders;
5. inadequate network between researchers and stakeholders to connect;
6. researchers perceived to play too limited a role

4.4 Lobbying

On this subject, the report focuses mainly on the impact of lobbying at the European level.

- **The Impact of Animal Welfare Lobbyists**

  In the past, animal welfare organizations have proven very capable of mobilizing politicians and the public, resulting in the Cosmetics directive for example. However, respondents did point out that they are most successful in areas where the ethical debate is relatively unambiguous.

  The animal welfare lobbyists seem to focus on the agenda-setting stage and the beginning of the policy-making stage. They target their message mainly at politicians and policy-makers. The same goes for the Eurogroup for Animal Welfare, which primarily lobbies EU politicians. For example, the Eurogroup acts as the secretariat for the European Parliament's Intergroup on the Welfare and Conservation of Animals and is therefore close to the relevant members of the European Parliament. This is a structural opportunity to lobby and influence politicians on animal welfare.

  According to respondents, the Eurogroup has the great advantage that it understands legal procedures and knows the ropes in Brussels. In the area of expertise, however, the Eurogroup cannot keep pace with the intensive industrial lobby, various respondents stated. This is because the Eurogroup has only a fraction of the personnel and budget that the industry has at its disposal.

  Respondents indicated that animal welfare NGOs have little impact on regulators (policy implementation), in both the European and Dutch contexts. Their ability to raise the alarm in the implementation stage, when national authorities are interpreting regulatory requirements, has so far been limited.
  A number of respondents stated that animal welfare organizations are professionalizing. One example cited is that observers from animal welfare organizations have been attending OECD meetings, bringing them close to the actual decision-making process. However, animal welfare organizations still lack funds and an internationally coherent approach.

  Several respondents also indicated that the animal rights movement does not do the image of the animal welfare organizations any good. As one respondent put it:

  You should not underestimate the resistance politicians in the European Parliament feel towards animal lobbyists. They lump all these organizations together. Therefore, animal protection organizations do not have a good reputation in all quarters. They are seen as pushy and violent in their campaigns. These give the organizations a bad name.

  One respondent stated that the influence of Dutch animal welfare organizations seems to have decreased in recent years. He ascribes this partly to a decrease in public concern for animal welfare issues, and partly to the declining effectiveness of animal welfare organizations.

- **The Impact of Industry Lobbyists**

  Respondents referred frequently to the strong and well-organized industry lobbyists in Brussels. Respondents characterized them as primarily profit driven. In other words, they lobby for

legislation that gives the industry as much freedom as possible to do business, and for regulations that minimize the costs of regulatory testing. Respondents frequently mentioned the large-scale industrial lobby to influence REACH.[85] They acknowledged that the industry, in this case, has a positive effect on the 3Rs because it has no interest in regulations that increase the number of required tests any further. In this context, the industry and animal welfare organizations are allies.

Industrial lobbyists seem to be most active in the policy-making stage, according to a few respondents, but their presence is felt in other stages too. The industrial lobby is active at all policy levels: national, European and global.

Pharmaceuticals

Respondents made the following observations about lobbying in the field of pharmaceuticals:

- **The Impact of Pharmaceutical Industry Lobbyists**

  As mentioned earlier, industry in general has a strong lobbying apparatus in Brussels. This is especially true of the pharmaceuticals industry. The European Federation of Pharmaceutical Industries and Associations (EFPIA) is believed to lobby very actively in Brussels and in the ICH with the aim of harmonizing legislation. One respondent from the pharmaceuticals industry pointed out that the EFPIA hardly lobbies at all for alternative test methods.

  Respondents remarked that EFPIA has a clear say in the policy-making process at the European and global levels when test protocols are drafted. This influence is due to the pharmaceuticals industry's abundant experimental expertise, budget and manpower.

- **The NGO Lobby in Pharmaceuticals**

  So far, animal welfare organizations have kept relatively quiet about the more complex issues, for example animal testing for drug safety. This is because the ethics of the debate are complicated, respondents say.

  Patient organizations do not directly lobby in favour of animal testing. However, they do lobby for more research to develop new treatments, which could lead to more animal experiments. One respondent observed that patient organizations do lobby directly in several countries where the anti-animal testing movement is relatively active, to ensure that all research options including animal testing remain on the table and open to development.

4.5 Conclusions

The most important findings per theme are listed below.

[85] On 29 October 2003, the Commission adopted a proposal for a new EU regulatory framework for chemicals. The proposed new system is called REACH (Registration, Evaluation and Authorisation of CHemicals), europa.eu.int/comm/environment/chemicals/reach.htm; consulted on April 13, 2005.

Regulatory Requirements

- Regulators have a curbing effect; new policy is often seen as a potential liability. Regulators are conservative because of the heavy responsibility they bear.
- In pharmaceuticals, member states are given relatively great discretion to interpret European directives within the limits of national law. Therefore, there are great differences between EU member states and the extent to which they are open to alternatives.
- Harmonization is an important boost, but an onerous process.
- Directive 86/609 has less of an impact than other regulatory requirements. Other legislation and regulations are supposed to take 86/609 into account, but as yet this is often done insufficiently or not at all.
- At the European level, policy-makers in different areas do not cooperate enough. For example, there is a lack of cooperation between the various committees involved in drafting separate regulations. This is why different directives can, and often do, conflict.
- There is no European requirement to evaluate animal testing policy or conduct an ethical review of animal tests, even though this can raise awareness of careful use of animal testing and the existence of alternatives that meet regulatory requirements.
- The industry tends to play safe and anticipate strict registration requirements from regulatory agencies in the USA, Japan and elsewhere. This often leads the industry to conduct more animal experiments than strictly necessary.
- In the R&D stage, the industry has much more freedom than in the registration and release stages. Alternative test methods are commonly used in this stage to minimize costs. Ultimately, this may also positively affect the development and acceptance of alternatives for use in registration and safety evaluations.
- There are few opportunities for the use of alternatives in the registration and release procedures. Minimizing risk is the main priority. This makes it difficult to get alternatives included in this stage.
- REACH and the Cosmetics directive have encouraged consideration and implementation of the 3Rs in regulatory requirements.

Political Agenda

- Animal welfare ranks lower on the political agenda than issues such as public health and safety.
- Growing concern about food safety will increase the number of animal experiments.
- Politicians' personal affinities and interests affect the political agenda.
- Politicians' limited knowledge of alternatives is an obstacle.
- Politicians are 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 on alternatives.

Lobbying

- Animal welfare organizations constitute an important actor in the struggle to get the 3Rs on the political agenda and keep them there.
- Global animal welfare lobbying requires further professionalization and coordination.
- Unlike the industry, animal welfare organizations have very limited means at their disposal for lobbying.
- Animal welfare organizations play only a limited role in the pharmaceuticals field.

- In order to influence the political agenda, the content and form of the lobby should be well geared towards politicians' interests.
- The strong industry lobby is basically driven by economic factors. In the best scenario, cost efficiency and reducing animal testing converge.

Chapter 5

Social Factors

5.1 Introduction

This chapter divides the social factors influencing regulatory animal testing into three categories, namely public opinion, risk acceptance and attitude. As in Chapters 3 and 4, this chapter provides a review of the more widely shared findings and, where applicable, any specific pharmaceuticals-related aspects. The conclusion, Section 5.5, gives an overview of the social factors that influence the replacement, reduction or refinement of regulatory animal experiments.

5.2 Public Opinion

- **Public Opinion on Animal Testing**
  An opinion poll commissioned by the Dutch Society for the Protection of Animals (Dierenbescherming) and conducted by Intomart GfK in March 2004 showed that 67% of the Dutch population rejected animal testing - regardless of its purpose - if this causes animals serious suffering. Approximately 60% felt that scientists generally should not conduct experiments on living creatures. Just over 50% felt that animal experimentation should be cut back, even if this meant that people would have to sacrifice a number of advantages.[86] [87]

- **The Impact of Public Opinion on Other Sectors**
  If the public has a strong opinion on a relatively high priority issue, then public opinion is very influential. The opinion poll cited above reveals rather strong public resistance to animal testing. However, animal testing has lower priority than issues such as health, safety and risk minimization. The appeal for less animal testing is drowned out by the louder call for safer products.

  Politics, industry and even regulators are very sensitive to public opinion. As one respondent put it:

  If you can mobilize public opinion, you can influence all those stakeholders.

[86] Intomart GfK, Publieke opinie over dierproeven in Nederland, Hilversum 2004.

[87] It should be noted that this Intomart opinion poll was criticized for being very biased.

With the current trend to minimize risk, none of the parties is willing to take risks in favour of the 3Rs. If the call to reduce animal testing grew louder, this would certainly have a positive effect on readiness to consider and develop alternatives, according to the respondents.

- **Actors Influencing Public Opinion**
  In the present mediacracy, public opinion is strongly affected by the media. Respondents observed that NGOs such as animal welfare organizations have in the past proven particularly effective at swaying public opinion, often using the same media. One important precondition to mobilize the public on the animal testing issue is the availability of data proving the effectiveness of alternative test methods.

- **Alternatives and Corporate Social Responsibility**
  Industry maintains it has little influence on public opinion due to deep-seated public suspicion of the information it provides. However, companies do wish to convey a positive image of themselves and their products. This is why many of them actively promote Corporate Social Responsibility (CSR). Respondents indicated that actively encouraging alternatives would be one way of improving their image in the public eye.

Pharmaceuticals

Respondents made the following observations about public opinion regarding pharmaceuticals.

- **Public Opinion on Animal Testing for Medical Purposes**
  Intomart's opinion poll showed that a large segment of the population finds animal testing for medical purposes acceptable under certain condition.[88] Despite this, even the pharmaceutical industry finds animal testing a delicate matter, contended some respondents.

  One respondent from the pharmaceutical industry had this to say on the public's critical attitude towards animal testing:

  > *It forces us to continually re-evaluate animal testing's purpose and necessity. The public accepts the fact that you have to use animals to test drugs on, I think. But it does not accept it if you do too many tests or do them in a careless manner.*

5.3 Risk Acceptance

- **The Effect of Risk Minimization**
  Today's society is obsessed with consumer safety, respondents indicated. Risks must be limited as much as possible, so many regulations are aimed at minimizing health risks. Politics is also very focused on safety and risk minimization. This is an important obstacle to the use of alternatives for animal testing, according to the respondents. Every new product is subjected to an exhaustive test regime. The regulators, in their effort to minimize risks, become reluctant to include alternatives to

[88] Intomart GfK, Publieke opinie over dierproeven in Nederland, Hilversum 2004.

animal testing. Respondents indicated that much would be gained if society accepted a more realistic degree of risk. Politicians play a key role in this. After all, they decide what level of risk is legally acceptable. Politicians' attitudes are in turn strongly affected by public sentiment. This type of risk avoidance is detrimental to the acceptance of alternative test models.

- **The Influence of the Precautionary Principle**
  Various respondents expressed concern about environmental groups and other organizations which have put the potential dangers of chemicals high on the REACH agenda. Applying the precautionary principle, they demand research to determine whether substances are harmful to humans and the environment. However, such research is performed largely on laboratory animals, which means the number of animal tests increases. In this respect, respondents would like the organizations to accept a more realistic risk level and to consider the consequences of their demands in terms of the number of animal tests required.

- **The Importance of Risk Communication**
  Respondents indicated a need to consider risk management and risk communication. First of all, they said, it is necessary to clearly convey the message that zero risk is impossible. Secondly, open communication about potential risks may foster a sense of freedom of choice. This is precisely the sense that seems to determine how much risk individuals are willing to accept (comparable to the risk that people voluntarily take when they decide to smoke or drive a car).[89]

Pharmaceuticals

Respondents made the following observations about risk acceptance concerning pharmaceuticals:

- **Cost/Benefit Assessment Involving Medications**
  Respondents frequently remarked that the assessment of acceptable risk versus product benefit is different for medications than for other products. The assessment can go both ways. On the one hand, fewer risks are accepted because the products are intended for already vulnerable patients. This is even more pronounced when it comes to children's medications. On the other hand, greater risks are accepted for drugs that treat more serious diseases. In that case, it is felt that the end justifies the means.

5.4 Attitude

- **The Attitude of Regulators**
  (see also 3.2: Regulatory Requirements and 5.3: Risk Acceptance)
  Regulators have a particularly strong influence in the policy implementation stage. Their attitude towards alternatives to animal testing is characterized as reluctant. Respondents expressed a degree of understanding for this reluctance. Regulators operate with the objective of risk minimization and therefore maintain large safety margins.
  As one respondent from industry put it:

[89] Presentation by B. Garthoff, Ecopa workshop, November 27, 2004.

The aim is to protect the consumer. And that is right, that is what those authorities are there for. And I understand very well why they work this way and do not take our documentation at face value. They are very careful.

Apart from the possible explanations mentioned earlier (see Section 3.2), respondents gave another reason why regulators are so reluctant: they hold power based on their knowledge of the old frame of reference (animal testing models). If regulators have to assume a new frame of reference they run the risk of losing (part of) this power.

The new generation of regulators has had more exposure to alternatives in the course of their education. Some respondents predict that the next generation will see it as self-evident to work towards the introduction of alternatives. However, several respondents argued that the current regulators already have the right attitude to take alternatives into account. The debate on banning the LD50 test was crucial in that respect, according to one respondent.

In addition, regulators have a great sense of responsibility which leads them to adhere to the old frame of reference. They are particularly susceptible to a negative sense of responsibility ("If anything goes wrong, we will be held accountable".) Only when there is a wide consensus for the use of an alternative is the road clear for a regulator to apply it.

Along with the reluctance of regulators, respondents often mention the similarly cautious attitude encountered in the regulatory affairs departments of industry (see also section 5.4). They indicate that these departments are not particularly eager to implement alternative methods to meet regulatory requirements. They believe this conservatism stems from industry's habit of anticipating the presumed wishes of regulators. However, some respondents feel that duty of care requires industry to take more initiative and that responsibility must be shared.

- **The Importance of Personal Commitment**
  A positive attitude towards the 3Rs depends to a great extent on personal commitment, the respondents asserted. Many steps towards the 3Rs in the past were taken because someone personally championed the cause. There are advocates in the industry, for example, who find alternatives important and promote them internally. According to respondents, these key figures may act as catalysts, sparking off a new culture conducive to the development and acceptance of alternatives to animal testing. Clearly, personal commitment is an important driving force behind the issue.

Pharmaceuticals

Respondents made the following observations about attitude in reference to pharmaceuticals:

- **The Attitude of Regulators in Reference to Pharmaceuticals**
  Some of the respondents in the field referred to regulators' so-called 'pharmaconservatism'. The most conservative of the regulators have a basic attitude of suspicion towards the industry. In toxicological evaluations, however, some progress has been made through harmonization. According to one respondent, conservatism among regulators is found mainly in carcinogenicity testing, a type of testing in which large numbers of laboratory animals are used.

One respondent contended that - in the field of pharmacological/toxicological research - the EMEA seems to be less conservative towards alternatives than the national regulators in most member states.

Other respondents do not share these views on pharmaconservatism. One respondent stated:

> *Looking at that field, it seems that smaller safety margins are accepted for medicines than for food. And rightfully so, because your product has to be effective, which means you have to accept a certain risk*.

- **The Industry's Response to the Regulators' Attitude**

  Respondents argued that the industry takes a fairly passive approach to drug registration and release procedures. Several respondents said the pharmaceutical industry's departments of regulatory affairs tend to put on the brakes for fear of legal claims. These actors play it safe and therefore adhere to trusted methods. According to some respondents, regulatory affairs departments sometimes go so far as to have their companies conduct extra, non-regulatory, tests in order to satisfy the authorities in the most conservative countries (such as Japan). The regulatory affairs departments fear the authorities might reject certain results, so they take pre-emptive action.

  Alternatives being used in companies could be more actively brought to the attention of regulators. Currently, this occurs only to a limited extent.

5.5 Conclusions

Public Opinion

- There is public resistance to animal testing in general. Animal testing for medical purposes is more widely accepted.
- The growing focus on consumer safety has so far taken priority over animal welfare.
- Public opinion has the potential to have a great impact on the various stakeholders (politics, industry, regulatory agencies). This can encourage implementation of the 3Rs, or hamper it if the public is focused mainly on safety.
- Public opinion is influenced primarily by the media and NGOs.
- Public opinion is of great importance to the image of companies and products in the industry. This has prompted various companies to promote alternatives as part of a Corporate Social Responsibility concept.

Risk Acceptance

- The 'zero risk' concept is a serious threat to replacing, reducing and refining regulatory animal testing. The appeal for extra research based on the precautionary principle is another manifestation of this.
- Currently, not enough risk/benefit assessments are made. Many products offer great benefits, but the question remains how much of a risk consumers are willing to accept in return.

- Open communication about potential risks fosters individual freedom of choice and creates an opportunity to bring risk acceptance back to more realistic proportions.

Attitude

- The attitude of regulators hinders rather than promotes the use of alternatives. Regulators' generally conservative attitude is ascribed to the social demand for further risk minimization.
- The new generation of regulators is expected to have a more internalized concept of the 3Rs because of greater emphasis on the issue during education.
- Personal commitment to the issue is seen as an important condition for successfully encouraging the implementation of alternatives.
- The industry's tendency to anticipate the presumed conservatism of regulators acts as an obstacle.

Chapter 6

Case Study: Quality Control of Veterinary Vaccines

6.1 Introduction

The researchers opted to do a case study to see how their research findings relate to a real situation. This case study describes the process surrounding the registration of a veterinary vaccine. It serves to check the research findings against an actual situation. It also shows how constraints and conducive factors work in practice. In the analysis of this case, the same concepts are used as in previous chapters (technical, political/administrative and social factors).

The information for this case study was made available by Intervet, a manufacturer of veterinary vaccines. Information was derived from the correspondence between Intervet and the EU Directorate General for Enterprise & Industry and from interviews with two Intervet employees and a staff member employed at the DG Enterprise of the EU.

6.2 Relevant Regulations and Facts

The focus of this case study is an attempt by Intervet to reduce the number of regulatory tests for registration and release of a US-produced veterinary vaccine onto the European market. The main actors in this case are Intervet and the European Commission / Enterprise & Industry DG. A third actor is Ashurst, a Brussels law firm that provided legal advice to Intervet and the International Federation for Animal Health (IFAH; a global organization representing the animal health industry).

In the European Union, registration and testing of veterinary drugs is subject to approximately the same regime as the registration and safety evaluation of drugs for human use. Legislation pertaining to veterinary drugs is derived from the laws on drugs for human use (Directive 2001/83/EC for medications for human use and Directive 2001/82/EC for veterinary medicinal products). This accounts for the strict nature of this legislation, which imposes much more stringent norms on the production and quality control of veterinary drugs than those applied in the USA. Veterinary vaccines and drugs differ from those intended for human treatment in that they are produced for a wide range of species instead of just one. Therefore, the range of diseases, and hence vaccines, is much larger. In this respect, veterinary vaccines are a more complex field than vaccines for human use.

There are two categories of tests that apply to veterinary drugs. First of all, there are tests conducted during the research and development of a new drug for registration. Here, the guidelines of Good Laboratory Practice (GLP) apply. Secondly, there are tests performed for the production and quality control of existing, registered products to be released onto the market. The guidelines of Good Manufacturing Practice (GMP) apply to these production and quality control tests. Quality control tests three things: quality, efficacy and safety.
Company compliance with GLP and GMP principles is audited by the authorities in the country where a production facility is located. A qualified employee of the manufacturer is responsible for maintaining GLP and GMP conditions.
This case study deals with tests conducted for the quality control of an existing vaccine. The vaccine is manufactured in the USA at a site that complies with European GMP standards for production and quality control, according to a European authority which has audited and certified this. Once GMP certification was in place, there was no objection to production in the USA. Quality control of the vaccine also takes place in the USA. This, however, did meet with objections from the EU member states. The EU and USA have no Mutual Recognition Agreement of GMP. The control location was approved by only one EU member state. In other words, because there is no agreement between the EU as a whole and the USA, and because the quality control tests in this case are performed in the USA, the products have to be re-tested in Europe according to European directives.[90] This applies not only to veterinary vaccines, but also to vaccines for human use.
The industry was faced with the situation that if it wanted to import this vaccine into the EU, quality control testing would have to be performed again here. The industry saw this as a superfluous duplication which would entail needless costs and animal testing. Therefore Intervet applied to the Enterprise DG for an exemption from the tests it considered unnecessary. From Intervet's point of view, the EU was unclear because of the ambivalence in its recognition of GMP status. It recognized GMP status for production purposes, but the requirement to re-test for quality control purposes remained in place. Intervet asserted, moreover, that Directive 86/609 should be taken into account. The company felt that re-testing conflicted with this directive.

Intervet's request was turned down by the Enterprise DG, however. The DG based its decision on Article 55 (1b) of Directive 2001/82/EC, which clearly demands complete re-testing of the vaccine in the EU.[91] Intervet maintained that the wording of the article in question could be interpreted differently. The Enterprise DG also pointed out that there was no Mutual Recognition Agreement with the USA, which meant there was no room for individual agreements between a member state and a company. Exempting Intervet from re-testing would contradict community law in all respects, according to the DG for Enterprise.
The EC did not respond to the argument that their decision would contradict the directive relating to animal testing (86/609). Lawyers from Ashurst explained that this directive was not applicable to countries outside the European Union.

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[90] EC (2001), Article 55 (1b)

[91] (1b) in the case of veterinary medicinal products coming from third countries, each production batch imported has, in the importing Member State, undergone a full qualitative analysis, a quantitative analysis of at least all the active substances and all other tests or checks necessary to ensure the quality of veterinary medicinal products in accordance with the requirements of the marketing authorization.
http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2001/nov/Codifications/VetCode2001-82/2001-82EN.pdf, consulted on June 12, 2005.

6.3 Factors Reinforcing the Requirement to Retest

From this case description, a number of factors can be distilled that explain why this attempt to reduce the number of tests, and consequently the number of animal experiments, failed. These factors are described below. The technical factor of expertise is discussed first, followed by the political/administrative factors.

- **Expertise**

  As Chapter 3 mentioned, there are only a few people who have all the expertise needed to assess whether testing is necessary. This requires expertise in research and testing methodologies as well as knowledge of regulations and administrative procedures. The expertise issue affects all parties, namely the industry itself, the representatives of member states and actors at the European level. It is most strongly felt at the decision-making level. In the negotiations that surround the amendment of a directive or the conclusion of an MRA, it is the political decision-makers who do the bargaining. It is practically impossible for them to possess all the necessary expertise.

- **Strict Interpretation of Legislation**

  In this case, legal arguments seem to have played a decisive role in determining whether re-testing was required. Since there is no MRA between the USA and the EU, re-testing on the basis of directive 2001/82 was necessary. In this case, the outcome negatively affected the industry's desire to reduce the number of tests and, by extension, animal experiments. Intervet put forward reduction of animal testing as an argument, but neither the Commission nor the Ashurst legal advisors adopted the argument. They interpreted Article 55 of Directive 2001/82/EC very strictly and literally.

  As is indicated elsewhere in this study, the literal interpretation (as opposed to a more flexible reading in the spirit of the regulations) seems characteristic of those who make decisions about the registration and release of veterinary medicines (legislators and regulators). Various respondents stated that it is easier to go along with existing regulations than to deviate from them. Deviating from the letter of the law involves taking potential risks that no one wants to take responsibility for. In short, adhering to provisions and literal interpretations avoids unwanted 'fuss'.

- **Risk Avoidance by Civil Servants and Politicians**

  This case study clearly illustrates that risk minimization is given priority over the reduction of animal testing. The rest of this study shows that policy-makers and administrators dread the possibility of an incident and therefore opt to play safe. They prefer to have more tests conducted rather than fewer to avoid the risk of a potentially unsafe vaccine. Incidentally, a number of respondents questioned whether the current tests actually rule out the main risks. The real issue here is perceived risk in relation to individual responsibility. This point is well-illustrated by the following anecdote about 'the hand of God and the hand of the government' from one of the respondents:

A company wants to register and market a veterinary vaccine for a swine disease in a given European country (X). The vaccine is already being sold in other EU countries. However, Country X has had bad experiences with a similar vaccine from another manufacturer and therefore decides not to authorize it. The department responsible for this policy prefers to take the risk that the swine disease might break out (resulting in severe damage to Country X's entire pig industry), rather than run the risk of adverse side-effects from the vaccine. As the civil servant involved puts it: *"That is the difference between the hand of God and the hand of the government. The government cannot control whether a disease breaks out, that is in God's hands, but it does have a hand in allowing a vaccine with possible side-effects onto the market. As a consequence, we choose a course of action which we can influence."*

- **Ignoring Conflicting Directives**

  In its response, the European Commission did not address Intervet's argument regarding the reduction of the number of animal tests. At the same time, the EC did not indicate that directive 86/609 was not applicable. This could mean various things. For example, the topic may be so far down the priority list that it does not even warrant a reply. When asked, however, the Enterprise DG insisted that reduction of animal tests is a priority. The Enterprise DG explained that there was no response to the reduction argument because there was no MRA between the US and the EU. Some respondents suggested that the EU deliberately avoids making statements on the conflict of interest between the directive on the registration and release of drugs and the directive relating to animal testing. The moment they take a position on this issue, they will fuel a debate that the civil services would rather do without, a number of respondents intimated.

  According to a few respondents, it is sometimes suggested 'off the record' that the industry should start proceedings to make the Court of Justice clarify the relationship between the various directives and how they should be interpreted. However, this option is not appealing to the industry since it would be costly and time-consuming. Clearly, the industry has weighed the costs and benefits. After all, the industry is active on a global scale and has to contend with other regulations aside from the EU legislation. It is unlikely that the industry would invest so much to possibly win one case when there are so many other potential legal battles on the horizon.

- **Few Policy Windows**

  The moments when it is possible to effect a change in regulatory requirements are few and far between. Agreeing on an MRA or amending a European directive are time-consuming processes. They involve many actors with divergent interests, and the subject matter itself is complex. When the decision-makers convene, they must get down to business too. If they let such an opportunity go by, it will be a long time before another policy window presents itself.

- **Wish to Reduce Testing**

  An encouraging factor in this case is that almost all those involved would like to see the number of tests reduced. The industry would like to perform fewer tests with a view to reducing costs. The civil servants from the Enterprise DG are working towards harmonization of the legislation and towards reducing the number of animal tests. The EU member states are generally in favour of reducing the number of mandatory tests as well. It should be noted, however, that individual states have different ideas as to which tests are needed. With respect to veterinary vaccines, for

example, Hungary and Germany are seen as critical nations that deem re-testing in their homeland necessary. Other, mostly newly acceded European member states, have neither the means nor the infrastructure to comply with all the regulatory tests. Therefore, they advocate simplification. Respondents also pointed out that increasing control of production processes makes quality control of the end product less necessary.

In short, there are many factors at play and if they concur at the right time, this could lead to reduction of the number of animal experiments required for quality control of veterinary vaccines.

6.4 Conclusions

This case makes clear that regulatory requirements and the strict interpretation of regulations prevent a reduction in the number of experiments on animals from happening 'overnight'. The requirement to retest is due to the absence of an MRA between the US and the EU. This is compounded by the risk avoidance and lack of expertise found among civil servants and politicians. In addition, there are precious few policy windows during which policy changes can be achieved, and there are many actors with widely divergent interests involved in the decision-making process. A positive factor is the widespread desire for harmonization and cost reduction on the part of the industry, the European Union and most individual member states.

A concrete way to reduce the number of regulatory animal tests is for the EU and the USA to reach an MRA. However, respondents do not expect this to happen any time soon. An MRA for veterinary vaccines is part of a more far-reaching agreement on vaccines for human use. Negotiations about this have been suspended. The specific nature of the deadlock preventing the signing of an MRA for veterinary vaccines is not known. Therefore, it is unclear whether the less stringent requirements for veterinary medicines in the US play a role in this.

Chapter 7

Characterization of the Political Arena

7.1 Introduction

The previous chapters have dealt with the sub-questions that served to find an answer to the main question posed in this study.[92]
Sections 3.7, 4.5 and 5.5 summarized the factors and actors influencing the policy-making process. These summaries also indicated what kind of influence the various stakeholders have (either encouraging or constraining the use of alternatives for regulatory testing, or even a combination of both). Chapter 7 analyzes these findings in more detail and draws conclusions about the degree of influence the various actors have on the policy-making process. To this end, it first sketches the general political forces affecting decisions regarding regulatory animal testing, and subsequently it focuses on the pharmaceuticals arena. In both cases, the emphasis is on the European context.

7.2 The General Political Arena

The picture which emerges of the forces influencing regulatory animal testing is based on the findings derived from interviews with respondents. The respondents indicated that the different stakeholders have varying degrees of influence on policy-making for animal testing depending on the field. Degree of influence also varies within each field. Nevertheless, nearly all respondents also made observations about the general tendencies in the political arena surrounding regulatory animal testing. This picture is based upon a combination of individual perceptions. It is therefore only intended as an approximation of the existing situation. However, the picture based on these perceptions is fairly unambiguous.

As Chapter 1 indicated, the study differentiated between the following main categories of stakeholders:
- Legislators
- Regulators
- Science
- Industry

[92] "Which factors and actors influence the policy-making process at EU level in reference to the use of animal testing, and in which ways?"

- NGOs / special interest groups
- General Public

These categories are used in the diagram below that represents the forces influencing the use of animal testing. The diagram shows the respondents' views as to which stakeholders influence policy-making on regulatory animal testing, and to what extent. The arrows indicate whether influence is direct or indirect (through another stakeholder). The width of the arrows represents the degree of influence. It should be noted that this is an approximation of relative influence based on respondents' perceptions. The diagram is not a factual, quantifiable representation of the degree of influence.

The key actors are entitled to formal influence on the grounds of their authority in the decision-making process. Other actors have influence based on other qualities: strong views on the relevant issues, formal/informal power, authority, media support, public opinion and social position.

The diagram shows that four stakeholders are seen as most dominant in the policy-making process. As the assessors of new products and substances, regulators have most influence on the implementation of legislation, and therefore on the feedback loop as well (see Figure 1.2).
Regulators also exert direct influence on the policy-making process in the shape of experts who advise legislators on drafting new policy or revising existing policy. Regulators also have a great deal of indirect power through their influence on the industry regarding authorization and release of substances and products. The industry, in turn, exerts great influence on legislators through their strong lobby.

Experts, who are shown in this study to have a great deal of influence in the development of policy, fall under either of two categories: regulators or scientists.

Among the NGOs/special interest groups, it is particularly animal welfare organizations that have both direct and indirect (through public opinion) influence on the policy-making process. This influence is aimed primarily at the initial stages of the process: the agenda-setting stage and partly the policy-making stage (see Figure 1.2). It is especially their ability to mobilize public opinion that gives these organizations the power to influence the political agenda. Therefore, they can be a driving force behind reforms that implement the 3Rs. However, animal welfare organizations have very little direct influence on regulators, respondents remarked, since regulators take their cues first and foremost from the heavy responsibility they bear.

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 supply the experts that help draft and revise regulations at every level. And the member states' influence is even greater in the implementation of EU regulations. European legislation usually leaves member states enough discretionary room for their own interpretation of policy. All in all, this means that national experts (scientists and regulators) play a dominant role in policy-making, while regulators play a dominant role in policy implementation.

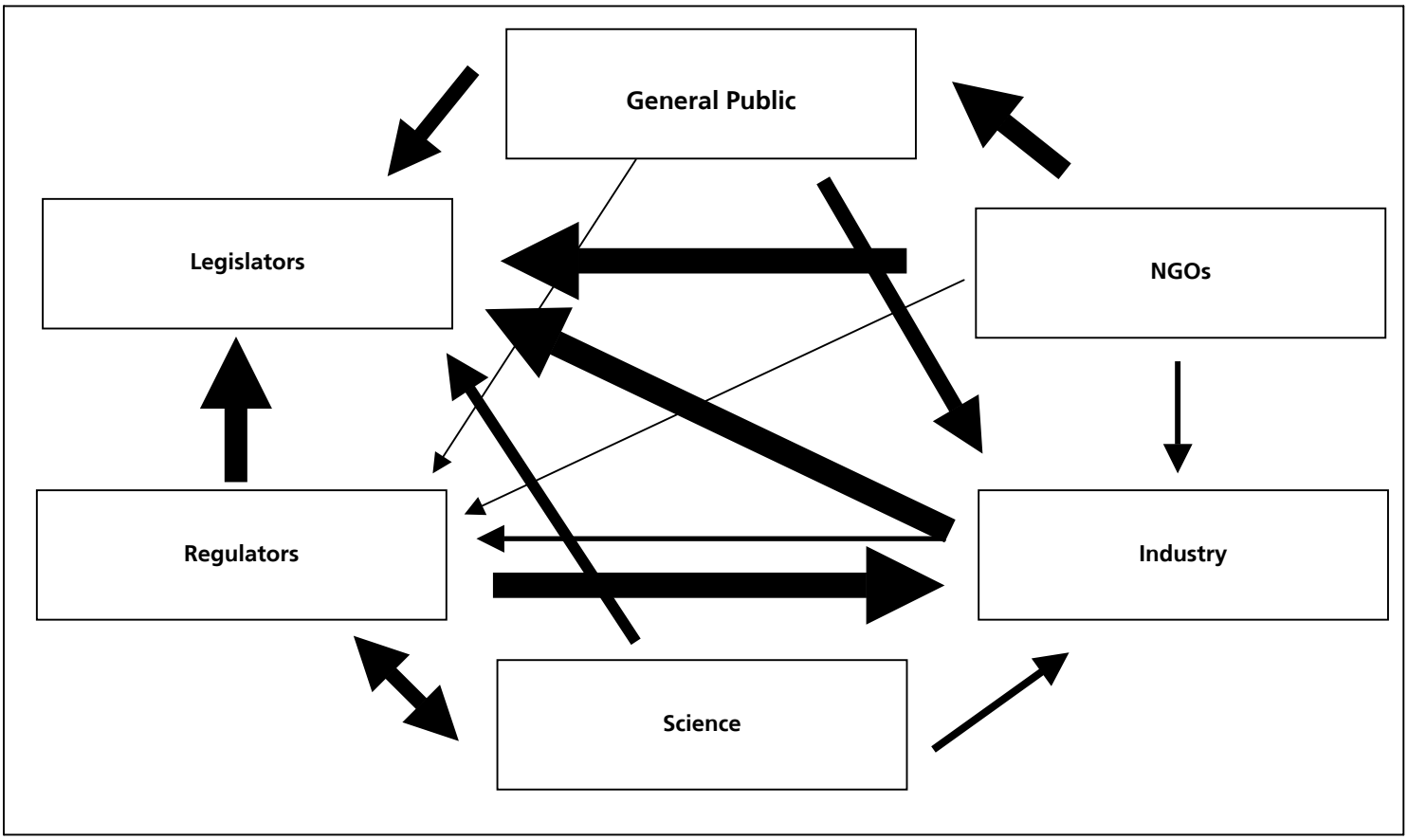

Figure 7.1 General Political Arena. Approximation of the relative influence stakeholders exert on the policy-making process at EU level concerning the use of animal testing.

7.3 The Pharmaceuticals Arena

This section depicts the arena for policy-making regarding regulatory animal testing for pharmaceutical ends. Again, this is an approximation based on the respondents' opinions.

To an extent, the same forces that play a role in the general political arena also play a role in the pharmaceuticals arena. Here too, regulators exert great influence on the policy-making process. In this case the regulators are the EMEA, the European Pharmacopoeia and the Dutch Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen; CBG). The EMEA mainly influences decision-makers' opinions on new policy or policy revisions regarding registration and release of medicines onto the European market. In the pharmaceuticals arena too, experts have a great deal of influence on policy-makers and, again, these experts are usually regulators or scientists.

The pharmaceutical industry is characterized as one of the most influential industrial sectors. This is mainly because pharmaceutical products are of such immediate importance to human beings. Yet even the pharmaceutical industry is more of a follower than a leader when it comes to influencing regulators about regulatory animal testing.

The pharmaceuticals arena in Europe is largely shaped by the global context of the ICH, and hence by the USA and Japan. Japan is a very conservative force with regard to the use of experiments on animals.

In the pharmaceutical arena, NGOs such as animal welfare organizations have much less influence than they have in the general political arena. However, patient organizations are far more prominent in the pharmaceutical arena. Their influence is mainly directed at promoting new research that can benefit patients. In this way, such organizations indirectly affect the use of experiments on animals.

The general public is less opposed to the use of animal testing for medicinal purposes than to the use of laboratory animals for other purposes. For this reason, public opinion is one of the weaker forces determining the use of animal testing in the pharmaceutical arena.

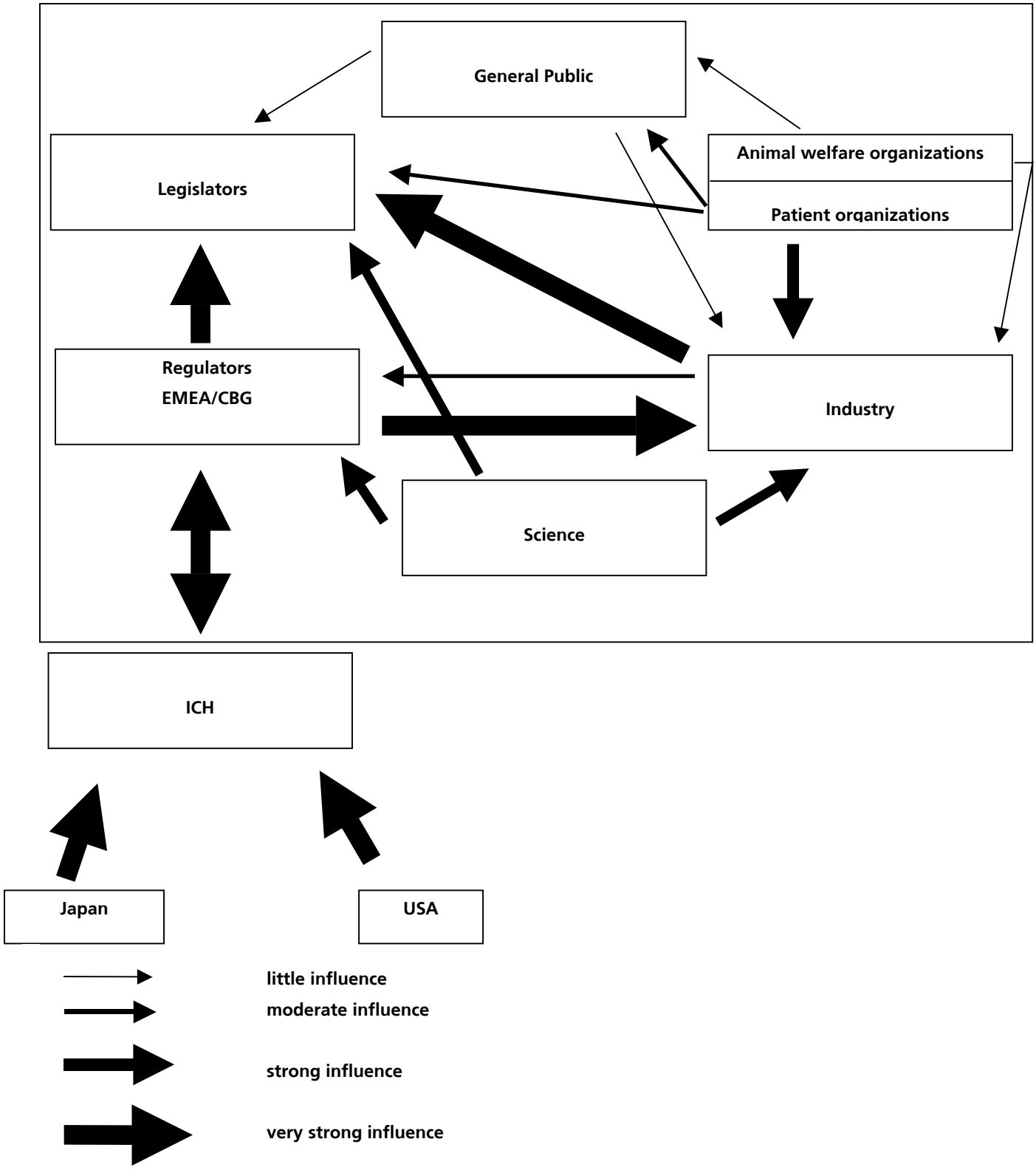

Figure 7.2 The pharmaceuticals arena. An approximation of the relative influence stakeholders exert on the policy-making process at EU level in relation to the use of animal testing for the registration and release of drugs onto the European market.

Chapter 8

Conclusions and Recommendations

8.1 Introduction

This study, entitled "Regulatory Animal Testing", has answered the question posed in Chapter 1:

Which factors and actors influence the policy-making process at EU level in reference to the use of animal testing, and in which ways?

The study has shown that regulatory animal testing is persistent and that there are limited opportunities to implement alternatives. It has described various obstacles to implementing the 3Rs in regulatory testing. In addition, a number of opportunities to implement the 3Rs for regulatory requirements have been identified. The findings of this study are to be used as input for a follow-up project focusing on one or more of these opportunities and threats, with the aim of reducing regulatory animal testing. To this end, a number of recommendations follow.

This chapter discusses three categories of opportunity that can be used to tackle the problem of the large number of regulatory experiments on animals.

I Technology. There is a need for research and development of new, supplementary techniques to replace, reduce or refine animal experimentation.

II Communication. There is considerable room for improvement of the exchange of knowledge between stakeholders about methodologies, results, etc. The necessary improvements range from basic awareness-raising to the implementation of a communication strategy.

III Coordination and harmonization. Following naturally from a better communication strategy, the stakeholders should coordinate their actions more closely. The desired result is harmonization, 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 creates a policy window (see Section 1.4). The technology category deals with new ways to enlarge 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 harmonization can 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. This can be facilitated by entrepreneurs or advocates (see Section 1.4). The dominant actors that are conducive to implementing the 3Rs in regulatory animal testing (these were described in Chapter 7) could play a role in this. Some examples of such actors are: progressive companies in the field, experts in the field of the 3Rs, animal welfare organizations, ethical review committees, the inspectorate, and committed individuals in any stakeholder group.

In every category, a number of opportunities have been identified. The focus is mainly on improved communication and coordination. We believe the follow-up study, to be funded by European subsidy, should be aimed at exploring communication and coordination. These aspects can be seen as preconditions for new and existing technological developments in the field of alternatives to take root.

8.2 Technological Opportunities

This study has identified a number of opportunities in the field of technology. Since technological solutions were beyond the scope of this study and outside the expertise of the USG researchers, what follows here is simply a list of the opportunities identified by the respondents and summarized in Chapter 3.

- Investment in datasharing and retrospective analyses to ensure that valuable information is preserved and can be used to its maximum potential.
- More emphasis on a strategic approach to assessment procedures for registration and release of substances or products onto the market (like the step-by-step approach used in toxicity tests or the consistency approach used for organic products).
- Cost assessment (in money, time, and numbers of laboratory animals) of regulatory animal experiments, relative to the cost of possible alternatives.

8.3 Communication Opportunities

Communication between the various stakeholders has been identified as a key precondition to increasing the implementation of the 3Rs. Communication between alternatives experts and regulators and legislators is crucial, for instance. There have been initiatives in this respect, but communication between stakeholders still leaves room for further professionalization. The following is a list of the main recommendations for better communication.

Increased use of Risk Communication

The degree of risk minimization that modern society strives for is seen as unrealistic (see also Section 4.3.5). Wider use of risk communication to inform the public about actual risks may lead to a more realistic level of risk acceptance which would in turn decrease the need for testing. To begin with, it might be useful to do a study into public risk acceptance with regard to medications, for instance.

This angle could be used in an attempt to influence the level of risk acceptance, although this would hardly be feasible as a follow-up project in the short term because society's demand for consumer safety seems only to be growing stronger.

Broader Communication on Available Alternatives and Opportunities

A number of stakeholders are unable to judge alternative test models on their merits because they lack expertise in modelling and the attending statistical analyses. Scientists would therefore do well to publicize alternative methods more widely and more accessibly. What is needed are ways to improve the dialogue between alternatives researchers and policy-makers. This applies to the preparation and conducting of research as well as implementation of the results. What seems to work especially well is a long-term advisory relationship between legislators and regulators on the one hand and trusted researchers on the other. These must be researchers who have earned respect and trust, in part by displaying thorough knowledge of the subject matter.[93]

The inspectorate and ethical review committees can facilitate this by calling companies' attention to the existence of alternatives and encouraging implementation of 3R methods which have been recognized in regulations but are still hardly, if at all, applied in practice.

Scientists are usually not very adept at making their research findings accessible to a wide audience. They could be trained in this area, or receive support.

Differentiating Information for Different Target Groups

If experts, NGOs or the industry want to widely publicize information about the 3Rs, they will have to differentiate their messages and publications. This is necessary to ensure the message gets across to the recipients (whether legislators, regulators, the industry, scientists or the general public). In other words, the communication process and the resulting messages must be adapted to the various stakeholders' needs.

Members of Parliament, for instance, have a great deal of information to digest. Therefore, the information offered to them must be concise, not too complicated and, preferably, geared towards one or more of their interests. In addition, the message should be coordinated with the political agenda. Good timing is essential. When informing politicians it is very important to address the information to their close assistants as well. It is also advisable to target not just politicians, but to disseminate the information through various channels in order to generate public support.

Regulators have very different information needs when it comes to alternatives to animal testing. Unlike politicians, this target group usually wants in-depth information. It is important to consider the level of expertise of the regulator in question.

Improving Communication between the Stakeholders

In preparing legislation for REACH, a stakeholder group was established to take stock of the alternatives to animal testing. This turned out to be a successful way of joining expertise and interests; as a result the 3Rs were implemented more within REACH. Despite the growing number of initiatives to improve

[93] Elliot H., Evidence-based policy-making in the NHS: a study of the interface between research and the purchasing process. Public Health Research & Resource Centre, The University of Salford, 1996.

communication between stakeholders, respondents felt there was plenty of room for improvement in this area, particularly to persuade the more conservative stakeholders of the importance of the 3Rs.

In providing stakeholders with feedback about research findings, subjective judgment is much more influential than 'scientific proof'.[94] Therefore, Sauerborn et al. recommend that researchers actively engage with the stakeholders at the feedback stage. The main risks (for example, selective use of results) can be prevented by adequately informing all the stakeholders. In order to encourage the use of research findings, it is advisable to follow a process-based rather than content-based strategy. This will facilitate the use of research findings in the future by institutionalizing mutual contacts.

There is a need to find ways to further improve the dialogue between researchers and policy-makers. This is needed during the preparation and conducting of research as well as the implementation of research results.

A Closer Look at the Representation and Perception of the 3Rs

In order to effectively promote the implementation of the 3Rs, it is important to map out the various arguments for applying this concept and to analyze the interests of the different stakeholders. This study has made a start at this. A follow-up study can zoom in on the perception of one dominant stakeholder in particular (either legislators, regulators or the industry). Such a study could try to reveal the conditions under which the target group in question would be prepared to make a change. Another option would be to focus on the EU countries that conduct most animal experiments and to get a clear picture of the arguments used to justify this. In such a study, it would be advisable to treat the new EU member states separately.

8.4 Coordination and Harmonization Opportunities

Further coordination and harmonization of legislation is seen as an important step towards reducing the number of regulatory animal tests. Harmonization could potentially generate a win-win situation. Companies would benefit from the clarity and uniformity of the regulatory requirements for the registration and release of substances and products in the different market segments. Governments would benefit from uniform regulations which no longer require business to comply with a different set of rules for every market segment or market. It is also important to avoid conflicting regulations. Harmonization is a difficult process. With a view to potential follow-up projects, we do not see many short-term opportunities in this area. In harmonization, communication is again the key word. Communication is essential to bring about a scientific consensus and, subsequently, the administrative consensus needed to make continued harmonization possible.

Strengthening the Policy Network

Because the popularity of certain policy issues can rapidly dissipate, it is important to ensure that the issues are administratively and politically well embedded, in terms of both content and support. Organizations that want to achieve this must have inside knowledge of the European playing field and the rules of the

[94] Sauerborn R., S. Nitayarumphong and A. Gerhardus (1999): 827-835.

game. They must also have a strong case and be able to orchestrate the process extremely well. It is important to recognize that the policy commitment of the EU can vary widely per sector.[95]

In order to address weaknesses in the exchange of information between actors and the need for differentiated communication, it is important to more strongly position the policy network that connects mutual actors and topic areas. A follow-up project should therefore take a two-pronged approach:

1. Expansion and intensification of the policy network representing the various stakeholders.
   This can be achieved through an exchange of specific expectations, opportunities and knowledge pertaining to the 3Rs. For every activity, the most suitable actors/target groups must be identified. Education could be included in the process of building this policy network. To this end, it is crucial to establish a core group which can lead and steer this development both content-wise and in terms of the process. It is important to foster transparent and constructive relationships with legislators and politicians. Once a solid base of shared elements has been established, it needs to be maintained and reinforced, ultimately resulting in a stable policy network.
2. The policy network should formulate performance targets for the nature and content of animal experiments, the number of animals involved and the degree of suffering/distress. These performance targets must subsequently gain political approval.

Improving Coordination of Horizontal and Vertical Legislation

In order to address the lack of coordination between horizontal legislation such as EU Directive 86/609 and vertical legislation (see Chapter 2), clear traffic regulations need to be established. Animal welfare organizations could stimulate this process in cooperation with industry, by considering bringing to court various cases where the lack of coordination is causing problems. This could result in a court ruling that provides clarity and forces the legislature to fulfil its responsibilities.

To conclude

Regulatory animal testing is deeply ingrained in the procedures for evaluating substances and products before they are allowed onto the market. Society, however, is growing more and more critical of such animal tests required by protocol. There are various reasons for this. First of all, the objections are ethical in nature. Secondly, evaluation procedures often take too long, according to policy-makers and government institutions.[96] And thirdly, such testing is very expensive.

Hence, initiatives from a variety of backgrounds have been taken to reduce regulatory animal testing. This study is one of those initiatives. By having provided insight into the factors that influence the use of regulatory animal testing, the researchers hope to have contributed to the quest for possible solutions.

[95] This is closely related to the division of tasks and competences between the EU and its member states (subsidiarity).

[96] Gezondheidsraad, Onderzoek gezondheidsrisico's stoffen: naar een gerichtere benadering, Advies November 2001

Appendix 1

Research Project Organization

The members of the research project group are:

- Dr. B.J. Blaauboer: Interfaculty Institute for Risk Assessment Sciences (IRAS; Utrecht University)
- Dr J.M. Fentener van Vlissingen: Erasmus Animal Experimentation Centre (EDC; Erasmus University Rotterdam)
- Prof. Dr. C. F. M Hendriksen: Netherlands Centre for Alternatives to Animal Use (NCA; Utrecht University) / Dutch Vaccine Institute (NVI), Bilthoven.
- Drs. J. Kuil: Dutch Society for the Protection of Animals , The Hague
- Prof Dr. R. Remie: Solvay Pharmaceuticals, Weesp
- Drs. J.W.G.M. Thuring: Notox (Contract Research Laboratory), Den Bosch
- Ir. M.A. Vaal: Science Shop for Biology (Utrecht University)

The advisory committee consists of four members of the research project group, namely

- Dr. B.J. Blaauboer
- Prof. Dr. C. F. M Hendriksen
- Ir. M.A. Vaal
- Drs. J. Kuil

The group of experts consists of:

- Prof. Dr. R. Kroes: scientific director of the Interfaculty Institute for Risk Assessment Sciences (IRAS; Utrecht University) and president of EUROTOX and the International Life Sciences Institute (ILSI) Europe
- Dr. H.B.W.M. Koëter: scientific director of the European Food Safety Agency (EFSA), Brussels.
- Dr. Ir. B. Hakkert: national coordinator of the OECD/EU directives programme at the National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
- Dr. J. W. van der Laan: head of the Pharmacological and Toxicological Assessment Department at the Centre for Biological Medications and Medical Technology (BMT), RIVM, Medicines Evaluation Board (CBG); European Agency for the Evaluation of Medicinal Products (EMEA)).
- Prof Dr. T. Hartung: head of the European Centre for Validation of Alternative Methods (ECVAM), Joint Research Centre of the European Commission, Ispra, Italy.

The research was conducted by a USG project team:

Dr. G.H. Hagelstein (expert in public administration)

Gerrit Hagelstein is an expert in public administration and a lecturer/researcher/consultant at the Utrecht School of Governance. He has extensive experience in the analysis of administrative processes and served as the expert on public administration within the research project team.

He was also working for the European Commission on an Interact project, a network in which 12 European cities exchange knowledge and experiences in the field of strategic policy development for cities and urban regions and developed courses to transfer this knowledge (2002-2004). Partner cities in this project are Lyon, Munich, Budapest, Birmingham, Antwerp, Vienna, Genova, Venice, Malmö, Brno, Belfast, Utrecht and The Hague.

Hagelstein was also heading an international comparative research project on the effect of European policy and regulations on the organization of the regional administrative level in the Netherlands.

Drs. A. Harreman

Annemiek Harreman studied Law, Public Administration and Management at Utrecht University and is working as a consultant and researcher at the Management and Communication Research Centre (CMCO). Harreman is an experienced researcher of policy and organizational analysis in both profit and not-for-profit organizations. Her expertise is in the interface between organizational and legal issues. Apart from her consulting work, she also lectures at the Utrecht School of Governance. Some of the projects that she contributed to are: research into the role of regulatory agencies in the construction industry, commissioned by the Parliamentary Investigative Committee on the Construction Industry; an evaluation of the Dutch Financial Expertise Centre (FEC), commissioned by the Ministry of Finance and the Ministry of Justice; an international comparative study of the effect of European policy and regulations on the organization of the regional administrative level in the Netherlands.

Drs. M.J.W.A. Schiffelers (Project Manager)

Marie-Jeanne Schiffelers studied Environmental Social Science and is currently working at USG as a consultant and researcher in the field of organizational and policy issues. She has extensive experience with qualitative research methodologies and has worked in both the profit and not-for-profit sectors, for various government institutions, educational institutions and the commercial services industry. In the past, she headed an effectiveness study for the Science Shop for Biology in Utrecht. Other projects she partcipated in include: an evaluation of the Dutch Financial Expertise Centre (FEC), commissioned by the Ministry of Finance and the Ministry of Justice; an administrative analysis commissioned by the Netherlands School of Public Health (NSPH)/ the Netherlands Organisation for Applied Scientific Research (TNO). She is currently also involved in the evaluation of the Ministerial Decree on Biotechnology in Animals, commissioned by the Dutch Ministry of Agriculture, Nature and Food Quality.

Schiffelers has served as the project manager on behalf of the USG. In this capacity, she was the liaison and coordinator of the project.

Drs. A.M.J. van der Spek

Martijn van der Spek is a social scientist specialized in qualitative research. He is a consultant with the Utrecht School of Governance. He has conducted many organizational and policy analyses for various profit

and not-for-profit organizations. He recently headed a USG project, commissioned by the Research and Documentation Centre of the Dutch Ministry of Justice (WODC), to evaluate the Netherlands National Investigation Team for War Crimes (NOVO). Van der Spek was also responsible for conducting an administrative analysis commissioned by the Netherlands School of Public Health (NSPH)/TNO. He is currently heading the team evaluating the Ministerial Decree on Biotechnology in Animals, commissioned by the Dutch Ministry of Agriculture, Nature and Food Quality.

S.A.G van Wersch

Susan van Wersch is a fourth-year student at the Utrecht School of Governance. As a student assistant she has lent assistance during the execution of the project.

Appendix 2

Respondents

- Drs. I. Arendzen (Dutch Ministry of Health, Welfare and Sport / Inspectorate of the Food and Consumer Product Safety Authority (VWA))
- Dr. B.J.M. Arts (Faculty of Policy Sciences, University of Nijmegen)
- Dr. B.J. Blaauboer (Interfaculty Institute for Risk Assessment Sciences (IRAS; Utrecht University)
- Mr. E.C. de Bordes (Faculty of Veterinary Medicine, Utrecht University)
- Drs. B.R.A. van den Bos (PRAD/ former MEP for the D'66 party)
- Dr. J. H. Fentem (Unilever- Safety and Environmental Assurance Centre)
- Dr. J. M. Fentener van Vlissingen (Erasmus Animal Experimentation Centre (EDC; Erasmus University Rotterdam))
- Drs. B.J. Fernhout (Intervet)
- Dr. B. Garthoff (Bayer CropScience; European Consensus Platform for Alternatives (ecopa); the European Federation of Pharmaceutical Industries (EFPIA))
- A. Gautrais (Enterprise DG, European Commission) DVM
- Dr. E.R.M. Geuns (Solvay) Msc Pharm D.
- Dr. M. van der Graaff (Nefarma)
- Dr. Ir. B.C. Hakkert (national coordinator of the OECD/EU directives programme at the National Institute for Public Health and the Environment (RIVM))
- Prof. Dr. T. Hartung (European Centre for the Validation of Alternative Methods (ECVAM); Joint Research Centre of the European Commission)
- Mr. M. Heinen (Eurogroup for Animal Welfare)
- Prof. Dr. C. F. M. Hendriksen (Netherlands Centre for Alternatives to Animal Use (NCA); Dutch Vaccine Institute (NVI))
- Drs. E. Honig (Intervet)
- Dhr. H.B.W.M. Koëter : scientific director of the European Food Safety Agency (EFSA), Brussels
- Prof. Dr. R. Kroes: scientific director of the Interfaculty Institute for Risk Assessment Sciences (IRAS; Utrecht University) and president of EUROTOX and the International Life Sciences Institute (ILSI) Europe
- Drs. J. Kuil: Dutch Society for the Protection of Animals
- Dr. J.W. van der Laan (Medicines Evaluation Board (CBG); European Agency for the Evaluation of Medicinal Products (EMEA))

- Drs. W.A. de Leeuw (Inspectorate of the Food and Consumer Product Safety Authority; VWA)
- S. Louhimies (Environment DG, European Commission)
- Prof. Dr. G.J. Mulder (Leiden/Amsterdam Center for Drug Research (LADCR))
- Prof. Dr. I.F.H. Purchase (ICI/Zeneca, University of Manchester)
- Prof Dr. R. Remie (Solvay Pharmaceuticals)
- Dr. T. Rijnders (Vice President Research, Organon)
- Drs. S.C. Schutte (Organon)
- Dr. R. Stolp (Intervet) DVM
- Dr. P.W. van Vliet (Dutch Health Council)
- Dr. J.M.G. Vorstenbosch (Ethics Institute, Utrecht University)
- Dr. D. Wagner (Organisation for Economic Co-operation and Development (OECD))

In addition, the researchers attended:
- NCA symposium (November 25, 2004)
- ecopa workshop (November 27, 2004)

Appendix 3

Overview of Actors

Actors	National	European	Global
Legislators/ Policy-makers	First and Second Chambers Min. of Health, Welfare & Sport Min. of Agriculture, Nature and Food Quality Min. of Housing, Spatial Planning and the Environment	Eur.Commission: Enterprise DG DG Sanco DG Research DG Env. EP Intergroup Council of Europe	OECD ICH
Advisory Bodies	Dutch Health Council Central Commission on Animal Testing (CCD) Animal Experiments Committees (DECs) Dutch Association of Animal Experiments Committees (NVDEC)	Ecopa	
Regulatory Agencies	Medicines Evaluation Board (CBG)	EMEA Pharmacopoeia EFSA	FDA: USA MHLW Japan PMDA Japan
Enforcement Agencies	Inspectorate of the Food and Consumer Product Safety Authority (VWA)		
Judicial Power	Council of State	European Council of State?	
Science	Division of Laboratory Animal Science: Faculty of Veterinary Medicine, Utrecht University Royal Netherlands Academy of Arts and Sciences (KNAW)	JRC ECVAM FELASA EFAT EBRA	

	Netherlands Organisation for Applied Scientific Research (TNO). Dutch Association of Laboratory Animal Science (NVP) National Institute for Public Health and the Environment (RIVM) Netherlands Centre for Alternatives to Animal Use (NCA) Interfaculty Institute for Risk Assessment Sciences (IRAS)	ESF	
Industry	Nefarma Solvay Organon	CEFIC Syngenta EFPIA IFAH	
CROs	NOTOX	Huntingdon	
NGOs	Dutch Society for the Protection of Animals Anti-animal testing pressure group *Proefdiervrij* Patient Organizations (Dutch Genetic Alliance (VSOP)) Disease Research Foundations Dutch Consumers' Union	Eurogroup for Animal Welfare WSPA EPPOSSI RSPCA BUAV	
Media			
Other	PRAD ZonMw		

Glossary

ATLA	Alternatives To Laboratory Animals
BUAV	British Union for the Abolition of Vivisection
CBG	Dutch Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen)
CCD	Central Commission on Animal Testing (Centrale Commissie Dierproeven)
CEFIC	European Chemical Industry Council
CHMP	Committee for Medicinal Products for Human Use
COREPER	Committee of the Permanent Representatives
DEC	Animal Experiment Committee (Dierexperimentencommissie)
DG	Directorate General
DG SANCO	Directorate General for Health and Consumer Affairs
EC	European Community
ecopa	european consensus platform for alternatives
ECVAM	European Centre for the Validation of Alternative Methods
EFAT	European Federation of Animal Technologists
EFPIA	European Federation of Pharmaceutical Industries
EFSA	European Food Safety Authority
EMEA	European Agency for the Evaluation of Medicinal Products
EP	European Parliament
EPPOSSI	European Platform for Patients' Organisations
ESF	European Science Foundation
Eurotox	Association of European Toxicologists and European Societies of Toxicology
EU	European Union
FDA	Food and Drug Administration
FELASA	Federation of European Laboratory Animal Science Associations
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICI	Imperial Chemical Industries
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFAH	International Federation for Animal Health

ILSI	International Life Sciences Institute
IRAS	Institute for Risk Assessment Sciences
JRC	Joint Research Centre
KNAW	Royal Netherlands Academy of Arts and Sciences (Koninklijke Nederlandse Akademie van Wetenschappen)
LADCR	Leiden/Amsterdam Center for Drug Research
LD50	Lethal Dose 50 (lethal dose for 50% of lab animals)
MAD	Mutual Acceptance of Data
MEB	Dutch Medicines Evaluation Board
MEP	Member of the European Parliament
MHLW	Ministry of Health, Labour and Welfare (Japan)
MRA	Mutual Recognition Agreement
NCA	National Centre for Alternatives to Animal Use (Nationaal Centrum Alternatieven voor dierproeven)
Nefarma	Dutch Association of Research-oriented Pharmaceutical Companies (Nederlandse Vereniging van de Research-georiënteerde Farmaceutische Industrie)
NGO	Non-Governmental Organizations
NOTOX	Contract Research Organisation; Safety & Environmental Research
NVDEC	Dutch Association for Animal Experiments Committees (Nederlandse Vereniging van Dierexperimentencommissies)
NVI	Dutch Vaccine Institute (Nederlands Vaccin Instituut)
NVP	Dutch Association of Laboratory Animal Science (Nederlandse Vereniging voor Proefdierkunde
OECD	Organisation for Economic Co-operation and Development
Ph.Eur	European Pharmacopoeia
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
Prad	Programme Committee on Alternatives to Animal Testing (Programmacommissie A lternatieven voor D ierproeven)
R&D	Research and Development
REACH	Registration, Evaluation and Authorisation of CHemicals
RIVM	National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu)
RSPCA	UK Royal Society for the Prevention of Cruelty to Animals
SCALE	Science, Children, Awareness-raising, Legislation and Evaluation
SWP	Safety Working Party
TNO	Netherlands Organisation for Applied Scientific Research (Nederlandse Centrale Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek)
USG	Utrecht School of Governance
UU	University of Utrecht
VSOP	Association of Cooperating Parent and Patients' Organizations (Vereniging Samenwerkende Ouder- en Patiëntenorganisaties)
VWA	Dutch Food and Consumer Product Safety Authority (Voedsel en Waren Autoriteit)
Wod	Dutch Animal Testing Act (Wet op de dierproeven)

WSPA	World Society for the Protection of Animals
ZonMW	Netherlands Organisation for Health Research and Development (a combination of ZorgOnderzoek Nederland and NWO Medische Wetenschappen)

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