Issues Relating to the Release of Proprietary Information and Data for Use in the Validation of Alternative Methods

The Report and Recommendations of ECVAM Workshop 271,2

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Preface

This is the report of the twenty-seventh of a series of workshops organised by the European Centre for the Validation of Alternative Methods (ECVAM). ECVAM’s main goal, as defined in 1993 by its Scientific Advisory Committee, is to promote the scientific and regulatory acceptance of alternative methods which are of importance to the biosciences and which reduce, refine or replace the use of laboratory animals. One of the first priorities set by ECVAM was the implementation of procedures which would enable it to become well-informed about the state-of-the-art of non-animal test development and validation, and the potential for the possible incorporation of alternative tests into regulatory procedures. It was decided that this would be best achieved by the organisation of ECVAM workshops on specific topics, at which small groups of invited experts would review the current status of various types of in vitro tests and their potential uses, and make recommendations about the best ways forward (1).

The workshop on Issues Relating to the Release of Proprietary Information and Data for Use in the Validation of Alternative Methods was held in Munich, Germany, on 9–11 May 1997, under the co-chairmanship of Martin Todd (ZENECA Pharmaceuticals, Macclesfield, UK) and Bernward Garthoff (Bayer, Leverkusen, Germany). The main

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1ECVAM — European Centre for the Validation of Alternative Methods. 2This document represents the agreed report of the participants as individual scientists.
objective of the workshop was to discuss various issues relating to the accessibility of confidential/proprietary data. The recommendations and conclusions of the workshop participants are given at the end of this report, which summarises the discussions which took place at the workshop.

Introduction

All new chemical and pharmaceutical products are tested before humans are exposed to them, either intentionally or accidentally, in order to evaluate any potential hazards associated with such exposure. To determine the magnitude and target of any toxicity, tests are carried out in animals and, subsequently, in humans. Many of these tests are required by various national and international regulatory authorities. New compounds are tested for scientific, ethical and regulatory reasons, to identify possible adverse effects and mechanisms of toxicity. It is widely recognised that there is a need to improve the current testing methods, to maximise the relevance of the information generated with respect to the prediction of adverse effects in humans.

One way to achieve this is to develop and validate new in vitro methods, which could reduce the number of animals used in toxicity testing as well as contribute to improving its scientific basis. Appropriate and validated in vitro methods could play an important role in regulatory toxicity testing in the future.

The validation of new test methods requires the generation of data and comparison of these with historical (animal) data on the same compounds. While some of these data are in the public domain, there is a considerable amount of proprietary in vivo and in vitro data that could be valuable for use in validating new methods which is not generally accessible. Several ECVAM workshop reports have, independently of each other, indicated that there is a need for access to these data to accelerate the development and validation of in vitro methods (2–7). The advantages of making these data available include: a) the potential to increase the efficiency of the discovery and development of new industrial and agricultural chemicals, pharmaceuticals and cosmetics; and b) to contribute significantly to the reduction, refinement and replacement of animal experiments.

The large increase in chemical synthesis capability in all product research and development areas, through the synthesis of combinatorial libraries and use of automated synthesis procedures, together with the use of high-throughput testing systems, has resulted in many more compounds being evaluated as potentially marketable products. This increased capacity early in the new product discovery process has meant that conducting the necessary toxicology studies has become a rate-limiting step, if the classical animal procedures are used. This bottleneck, however, could be overcome if validated high-throughput in vitro toxicity tests, based on mechanisms of action or molecular outputs, could be used to enable selection of the most favourable candidates for further testing and evaluation. To avoid testing in several different species of animals, in vitro systems that provide information on species-specific metabolism, pharmacokinetics and toxicity are essential, so that the most relevant species to be used for toxicity testing can be identified. To develop these in vitro systems, data from animals and humans must be available.

The international regulatory acceptance of novel techniques requires that they have been scientifically validated with an appropriate range of chemical types, using biological data which are reliable and suitable for establishing the predictive abilities of the new methods. It is often possible, and is certainly preferable, to use existing historical data to undertake the comparisons necessary, rather than conducting new in vivo tests. Toxicity testing for regulatory purposes has generated a large amount of in vivo data on a large number of diverse substances. These data could be retrieved for use in the validation of in vitro test methods either directly from the industrial companies where the animal tests have been carried out, or from the regulatory agencies to which the information has been submitted for registration of the particular product. For validation purposes, the raw in vivo data would need to be of an acceptably high quality and the biological activities of the compounds would need to be adequately classified, so that data from studies carried out under similar conditions and with comparable endpoints could be combined and still maintain their value.
Proprietary data generated by industry on candidate products may have high economic value. They are provided to regulatory authorities on a confidential basis and are protected from disclosure by legally binding agreements. This workshop has addressed key issues pertaining to improving access to proprietary data, including: a) agreement on procedures for prioritising appropriate areas for the development and validation of new tests; b) confidentiality; c) liability; and d) definition of acceptable processes for data sharing.

Priority Areas for the Development and Validation of In Vitro Tests

There are insufficient in vivo data generally available which could support the validation of in vitro methods in the following areas of regulatory toxicity testing: a) local toxicity — skin penetration, skin corrosivity, skin irritation, skin sensitisation, eye irritation, phototoxicity, respiratory (inhalation) toxicity, and intravenous irritation; and b) pharmacology and systemic toxicity — bioavailability, pharmacokinetics/toxicokinetics, general toxicity, embryotoxicity, genotoxicity, and carcinogenicity. With respect to organ-specific pharmacology and toxicity testing, the following areas have been the focus for the development of new methods, and are therefore likely to be of most interest: a) neurotoxicity; b) hepatotoxicity; c) nephrotoxicity; and d) haematotoxicity. For example, current animal models for neurotoxicity testing either are not available or are not predictive of neurotoxic effects observed in humans. Thus, there is an urgent need for relevant and highly predictive tests for neurotoxicological effects which could be adopted by industry.

The development of new in vitro screening methods in these areas should include input from regulatory authorities (with respect to the acceptance of validated tests, and the provision of in vivo and in vitro data), industry, and animal welfare organisations. There is a need to agree upon a process by which areas for the development and validation of new tests could be prioritised, especially in relation to prototyping a system for data sharing. One possible way of determining the priority areas for data acquisition efforts would be to focus on those endpoints and methods scheduled for validation by ECVAM.

Accessibility of Proprietary Data

Proprietary information is any information which the owner considers to be confidential and for which precautions have been taken against involuntary disclosure. Such data, if submitted to regulatory bodies for the purpose of evaluating compounds for marketing, remain confidential, unless the owner has given consent for publication or has published the data. The same considerations apply to all data generated by industrial companies.

Such proprietary information may be of considerable economic value to the owner, especially in cases where patent protection has not yet been obtained. This applies to both efficacy and safety/toxicity data. Submission of these in vivo data to a third party for the purpose of trying to validate an in vitro test may risk unauthorised disclosure. This risk is even greater if the information is included in a databank to which others have access.

Data on new chemical entities and products are submitted to governmental agencies for registration purposes. These agencies receive and review the data on a confidential basis. It is clear that legal authorisation would be required for data residing with these regulatory bodies to be analysed for purposes other than those initially intended.

An example of where proprietary in vivo data have been made available is a study conducted by the Centre for Medicines Research (CMR) International concerning reduction of the time required for repeat-dose chronic toxicology studies from 12 months to 6 months (8). The CMR has published anonymised case studies (9), and information has been made available which has contributed to a debate on the appropriate duration for non-rodent studies (10). Other examples include: a) a study being carried out by the Centre for Documentation and Evaluation of Alternative Methods to Animal Experiments (ZEBET, BgVV, Berlin, Germany) on selection of the appropriate species for pesticides safety testing, and the possibility of omitting the requirement to use dogs (11, U. Gerbracht & H. Spielmann, submitted for publication); and b) a study on the
use of appropriate species for carcinogenicity testing (12). Both are examples of retrospective studies which could be carried out in other areas, such as the selection of appropriate species for various toxicology studies, in particular where non-human primates and dogs are involved.

For the development and validation of new tests in a non-regulatory context, access to proprietary data would also be of value, since data on compounds which have not been submitted for registration are rarely published. In particular, there are very few results reported where positive findings have precluded continued development of the chemical or product.

If industry were to reveal certain new information, any data sharing process would have to comply with the way in which basic patenting and safeguarding of proprietary information occurs. In a patent, information about the patented compound which has been synthesised from substituents of a core compound, as well as the data for the core compound, have to be kept confidential. Therefore, the “environment” of an existing patent has to be secured as far as possible. Once information is made public, a future patent may be invalid, and thus the patent holder has to take all reasonable measures to protect the proprietary data. In this respect, anyone who reveals any data associated with the compound to be patented in a public appearance, even to a small group of people in a seminar, is endangering the potential patent application. Therefore, access to the basic raw and aggregated data has to be limited to a small number of people, to avoid disclosure. This also applies to those people working with databanks.

Timing of the release of certain data can have a bearing on patenting since, during the development, or even after the launch, of a new product, adverse effects may occur in exposed individuals. For this reason, the amount of information that industry would be willing to share is limited, since this information could form the basis of a further patent (for example, one relating to a better tolerated substance from the same group of compounds, having different substituents to the compound for which the earlier patent has been obtained).

The risk of unauthorised disclosure of confidential data when sharing them with a third party is considered to be the most important factor that typically prevents industry from revealing such information. This risk has to be weighed against the potential benefits for industry if a suitable, relevant, time-effective and cost-efficient alternative method was accepted, which had been developed and validated based on data which industry had released specifically for this purpose. To deal with the potential risk of unauthorised disclosure of proprietary information, the liability of any third party receiving confidential data must be ensured. Evidence of unauthorised disclosure of information would definitely jeopardise the willingness of industrial companies to share data.

A special issue which needs to be considered is how to secure the confidentiality of data when they have been entered into databanks. The security of “fire-walls” has to be regarded with caution.

Regulatory agencies

For retrospective studies, data held by regulatory agencies could be used. Data submitted to regulatory agencies for the safety assessment of chemicals and products are proprietary, and are only submitted for safety assessment purposes. The use of this information may, to a certain extent, be in conflict with the interests of the industrial companies concerned, since many of these data are on existing chemicals for which the patent term has expired. Consequently, appropriate procedures would need to be implemented to safeguard confidentiality. The presentation of information on such chemicals in scientific journals will require that details of the most recently submitted proprietary data are protected, and that the owners of such data (as represented, for example, by their respective industry associations) have agreed to the terms under which the results are to be published.

In some countries (for example, Germany and The Netherlands), information obtained from proprietary data has been used successfully to improve the risk assessment process and to implement the Three Rs. Thus, the priority level for a chronic study can now be determined on the basis of a conservative estimate of a “safe” chronic exposure level obtained from a short-term study (13), and acute toxicity studies need not be conducted if the no-observed adverse effect level equals or exceeds 1000mg/kg (14). The German
Foundation for the Promotion of Research on Replacement and Complementary Methods to Reduce Animal Testing (SET) is currently funding a study with the Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV) on the use of dogs as the second species in the regulatory testing of pesticides (11). This study will involve analysis of the data on 220 pesticides submitted to the BgVV over the past 40 years.

Industry

Chemicals
The data that are produced by industry and submitted to regulatory agencies for safety assessment purposes, for the classification and labelling of industrial chemicals, etc., could be used as in vivo reference data in validation studies. The use of proprietary toxicity data, as well as physicochemical data and chemical structures, would facilitate considerably the development and validation of in vitro methods and better structure-activity models. Since most of these data have been produced according to OECD test guidelines, they are generally of acceptable quality. More than 1000 chemicals have been registered under the Dangerous Substances Directive (Directive 67/548/EEC) in the EU since 1982. These data should be made available for validation studies of methods to be used in regulatory toxicology.

Pharmaceuticals
Proprietary data are generated during both preclinical and clinical testing. There are three main scenarios which impact on sharing the toxicity data produced: a) a drug is toxic and testing is stopped during preclinical trials; this information may never be published and is kept in the archives of a particular company (for example, data on various antibiotics); b) a drug undergoes clinical testing which reveals unexpected side-effects in humans and thus it is not put on the market; the preclinical and clinical data are kept in the files of the company concerned and, in addition, in the files of certain regulatory authorities (for example, the US Food and Drug Administration, or the UK Medicines Control Agency); information on compounds which fail to reach the market because of “late stage” adverse effects is rarely published and is therefore not generally available; and c) “successful” drugs pass preclinical and clinical testing; the data on these are in the files of both regulatory authorities and industry, and this information may be published. In addition to the data held within regulatory agencies, the industrial company may possess other relevant data which could contribute to the development and validation of alternative methods.

Data on compounds that have been taken out of testing early on are particularly important with respect to the development of predictive in vitro tests and structure-activity models.

Cosmetics
No authorisation is required for cosmetics to be marketed in Europe, and thus there are no regulatory agencies specifically for cosmetics within Europe. However, according to the Sixth Amendment to the Cosmetics Directive (Directive 76/768/EEC), a unique dossier must be made available on official requests for all cosmetic products coming onto the European market. This dossier must contain both in vivo and in vitro data relevant to product safety issues and claim substantiation. The dossier is confidential and is kept within the company concerned. It is possible that the European Cosmetic, Toiletry and Perfumery Association (COLIPA) could play a key role in improving the general accessibility to these data.

Other sources of data
Toxicological data are not only stored in files of industrial companies and regulatory agencies, but are also collected by research institutions, such as CMR International. Data on chemicals are stored by the European Chemicals Bureau (ECB), which is a unit of the European Commission’s Joint Research Centre based at Ispra, Italy. A significant amount of these data are confidential.

Mechanisms for Data Sharing
Data generated by the pharmaceuticals, industrial chemicals, agrochemicals and cosmetics industries, both during the screening of new chemicals for their potential activities and during the regulatory testing which is required to obtain product registration for marketing authorisation, are not generally available to groups wishing to validate in
vitro tests. When discussing mechanisms for data sharing at the workshop, it was agreed that the aggregation of data in order to draw general conclusions (such as the value of short-term studies for predicting the outcomes of long-term studies), would not necessarily require revealing the chemical structures of the individual compounds. As such, it was felt that there should be no objection to performing such data analyses. Data sharing would only be feasible through a neutral third party intermediate, with whom the industry concerned is willing to work. Industry would provide appropriate in vivo information to the “neutral institution”, which would then be responsible for coding and aggregating the data before releasing them to any organisation or group wishing to use them to try to validate a particular alternative method. The number of people having access to the confidential data should be restricted to the minimum required to achieve the study objectives.

All parties involved would be “legal bodies” and work as partners. Thus, a formal agreement between all parties involved would be necessary. This should cover: a) confidentiality/secrecy (all parties involved must sign a confidentiality agreement); b) definition of restrictions on access to the data; c) description of the contents of the database and details of the partners involved; d) clear definition of the purpose of the study, the data required, and the tests concerned (the test[s] to be validated must be agreed between all parties, and the purpose of the validation study must be defined clearly. The data needed to achieve the objectives stated must also be defined, before any information is requested or collected from industry); e) definition of the format of the aggregated data to be released to the organisation/group conducting the validation study in advance, so that there is no concern that proprietary information would be released; and f) agreement on how the information generated will be disseminated, prior to initiating any validation study which uses data from industry (for example, to achieve a significant reduction of testing in animals, it would be essential to gain acceptance of any proposed strategy by the OECD; this would require peer-review and publication of the results of the validation study).

Consideration should be given to the need for an insurance policy for the “neutral institution”, to cover compensation to industry if there were any data leaks. In addition, careful consideration should be given to the choice of the particular confidential data to be used. Some data may be regarded as highly sensitive from the perspective of the provider. It could be that less-sensitive data are sufficient for the purposes of a specific validation study.

**Process for Data Acquisition and Analysis**

To provide proprietary data for the validation of in vitro test methods, processes for maintaining confidentiality are required. It is likely that data would only be made available for studies where the outcome could be seen to be advantageous to all of the parties involved. To gain access to data for use in the development or validation of a particular new method, it is important to establish a process which will provide data requesters and potential providers with sufficient and specific details relating to the type of data requested, by whom, for what purpose, and to what intended benefit. The process could be divided into two parts: initially an enquiry could be made through a third party intermediate about the existence and availability of the data needed, and about the willingness of data providers to engage in a data sharing process. Once a potential data provider has indicated an interest in sharing data, a more detailed data request could be submitted.

The second stage could involve providing the following information to the data provider: a) the intended use of the data requested; b) details of the personnel who will have access to the data; c) a statement regarding the expected benefits; d) details concerning the dissemination of the final outcome; e) a list of other potential data suppliers that have been, or will be, approached; and f) appropriate confidentiality agreements, for completion. In addition, data requesters should provide specific details on the following in their request: a) a description of the endpoints of interest, including method(s), doses, exposure, results, positive and negative controls, and statistical analyses; b) a description of the current format of the data generated with the new method (for example, notebooks, database, summary report); c) a query about the quality of the
data and the original purpose for generating the data (for example, in a screening study, during research and development, or in a fully Good Laboratory Practice [GLP]-compliant study); d) a standard data record form (as a hard copy or in an electronic format) which enables data to be entered into a “relational” database; and e) the structure, or at least the general class, of the compound (if appropriate).

The data requester and provider would then establish a work schedule and time-line for data transfer and assimilation. To facilitate and optimise data analysis, data should be entered into a relational database, such as Access™ or Oracle™. The database should incorporate a basic statistical analysis package, to facilitate comparisons between a number of endpoints. Once the data have been entered and analysed, the output could be reviewed by a recognised group of experts, who could provide an objective view of the quality and reliability of the conclusions for the data provider. The panel of experts could write a formal paper to send to the data providers for comment, prior to this report being used for its initial stated purpose. Acceptance of a newly developed test method will be achieved by the usual process of peer review and multi-laboratory validation on a worldwide basis, which should ensure acceptance internationally.

Conclusions and Recommendations

The sharing of data for the purpose of validating new test methods for industrial chemicals, agrochemicals, drugs and cosmetics is conceivable, if procedures which would protect the confidentiality of the data providers, via the use of a third party “data broker”, were developed and implemented. There is considerable value to be gained from identifying new in vitro methods which could be validated, accepted by industry and regulators, and have a positive impact on reducing the use of laboratory animals for testing new chemicals and products. The following recommendations were agreed upon by the workshop participants:

1. A survey of the priority areas for test development and validation should be carried out, initially to identify an area of widespread interest, so that a data sharing process which would aid the validation of appropriate new methods could be established and subsequently evaluated in a pilot study.

2. Careful consideration should be given to the choice of the particular confidential data to be used. Some data may be regarded as highly sensitive from the perspective of the provider. It could be that less-sensitive data are sufficient for the purposes of a specific validation study.

3. Data sharing is only likely to be feasible through a neutral third party intermediate with whom the industry is willing to work. Industry could provide appropriate in vivo information to the “neutral institution”, which would then be responsible for coding and aggregating the data before releasing it to any organisation wishing to validate a particular in vitro method.

4. To protect the interests of the companies and institutions which might provide data for the validation process, strict confidentiality precautions need to be implemented. Confidentiality agreements would have to be entered into by the organisations involved in the validation process, and by any other party using or obtaining access to proprietary data and patentable information in any form. In these agreements, the confidential information provided, and the specific and exclusive purpose(s) for which it could be used, would need to be defined.

5. Regulatory agencies and other bodies holding toxicological data should be approached with respect to gaining access to information which would enable the development and validation of new test methods. The validation procedure may require access to the original data held within the regulatory agencies and the industrial companies concerned. Permission for publication of such data in the scientific literature would need to be sought, to enable appropriate peer review and publication of the results of any validation study.

6. The proprietary information required would include toxicity, pharmacokinetic and metabolic data, produced in animals and in humans, where available. Only data of acceptable quality (for example,
those generated according to GLP requirements and in compliance with OECD or other such internationally recognised test guidelines) should be used. Data on compounds which have been taken out of testing, including negative test results, are particularly valuable.

7. ECVAM must explore ways to obtain access to data from external agencies, both in relation to the selection of reference chemicals to be used in validation studies and for conducting reviews of existing data aimed at implementing the Three Rs. To do this, ECVAM should investigate the possibility of establishing partnerships with industrial companies and with organisations which hold data on behalf of industry (for example, CMR International).

8. Aggregated industry data should only be made available to countries where appropriate measures exist to protect intellectual property rights.

References