

A Proposal to Establish a Brazilian Center for Validation of Alternative Methods (BraCVAM)

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Summary

Brazil recently approved law number 11.794/2008, which regulates the use of animals for scientific purposes. Many products on the Brazilian market are still required to be controlled by animal testing. In Brazil, there is no improved mechanism for funding collaborative studies, and there is no institution responsible for managing and coordinating such studies. Oswaldo Cruz Foundation (FIOCRUZ) assembles all the conditions to be the headquarter of the Brazilian Center for Validation of Alternative Methods (BraCVAM), since it is an internationally recognised scientific institution uniting a large number of scientific fields, including basic and applied research, drug and vaccine production, quality control, teaching, hospitals, etc. The multidisciplinary scientific infrastructure of FIOCRUZ could be used to establish a network in different fields of knowledge. The creation of BraCVAM would facilitate the development and validation of tests, not only in Brazil but also in South America and the Caribbean.

Keywords: BraCVAM, alternative methods, validation, regulatory acceptance

1 Introduction

The Brazilian Government approved law 11.794 in October 2008. This law, known as “Lei Arouca” (Arouca’s Law) in homage to the physician that first proposed it, regulates the use of animals in research and teaching (Brazil, 2008). Before this law, some other legislation touched upon this subject, i.e. laws that regulate environmental crime, veterinarian professionals, etc. Law 11.794 is specifically focused on the use of animals in experimentation and teaching, but not for agronomical purposes.

Law 11.794 creates the National Council of Animal Experimentation (CONCEA) that includes in its responsibilities monitoring of and evaluating the introduction of alternative techniques that replace the use of animals in teaching and experimentation (Marques et al., 2009). However, the law does not state that whenever an alternative method exists, animals may no longer be used (Machado et al., 2009). CONCEA is composed of members of related Ministries and scientific societies, including representatives of animal protection societies (Brazil, 2008). However, CONCEA lacks technical support.

Therefore, the creation of a Brazilian Center comparable to ECVAM, ICCVAM and JaCVAM would be an important step for such studies, which could then be coordinated in an efficient manner. In addition, the Center would be invaluable for contact and interaction with similar organisations in other countries throughout the world.

2 State of the art in Brazil

There are many animal rights protection groups in Brazil, some of them representatives of groups from other countries. Although this movement is not as intense as it is for example in Europe, the need to validate and establish alternative methods according to the 3Rs has compelled a large number of laboratories to perform studies in this field.

Currently about 15 to 20 groups are working on alternative methods. These groups are at official laboratories, universities, industry and private laboratories. Most of them are trying to validate alternative methods to replace animals in assays such as skin and eye irritation, pyrogen test and vaccine potency, while some others are studying alternatives in education, nutrition and environmental enrichment.

Brazil does not have an organisation that is responsible for the coordination of validation studies. The current research in this field is due to particular initiatives of the above mentioned institutions, which, motivated by precedents in other countries, have started working on the development of alternative methods.

Brazilian Decree Number 4725, dated 9th June 2003, dictates that one of the activities of the National Institute of Quality Control in Health (INCQS) is to establish the quality control rules and procedures for the health laboratory network (Brazil, 2003a). However, except when methods are already internationally validated, it is impossible to comply with this ruling without



conducting a collaborative study to harmonise the procedures and to define the parameters for the interpretation of the results they provide. Even when methods are already validated, some may need to be adapted for specific local needs since Brazil controls final products instead of raw material and some products are specific to the country and are not the object of international validation, etc.

Although Brazilian *Resolution No. 899*, dated 29th May 2003, published the *Guideline for the Validation of Analytical and Bioanalytical Methods* (Brazil, 2003b), the whole process is not defined, nor is the role of each entity during the various steps established, as was done in the EU initiative which established ECVAM (Anonymous, 1991) and subsequently in the OECD guidance on validation (OECD, 2005).

3 Backgrounds

It took a long time for Brazilian meetings to introduce a special session on alternative methods. Although there are no documents on it, it probably started to occur around 2000. Before this time, studies on alternative methods were presented at congresses and similar events as poster presentations in different sessions, i.e. only related to the specific subject (e.g. toxicology, animal welfare, etc.).

In 2005, INCQS organised the Brazilian Meeting on Alternative Methods to Animal Use for Regulatory Purposes (EMALT) where problems related to financial support for research in the alternative area and problems in validating assays were discussed (Presgrave and Boghal, 2005). That was the first time that the need of establishing a Brazilian Center for validating alternative methods was declared during the discussion of mechanisms of the validation process.

In 2007, at the XV Brazilian Congress of Toxicology, Prof. Dr. Thomas Hartung and Prof. Octavio Presgrave both presented the need for creating the Brazilian Center for Validation on Alternative Methods (BraCVAM) in their speeches. The BraCVAM proposal was first published in a recent article (Presgrave, 2008).

4 Validation centres around the world

Many institutions in the world work on development and validation of alternative methods and animal welfare based on the 3Rs principle. The BraCVAM idea was based upon some of them.

European Centre for the Validation of Alternative Methods (ECVAM)

ECVAM was created in 1991, as part of the European Commission's Joint Research Centre (JRC), in order to fulfil the requirements outlined in Article 23 of *EU Directive 86/609/EEC*, which aimed to stimulate the development and validation of alternative methods which would be able to supply at least the same level of information given by existing animal assays, but which would use fewer animals, or significantly reduce their suffering, or replace their use altogether (Anonymous, 1991).

ECVAM's role in achieving these aims is mainly via the coordination of the validation of these alternative methods.

ECVAM was located in the JRC in Ispra, Italy, since the JRC is a multilingual establishment, with a history of acting in the promotion of international scientific cooperation. This factor facilitated the design of the correct technical structure needed for ECVAM's work, besides providing a basis for expanding the role of the JRC in research (Anonymous, 1991).

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

ICCVAM was founded in September 1994 as an ad hoc committee for presenting a report to support the requirements of the 1993 *NIH Revitalization Act*. In this Act, the National Institute of Environmental Health Sciences (NIEHS) was required to establish criteria for the validation and regulatory acceptance of toxicological alternative methods (ICCVAM, 2008). This committee became permanent in December 2000 and nowadays comprises representatives from 15 US federal regulatory and research agencies.

At present, ICCVAM receives scientific support from National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), which is part of NIEHS, located at Research Triangle Park, NC, USA. ICCVAM's mission is to promote the development, validation and regulatory acceptance of alternative methods, emphasising the 3Rs principles, while scientific quality and human, animal and environmental health are upheld and promoted (ICCVAM, 2008).

Japanese Centre for the Validation of Alternative Methods (JaCVAM)

JaCVAM was established in November 2005 and is affiliated to the Japanese National Centre for Biological Safety and Research (NCBSR) of the National Institute of Health Sciences (NIHS) (Ohno, 2005a; Kojima, 2007).

The mission of JaCVAM is to propose and improve the validation of alternatives and to establish international cooperation besides developing new alternative methods (Ohno, 2005b; Kojima, 2007).

Centre for Documentation and Evaluation of Alternatives to Animal Experiments (ZEBET)

ZEBET was established in 1989 and its aim is to bring about the replacement of legally prescribed animal experiments with alternative test methods, to reduce the number of test animals to the absolutely necessary level and to alleviate the pain and suffering of animals used in experiments. ZEBET is also responsible for documenting alternatives to animal experiments. By this mode of action, ZEBET is the information office for alternatives to animal experiments for the federal authorities.

ZEBET also coordinate experimental validation of methods not involving animal experiments in order to include them in official safety toxicological test directives. ZEBET has the advantage of undertaking its own research and has a separate budget to promote specific projects on the development of alternative methods (ZEBET, 2008).

5 The Brazilian Centre for the Validation of Alternative Methods (BraCVAM)

Since Brazil does not have an institution that coordinates alternative studies and these studies are important for the development of research, it is imperative to create BraCVAM (Presgrave, 2008).

Oswaldo Cruz Foundation (FIOCRUZ) possesses all of the necessary attributes for it to become the headquarters of BraCVAM, since it is an internationally-recognised scientific institution that unites a vast range of scientific and medical fields, including basic and applied research, drug and vaccine production, quality control and teaching. This is an important aspect, since the multidisciplinary scientific infrastructure of FIOCRUZ could be used to form a working platform with a wide range of available knowledge on many relevant subjects.

Between 2001 and 2007, FIOCRUZ published 6,359 articles in Brazilian and international journals. In 2007, the ratio of published articles in the biomedical area was about 60% of the total articles (Teixeira et al., 2009).

INCQS, and some other groups in FIOCRUZ, have been studying alternative methods for a long time. Since INCQS is the official laboratory of the Brazilian Ministry of Health, it has to perform assays to guarantee that products that are on the market are sufficiently safe. For this purpose, INCQS routinely performs animal toxicological tests and, since 1989, has tested most of these products with alternative methods, for comparing results and evaluating correlations between animal and non-animal data.

INCQS has frequently participated in several Brazilian and international congresses, including the *World Congress on Alternatives and Animal Use in the Life Sciences*. It comprises a group of approximately 20 professionals and students working on alternative methods, mainly for the replacement of animals in testing for skin, eye and mucous irritation, and in sensitisation and pyrogen testing, as well as in vaccine control. During this period, a range of activities, such as poster presentations, lectures, organisation of meetings and round tables, paper publications, and post-graduate studies, have been undertaken.

BraCVAM action should not be restricted to the experimental area but must encompass studies on alternatives in education, environmental enrichment, etc. The Center must act in the development of alternative research in every area in which it is possible to apply the 3Rs concept. Of course these structures should be constructed step by step. Integration with similar institutions is very important in order to start establishing mechanisms of validation studies.

The BraCVAM structure should present a coordination division and divisions that reflect areas of action as recently proposed by Eskes and coworkers (2009, see Fig. 1). The scope of these areas may be as following:

- a) Promotion and Networking
 - Creation and maintenance of a centralised website & database on alternative methods
 - Monitoring and creation of a network of interested parties on alternative methods in Brazil
 - Organisation of seminars and specialised workshops
 - Publications

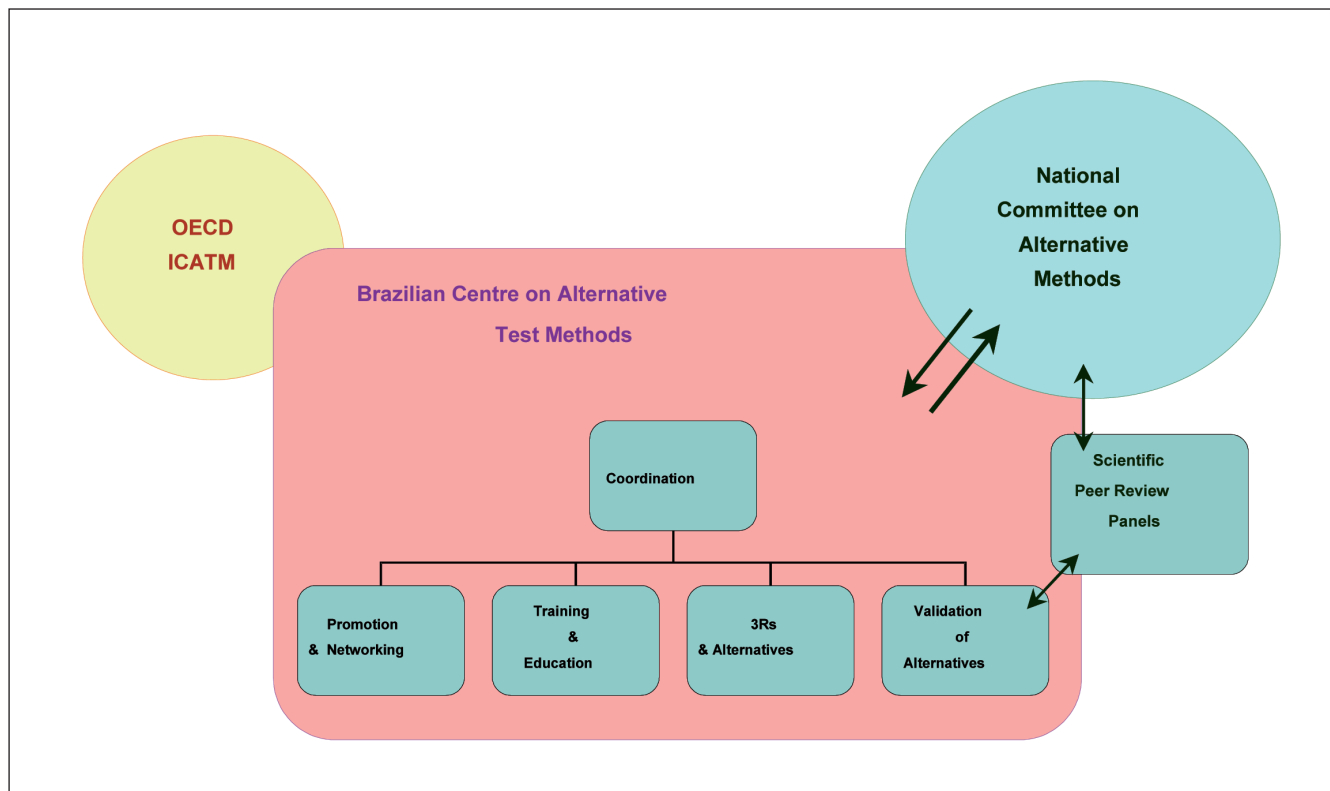


Fig. 1: Proposed organogram for BraCVAM and relationship with some external committees and institutions.



- b) Training and education
 - Training on the 3Rs principles
 - Practical courses on validated alternative methods
 - Training on the internationally agreed principles of validation
 - c) 3Rs and alternatives
 - Identification of current regulatory, industrial and academic needs
 - Identification of available alternatives
 - Creation of platforms of excellence on specific fields of expertise
 - Identification of most appropriate alternatives for specific applications
 - d) Validation of alternative methods for regulatory purposes
 - Coordinating studies on the development of alternative methods to animal testing
 - Coordinating validation studies of alternative methods to animal testing
 - Proposing and evaluating test protocols
 - Participation in international validation studies
 - Publication of reports about the progress of studies
- Once established, the activities of BraCVAM shall include:
- the development of new methods;
 - the coordination of studies on the development of alternative methods;
 - the coordination of the validation of alternative methods;
 - the proposal and evaluation of test protocols;
 - the analysis and evaluation of results obtained from studies;
 - participation in international cooperation;
 - the creation, maintenance and management of databases of technical procedures, substances, raw materials, finished products and any other aspects relevant to alternative methods;
 - the promotion of meetings, congresses, workshops or any other route of disseminating scientific information to regulatory organisations, industries, academia and any other institutions related to alternatives;
 - the publication of reports about the progress of studies; and
 - the improvement of any procedure that could help in the development of alternative methods.

6 Conclusion

The creation of a Brazilian Centre for the Validation of Alternative Methods (BraCVAM) would be very important, not only for, but for the whole of Latin America, since there is no similar institution in this part of the world.

Once established, BraCVAM should determine its structure, take all necessary steps to become officially viable, and determine the start-up period for its activities.

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